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ÓLEOS ESSENCIAIS E TERPENOS COMO ESTRATÉGIA DE CONTROLE DE CARRAPATOS E NEMATOIDES

ANILDES IRAN PEREIRA SOUSA

São Luís - MA
2022

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Tese de doutorado apresentada ao Curso de Doutorado do Programa de Pós-Graduação em Biodiversidade e Biotecnologia da Rede BIONORTE, na Universidade Federal do Maranhão, como requisito parcial para a obtenção do Título de Doutora em Biodiversidade e Biotecnologia.

Orientadora: Profa. Dra. Alexandra Martins dos Santos Soares
Coorientador: Prof. Dr. Livio Martins Costa Junior

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À vida!

A Deus, por sua eterna generosidade

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“Deem graças ao Senhor porque Ele é bom.

O Seu amor dura para sempre!”

Salmo 136,1.

SOUSA, Anildes Iran Pereira. Óleos essenciais e terpenos como estratégia de controle de carrapatos e nematoides**. 2022. 80 f. Tese (Doutorado em Biodiversidade e Biotecnologia) - Universidade Federal do Maranhão, São Luís, 2022.**

RESUMO

Carrapatos e nematoides são parasitos amplamente distribuídos de importância veterinária. O uso contínuo de acaricidas sintéticos e anti-helmínticos tem resultado em aumento da resistência, motivo pelo qual alternativas terapêuticas têm sido consideradas, como produtos naturais. A atividade parasiticida de óleos essenciais de plantas e seus componentes têm sido investigados contra carrapatos e nematoides. O objetivo deste estudo foi avaliar a ação de óleos essenciais e seus constituintes sobre o nematoide *Haemonchus contortus* e a ação de um shampoo contendo o terpeno carvacrol contra os carrapatos *Rhipicephalus (Boophilus) microplus* e *Rhipicephalus. sanguineus*. A ação de óleos essenciais obtidos de 16 cultivares de *Ocimum basilicum*, assim como a ação do linalol, metil chavicol, citral e eugenol, foi avaliada, *in vitro*, através do ensaio de inibição da eclosão de ovos do nematoide *H. contortus*. Adicionalmente, avaliou-se a ação de três cultivares, que foram simuladas usando uma combinação dos dois principais compostos de cada uma. Para os estudos com carrapatos, um shampoo contendo carvacrol foi formulado com lauril éter sulfato de sódio, cocoamidopropil betaína, lauril glucosídeo, carboximetilcelulose, metilparabeno e ácido cítrico. As características sensoriais do shampoo e o pH foram avaliados a 37, 25 e 5 °C. A eficácia do shampoo contendo carvacrol contra *R. microplus* e *R. sanguineus* foi avaliada pelo teste de imersão larval. Com relação aos ensaios sobre nematoides, os óleos essenciais de diferentes cultivares de *O. basilicum* apresentaram concentração para inibir 50% da eclodibilidade dos ovos (IC_{50}) de *H. contortus*, variando de 0,56 a 2,22 mg/mL. A cultivar com maior inibição de eclosão de ovos, napoletano, é constituída principalmente de linalol e metil chavicol. Entre os compostos individuais testados, o citral foi o mais eficaz (IC_{50} 0,30 mg/mL). A melhor combinação de compostos foi obtida com 11% de eugenol e 64% de linalol (IC_{50} 0,44 mg/mL). Como resultados dos ensaios com carrapatos, a mortalidade de larvas de *R. microplus* e *R. sanguineus* foi de 100% após o tratamento com 0,15% de shampoo contendo carvacrol (diluição 1:19 do shampoo em água). O shampoo com carvacrol apresentou-se estável nas condições analisadas. Concluímos que cultivares de *O. basilicum* apresentam diferentes eficácias sobre *H. contortus*, sendo as cultivares contendo linalol e metil chavicol as mais promissoras e, também, concluímos que o shampoo contendo carvacrol apresenta eficácia acaricida, sendo ser um potencial agente de controle de carrapatos.

Palavras-chave: Produtos naturais; Parasiticidas; *Haemonchus*; *Rhipicephalus.*

SOUSA, Anildes Iran Pereira. Essential oils and terpenes as a tick and nematode control strategy**. 2022. 83 f. Tesis (PhD in Biodiversity and Biotechnology) - Federal University of Maranhão, São Luís, MA-Brazil, 2022.**

ABSTRACT

Ticks and nematodes are widely distributed parasites of veterinary importance. The continuous use of synthetic acaricides and anthelmintics has resulted in increased resistance. Thus, therapeutic alternatives such as natural products have been considered. The parasitic activity of plant essential oils (EOs) and their components have been investigated against ticks and nematodes. This study aimed to evaluate essential oils and terpenes as a strategy to control nematodes and ticks. The action of essential oils (EOs) obtained from 16 cultivars of *Ocimum basilicum*, linalool, methyl chavicol, citral and eugenol was evaluated *in vitro* in the test of inhibition of the hatching of eggs of the nematode *Haemonchus contortus*. Additionally, the action of three cultivars was evaluated, which were simulated using a combination of the two main compounds of each one. For the tick studies, a shampoo containing carvacrol was formulated with sodium lauryl ether sulfate, cocoamidopropyl betaine, lauryl glucoside, carboxymethyl cellulose, methyl paraben and citric acid. The shampoo's sensory characteristics and pH were evaluated at 37, 25 and 5 °C. The effectiveness of shampoo containing carvacrol against *R. microplus* and *R. sanguineus* was evaluated by the larval immersion test. Regarding the tests on nematodes, the EOs from different cultivars of *O. basilicum* showed a concentration to inhibit 50% of the hatchability of eggs (IC_{50}) of *H. contortus*, ranging from 0.56 to 2.22 mg/mL. The cultivar with the most significant inhibition of egg hatching, napoletan, consists mainly of linalool and methyl chavicol. Among the individual compounds tested, citral was the most effective (IC_{50} 0.30 mg/mL). The best combination of compounds was obtained with 11% eugenol and 64% linalool (IC_{50} 0.44 mg/mL). As a result of the assessments on ticks, the mortality of *R. microplus* and *R. sanguineus* was 100% after treatment with 0.15% shampoo containing carvacrol (1:19 dilution of shampoo in water). The shampoo with carvacrol was stable under the conditions analyzed. We conclude that different cultivars of *O. basilicum* have different efficacies against *H. contortus*, with the cultivars containing linalool and methyl chavicol being the most promising; we also conclude that the shampoo containing carvacrol has acaricidal efficacy and is a potential tick control agent.

Keywords: Natural Products; Antiparasitic; *Haemonchus*; *Rhipicephalus*.

LISTA DE FIGURAS

LISTA DE TABELAS

Artigo 1: Essential oils from *Ocimum basilicum* cultivars: analysis of their composition and determination of the effect of the major compounds on *Haemonchus contortus* eggs

Artigo 2: In vitro assessment of the acaricidal activity of a carvacrol shampoo on tick larvae

LISTA DE ABREVIATURAS

OEs	Óleos Essenciais
L1	Larvas de primieiro estágio
L2	Larvas de segundo estágio
L3	Larvas de terceiro estágio infectante
GINs	Gastrointestinal nematodes
IC_{50}	Inhibition Concentration 50 %

SUMÁRIO

1. INTRODUÇÃO

As infecções parasitárias em ruminantes como bovinos, ovinos e caprinos, em áreas tropicais e subtropicais do mundo, podem diminuir a produtividade devido aos danos severos, incluindo a morte do animal, levando a perdas econômicas importantes (EHSAN et al., 2020).

Dentre esses parasitos, os endoparasitos, como nematoides gastrointestinais, causam efeitos negativos nesse panorama econômico (VANDE VELDE et al., 2018). *Haemonchus contortus,* por exemplo, é um dos parasitos mais relevantes no que se refere a infecção de pequenos ruminantes em todo o mundo (RODRÍGUEZ et al., 2015; EL-ASHRAM et al., 2017).

A infecção por *H. contortus* no animal é caracterizada clinicamente por anemia grave e hipoproteinemia (perda de 200-600 mL de sangue/dia), diminuição da produção de lã, má qualidade da carcaça, edema submandibular e até morte de animais infectados (EHSAN et al., 2020). Estima-se que as perdas econômicas anu/ais causadas pelo *H. contortus* para a indústria pecuária representaram US$ 30-300 milhões globalmente (ROEBER et al., 2013; EMERY et al., 2016).

Além dos endoparasitos, os ectoparasitos como os carrapatos representam um grande problema para a indústria pecuária. Dentre eles, destaca-se o carrapato *Rhipicephalus (Boophilus) microplus*, que é encontrado em todo mundo, sendo vetor de protozoários, como *Babesia bovis* e *B. bigemina*, e da bactéria *Anaplasma marginale*, que são os principais patógenos da babesiose e anaplasmose bovina (FUTSE, 2003; GIGLIOTI et al., 2018). *R. microplus* leva a diferentes condições mórbidas aos seus hospedeiros, que em geral são bovinos levando a altas perdas econômicas (GRISI et al., 2014).

O carrapato *R. microplus* pode infestar também burros, ovelhas, cães, cabras, dentre outros animais (BRITO; SANTOS, GUERRA 2005; POUND et al., 2010; SILVA et al., 2018). Em cães, o carrapato *Rhipicephalus sanguineus* é o mais prevalente, apesar de infestar humanos ocasionalmente (RENÉ-MARTELLET et al., 2015). *R. sanguineus* é considerado um importante vetor, devido à sua capacidade de se replicar e transmitir muitos agentes bacterianos e parasitários, que incluem *Ehrlichia canis*, *Mycoplasma haemocanis*, *Babesia vogeli*, *Hepatozoon canis e Rickettsia conorii* (DANTAS-TORRES, 2008; SALANO-GALLEGO, BANETH, 2011).

Diante da ameaça que estes parasitos representam para a saúde humana, animal e para a economia, é altamente relevante que haja estratégias de controle dos mesmos, o que em geral é feito com produtos químicos (OLIVEIRA et al., 2015). Entretanto, esse método tornou-se vulnerável principalmente devido ao alto nível de resistência a esses produtos convencionalmente relatados (ALBUQUERQUE et al., 2017; LOVIS et al., 2013; CASTRO JANER et al., 2015). Além disso, o efeito negativo de muitos produtos químicos no ambiente não é desejável no contexto da produção animal sustentável (ABOSHADY et al., 2020).

Neste cenário, compostos bioativos de plantas, como os óleos essenciais (OEs), surgem como alternativas potenciais de controle de carrapatos e nematoides (ANDRE *et al*., 2016; GARCIA-BUSTOS et al., 2019). Os OEs de plantas e seus principais constituintes (terpenóides e fenilpropanóides) apresentam atividade sobre nematoides e carrapatos (ANDRÉ et al., 2018; SANTOS et al., 2021; FERREIRA et al., 2019) e apresentam vantagens em relação aos produtos sintéticos, como baixa toxicidade ao ambiente, ao homem e animais, e possivelmente exercem baixa pressão de seleção desses parasitos (KATIKI et al., 2012; ANDRÉ et al., 2018; CASTILHO et al., 2017; FERREIRA et al., 2018; BORGES; SOUSA; BARBOSA, 2011; GOVINDARAJAN; SIVAKUMAR, 2011).

O óleo essencial (OE) obtido de diferentes cultivares de manjericão (*Ocimum basilicum* L.) é constituído principalmente por linalol, metil chavicol, citral e eugenol (VIEIRA; SIMON, 2000; PASCUAL-VILLALOBOS; BALLESTA-ACOSTA, 2003; SAJJADI, 2006; MARTINS; et al., 2010; OTTAI; AHMED; EL DIN., 2012). O OE de *O. basilicum* tem comprovada ação parasiticida (SANTOS; VOGEL; MONTEIRO, 2012; TIWARI et al., 2017).

Assim, o objetivo deste estudo foi avaliar a ação de óleos essenciais de diferentes cultivares de *Ocimum basilicum* e seus constituintes sobre o nematoide *H. contortus*, assim como desenvolver um shampoo carrapaticida, efetivo contra *R. microplus* e *R. sanguineus,* contendo o terpeno carvacrol,

2. REVISÃO BIBLIOGRÁFICA

Endoparasitos e ectoparasitos são responsáveis por perdas econômicas significativas na produção de ruminantes. As doenças infecciosas e parasitárias levam a reduções no desempenho produtivo, reprodutivo e também morte de animais (STOTZER et al., 2014).

Os helmintos gastrintestinais, em especial o nematoide *Haemonchus contortus*, são responsáveis por uma das maiores causas de perdas econômicas, principalmente em caprinos e ovinos (STEPEK et al., 2004; BESIER, 2016). O carrapato *Rhipicephalus sanguineus* é um dos principais ectoparasitos de cães, sendo alvo para desenvolvimento de drogas de diversas indústrias farmacêuticas atuantes no seguimento de medicina veterinária (BECHARA et al., 2000). Como outro exemplo de carrapato, o *Rhipicephalus (Boophilus) microplus*, causa grandes prejuízos e desconforto aos bovinos (CARVALHO FILHO et al., 2003).

Exemplificando, no Brasil, as perdas anuais do parasitismo sobre a produtividade do gado foram de 7,11 bilhões de dólares para nematoides gastrointestinais; 3,24 bilhões de dólares para *Rhipicephalus (Boophilus) microplus*; 2,56 bilhões de dólares para *Haematobia irritans*; 0,38 bilhões de dólares para *Dermatobia hominis*, 0,34 bilhões de dólares para *Cochliomyia hominivorax* e 0,34 bilhões de dólares para *Stomoxys calcitrans*, totalizando cerca de US$ 13,96 bilhões (GRISI et al., 2014).

2.1 *Haemonchus contortus*

Dentre as doenças causadas por endoparasitos, destacam-se as parasitoses gastrintestinais, que causam prejuízos extremamente significativos à criação de ruminantes (COSTA et al., 2009, SILVA et al., 2018), em decorrência do crescimento retardado, perda de peso, redução no consumo de alimentos, queda da produção de leite, baixa fertilidade e até mortalidade (PAIVA; NEVES, 2009). As infecções parasitárias normalmente são mistas e compreendem diversas famílias e gêneros, sendo que as mais representativas para a produção de ruminantes, pertencem à família *Trichostrongylidae*, com destaque para os gêneros *Haemonchus* spp., *Ostertagia* spp., *Trichostrongylus* spp., *Cooperia* spp. e família *Strongylidae* representada pelos gêneros *Chabertia* pp. e *Oesophagostomum* spp. (VIVEIROS, 2009; BRITO et al, 2005).

Haemonchus contortus é um nematoide considerado o principal parasito de pequenos ruminantes, devido à alta taxa de mortalidade (STEPEK et al., 2004; BESIER, 2016; PERRY; MOENS, 2011; TSUKAHARA et al., 2021). Este parasito, de alta prevalência em zonas climáticas tropicais, pertencente ao filo nematelmintos, classe nematoda, ordem Strongylida, família trichostrongylidae e gênero *Haemonchus* (MELO et al., 2003; CARVALHO, 2012).

O ciclo de *H. contortus* (Figura 1) inicia-se com a eclosão dos ovos na massa fecal do hospedeiro, que ocorre através de estímulos ambientais e pelas enzimas da eclosão, liberadas pelo embrião (ENGSTRÖM et al., 2016). As larvas rompem os ovos e se alimentam de bactérias no estágio (L1). No estágio infectante (L3), as larvas obtêm motilidade, e alcançam as folhagens dos pastos, em que seus hospedeiros se alimentam e ingerem estas larvas. No interior de seu hospedeiro, ocorre o processo de desembainhamento, proveniente dos estímulos a secreção de fluido rico em enzimas promovendo a digestão da bainha e a liberação das larvas no abomaso, onde passam por mais duas fases. Ao atingir a fase adulta os organismos podem chegar a tamanhos entre 1 a 3 cm de comprimento com uma cavidade bucal especializado com uma lanceta que permite fixar-se no intestino do animal (JACQUIET et al., 1998; AMARANTE et al., 2005).

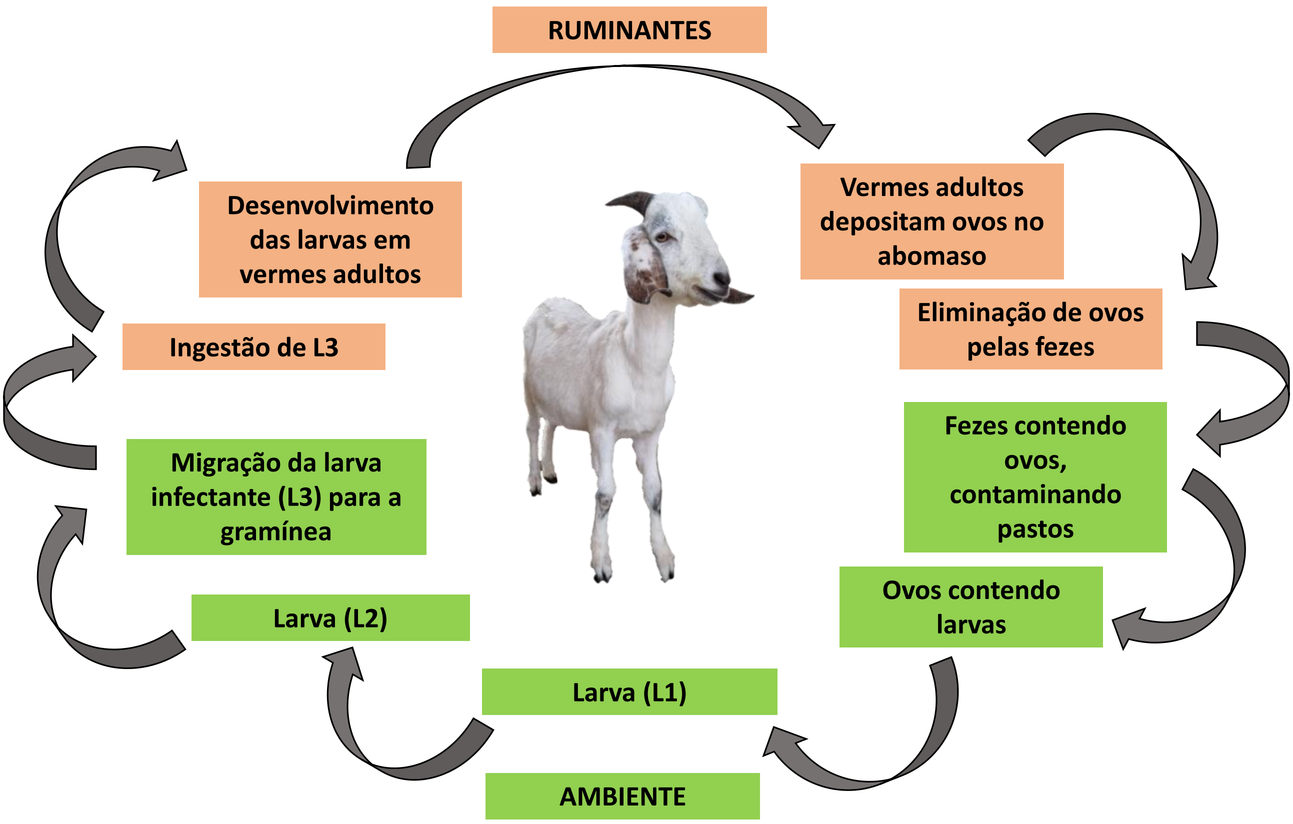

Figura 1. Ciclo de vida do nematoide gastrointestinal *Haemonchus contortus*. L1, L2 e L3: estágios larvais. Em verde verde, fase de vida livre e em laranja, fase parasitária.

Fonte: daptadado pela autora

2.2 *Rhipicephalus (Boophilus) microplus* e *Rhipicephalus sanguineus*

Dentre os diversos ectoparasitos que impactam a produção animal, os carrapatos (subordem *Ixodidae*) são o grupo mais importante de vetores de patógenos dentro do filo Arthropoda, sendo comparáveis apenas aos mosquitos (família *Culicidae*) (KLAFKE, 2008). Eles são responsáveis pela manutenção e transmissão de muitos patógenos que afetam animais domésticos e humanos (JONGEJAN, UILENBERG, 2004).

O carrapato *Rhipicephalus (Boophilus) microplus* (CANESTRINI, 1887) (Acari: Ixodidae) representa o principal ectoparasito de bovinos nas regiões tropicais e subtropicais. Foi identificado parasitando bovinos, caprinos e equinos, em estudos sobre ixodofauna de mamíferos domésticos da ilha de São Luís, Estado do Maranhão, no Brasil (BRITO; GUERRA, 2005; COSTA et al., 2008). Pertence ao reino metazoa, filo artropoda, classe aracnida, subclasse acari, superordem parasitiformes, ordem ixodida, superfamília ixodoidea, família ixodidae, subfamília rhipicephalinae, gênero *Rhipicephalus*, subgênero *boophilus*, espécie *Rhipicephalus (Boophilus) microplus.* Recentemente, este carrapato teve o nome da espécie alterado, de *Bophilus microplus* para *Rhipicephalus (Boophilus) microplus,* devido a estudos utilizando metodologias taxonômicas moleculares, que demonstraram a proximidade filogenética do gênero *Boophilus* com o *Rhipicephalus* (MURREL et al., 2001; BEATI, KEIRANS, 2001; SILVEIRA; CARVALHO; PECONICK, 2014).

Por serem ectoparasitos hematófagos, se tornam os principais vetores dos três agentes causadores da tristeza parasitária bovina, um dos problemas sanitários de maior prejuízo econômico na pecuária bovina (REGITANO, PRAYAGA, 2010). Estudos comprovam ainda que altas infestações por *R. microplus* favorecem o aparecimento de outras doenças, como a miíase nos bovinos (RECK et al., 2014).

R. microplus é um carrapato de um hospedeiro, preferencialmente nos bovinos (FURLONG, 2005), apresentando um estágio de vida livre e um estágio parasitário que vive no corpo do hospedeiro. O ciclo de vida deste carrapato está representado na figura 2 A. O ectoparasito se alimenta e muda de larva para ninfa e de ninfa para adultos no mesmo hospedeiro em um período que dura cerca de três semanas. Após o acasalamento, a fêmea adulta inicia a fase de alimentação lenta, que dura cerca de 5 dias, quando o carrapato ingere quantidades moderadas de sangue. A fase de ingurgitamento rápido leva cerca de 2 dias, em que uma grande quantidade de sangue é ingerida (ROBERTS, 1968). A fêmea totalmente ingurgitada se desprende do hospedeiro bovino e realiza a oviposição no solo. Terminada a postura dos ovos, a fêmea morre e a larva eclode. Após a eclosão as larvas parasitam um novo hospedeiro, o mesmo é localizado pelo odor, vibrações, sombreamento, estímulo visual e pela concentração de CO_2 (SONENSHINE,1991).

O carrapato *Rhipicephalus sanguineus* (LATREILLE, 1806), descrito originalmente como *Ixodes sanguineus*, foi reclassificado como pertencente ao gênero *Rhipicephalus* por Koch em 1844, sendo a espécie-tipo desse gênero (Figura 2B). *R. sanguineus*, conhecido também como "carrapato marrom", é o carrapato mais difundido no mundo. O cão doméstico é o principal hospedeiro do *R. sanguineus* em áreas urbanas e rurais (BECHARA et al., 2000). Ocasionalmente, esses carrapatos podem infestar uma ampla gama de hospedeiros domésticos e selvagens, incluindo gatos, roedores, pássaros e humanos (SAXENA, 1985; DANTAS-TORRES et al., 2010). Segundo Dantas-Torres (2010), esta é uma das espécies mais estudadas devido a sua relevância do ponto de vista da saúde pública e veterinária.

Este carrapato de mais ampla distribuição no mundo, encontra-se presente em todos os continentes habitados por humanos e cães domésticos (WALKER et al., 2000). É um vetor de muitos agentes de doenças, alguns deles (*Coxiellaburnetii, Ehrlichia canis, Rickettsia conorii* e *Rickettsia rickettsii*) sendo de preocupação zoonótica (DANTAS-TORRES, 2008; GRAY et al., 2013; DANTAS-TORRES et al., 2013).

Em condições favoráveis de temperatura e umidade, o ciclo biológico do *Rhipicephalus sanguineus* (Figura 2 B) se completa entre 63–91 dias (LOULY et al., 2007). Entretanto, a duração do ciclo de vida pode variar conforme sua região. No Brasil, onde as condições ambientais são bastante favoráveis, *R. sanguineus* pode completar até quatro gerações por ano (DANTAS-TORRES et al., 2006; DANTAS-TORRES, 2010).

As fêmeas adultas de *R. sanguineus* se alimentam do sangue do seu hospedeiro. Uma vez ingurgitadas, se desprendem do hospedeiro para realizar a digestão sanguínea, maturação e postura dos ovos. As fêmeas põem em média 4.000 ovos. Após a postura dos ovos, a fêmea sucumbe e os ovos são depositados em locais estratégicos, como frestas e buracos, normalmente acima do nível do solo (DANTAS-TORRES, 2008).

Após incubação, pequenas larvas eclodem e, após o enrijecimento da cutícula, passam imediatamente a procurar um hospedeiro para realização do repasto sanguíneo. Larvas se alimentam por três a 10 dias, antes de se desprenderem do hospedeiro e mudarem para ninfas. O período de muda de larva para ninfa varia de 3 a 14 dias. As ninfas se alimentam, e então se desprendem do hospedeiro (BARROS-BATTESTI, 2006; JITTAPALAPONG et al., 2000). O período de muda de ninfa para adultos varia de 9 a 47 dias. Um estudo demonstrou que a temperatura parece interferir na especificidade de hospedeiro do *R. sanguineus*, aumentando a probabilidade desse carrapato se alimentar em seres humanos (PAROLA et al., 2008; ENCINOSA GUZMAN et al., 2016).

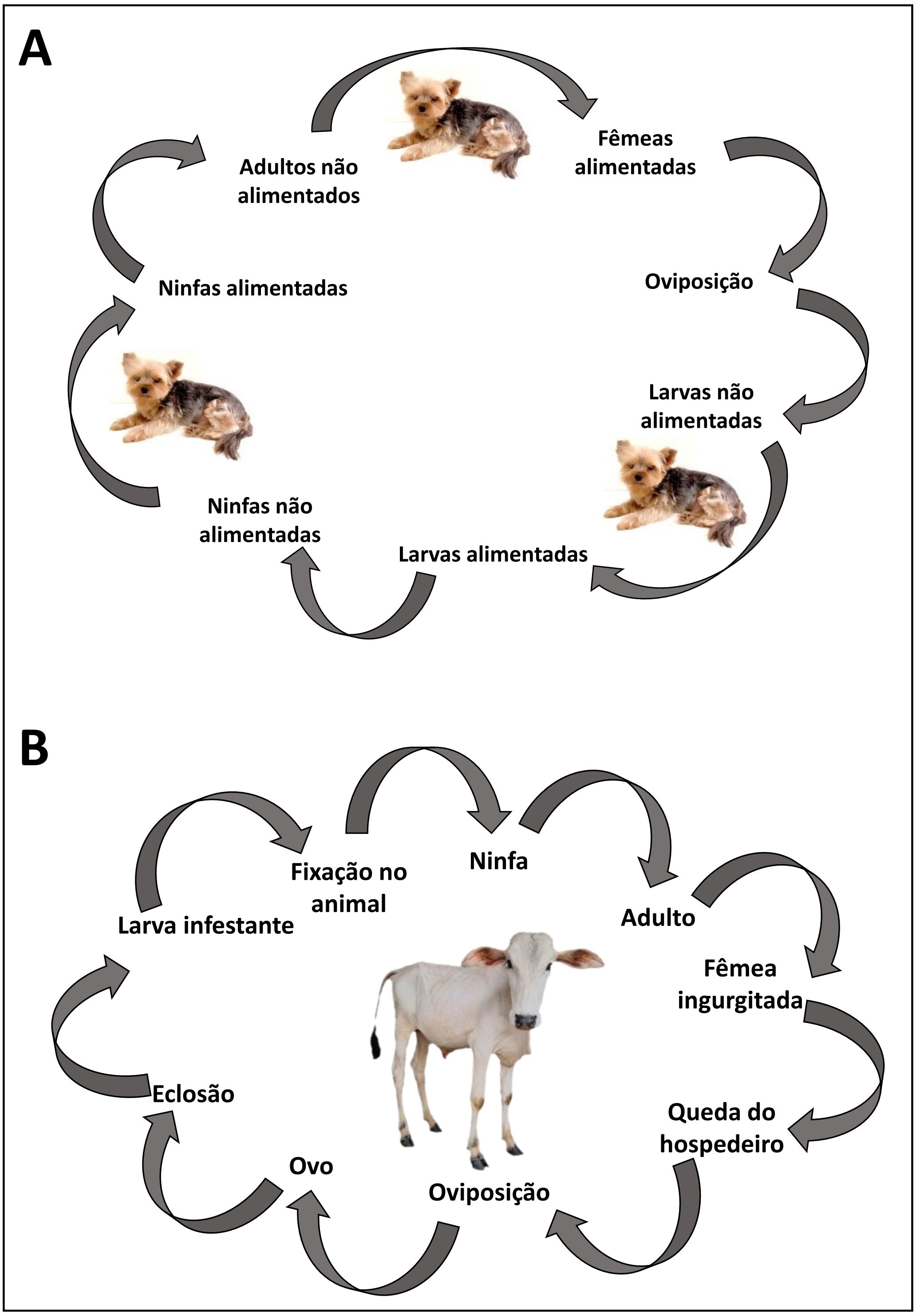

Figura 2. Ciclo de vida do carrapato (A) *Rhipicephalus microplus*; e do carrapato (B) *Rhipicephalus sanguineus*. **Fonte:** Adaptado pela autora.

2.3. Controle de helmintos e carrapatos e resistência aos antiparasitários

O controle de parasitos deve ser estudado de acordo com a dinâmica populacional destes nos rebanhos e pastagens. Desta forma, é possível desenvolver as estratégias de controle para eliminar os parasitos dos animais e prevenir a contaminação do ambiente.

É considerado um anti-helmíntico ideal, uma substância nematicida que causa a expulsão do parasito, sem causar danos significativos ao hospedeiro, com tratamento multivalente, não tóxico e rapidamente eliminado, fácil de administrar e economicamente viável (MARTIN; ROBERTSON; BJORN, 1997). Existem oito classes químicas de anti-helmínticos de amplo espectro utilizadas em ruminantes (AMARANTE; RAGOZO; SILVA, 2014). Esses anti-helmínticos convencionais, por muitos anos, demonstraram ser eficazes. No entanto, devido à resistência adquirida pelos parasitos, essas substâncias atingiram seus limites de eficácia (AMARANTE; RAGOZO; SILVA, 2014; COSTA JUNIOR et al., 2016).

Haemonchus contortus desenvolveu resistência a todas as classes de anti-helmínticos utilizados para seu controle (Lactonas macrociclicas, benzimidazol, organofosfatos, salicilanilidas, imidazotiazol e amino-acetonitrila) (WOOSTER *et al.,* 2001: VAN DEN BROM et al., 2015). No início de 2000, relatou-se os primeiros indícios acerca da ineficiência desses produtos sobre este parasito, pelo surgimento de isolados mostrando resistência a três ou mais anti-helmínticos de diferentes classes de medicamentos (CEZAR et al., 2008; ECHEVARRIA et al., 1996; EDDI et al., 1996; MACIEL et al., 2006), tornando o controle de *H. contortus* cada vez mais difícil (KOTZE et al., 2016).

O controle de carrapatos é fator indispensável para assegurar produtividade, benefícios econômicos e tornar a pecuária bovina uma atividade competitiva. Consiste na redução da exposição dos animais aos carrapatos em uma área específica durante um período determinado (FURLONG, 1993; BRITO et al., 2006). Os métodos de controle podem ser aplicados tanto na fase de vida livre, visto que a grande maioria dos carrapatos (95%) se encontram no ambiente, como na fase parasitária por meio do controle nos bovinos (BITTENCOURT, 1992; FURLONG, 1993). Existem vários métodos que são utilizados para controle de ectoparasitos, dentre eles estão o controle químico, biológico e orgânico, a fitoterapia, homeopatia, manejo de pastagem, rotação de pastagem, tipo da pastagem, rotação com lavouras, adubação de pastagem, aplicação de carrapaticidas no pasto, controle imunológico e vacinas (CAMPOS et al., 2012; SILVEIRA et al., 2014).

A utilização dos compostos químicos sintéticos representa o principal meio para o controle de carrapatos (LOPES, 2015), no entanto o uso indiscriminado dos carrapaticidas tem determinado um grave quadro de resistência, de ordem genética, dos carrapatos em relação as drogas (FURLONG, 1993; TAYLOR, 2001). Os carrapaticidas que atuam por contato direto pertencem a cinco famílias: organofosforados, amidínicos, piretróides sintéticos, fenilpirazóis e spinosad. Neste grupo ocorre a penetração do produto através da cutícula para que haja intoxicação e morte do carrapato. Os carrapaticidas sistêmicos são representados por dois grupos, as lactonas macrocíclicas e as benzofenilureas que são metabolizados, distribuídos pela circulação a todo corpo do animal, atingindo os carrapatos (FURLONG; SALES, 2007).

Ainda como forma de controle para carrapatos, shampoos podem ser utilizados, principalmente para *R. sanguineus*. Entretanto, a maioria dos shampoos comercializados têm como princípio ativo, piretroides e devido a seleção de populações resistentes de carrapatos à piretroides, a eficácia destes produtos vem reduzindo no decorrer do tempo (SUNKARA et al., 2022).

Geralmente, a ação dos compostos carrapaticidas ocorre no sistema nervoso do carrapato, afetando os mecanismos de crescimento, neuropeptídeos e o sistema neuroendócrino (TAYLOR, 2001). Entretanto, alguns destes carrapaticidas não podem ser utilizados durante a lactação, nem nos bovinos de corte antes de seis semanas do abate (GEORGE et al., 2004; FURLONG; SALES, 2007; VALENTE, 2014).

A resistência aos princípios ativos químicos disponíveis comercialmente pelo *Rhipicephalus sp* vem sendo relatada em alguns estudos (FURLONG; MARTINS, 2000; CAMILO et al., 2017; RAYNAL et al., 2013). O surgimento de populações resistentes aos acaricidas vem sendo crescente em todas as regiões onde o parasito encontra condições favoráveis ao seu desenvolvimento, como na maioria dos países da América do Sul e da América Central, África do Sul e Austrália. No Brasil, a resistência das populações de carrapatos aos carrapaticidas é generalizada (FARIAS CUNHA FILHO; VAZ JUNIOR, 2008; GRAF et al., 2004; HIGA et al., 2016).

Diante deste cenário, métodos alternativos para o controle dos ectoparasitos e endoparasitos são alvos de pesquisas científicas (BURKE; MILLER, 2006). A fitoterapia no controle parasitário é uma alternativa amplamente recomendado em fazendas orgânicas. Pode reduzir custos com tratamentos (VIEIRA et al., 2008), além de não apresentar efeito nocivo ao meio ambiente (FAJIMI; TAIWO, 2005). O uso empírico de plantas ou de extratos de plantas é bastante comum e de grande importância em algumas regiões (ATHANASIADOU; KYRIAZAKIS, 2004).

2.4 Produtos de Origem Vegetal

O metabolismo vegetal divide-se em primário e secundário. O metabolismo primário origina substâncias ou metabólitos essenciais para a vida do vegetal, que são de ampla ocorrência e comuns a todas as espécies, como açúcares, proteínas, nucleotídeos e lipídeos. O metabolismo secundário origina substâncias, denominadas de metabólitos secundários, a partir dos compostos primários e são de ocorrência específica, restrito a algumas espécies e que desempenham função de adaptação, proteção, polinização, atrativa como exemplos compostos fenólicos, alcaloides, flavonoides, terpenos e outros (DEWICK, 2002).

Estima-se que mais de 30% dos fármacos são direta ou indiretamente baseados em estruturas químicas de produtos naturais (BEN-ERIK; WINK, 2017). Assim, os produtos de origem vegetal podem ser uma alternativa de grande importância em substituição as drogas sintéticas ou serem utilizadas conjuntamente (BROGLIO-MICHELETTI et al., 2009).

As plantas e seus produtos, podem apresentar atividades antimicrobianas, antivirais, fungicidas e inseticidas (CHAGAS et al., 2012), possuindo vantagens como suprimento sustentável, baixo custo, e biodegradabilidade (HEIMERDINGER et al., 2006). Acredita-se que o uso de extratos vegetais de uma forma isolada ou associada pode dificultar o processo de resistência de microrganismos (ROEL, 2001; PEREIRA et al., 2015).

Os terpenos compõem um grupo de produtos naturais, com mais de 35 mil substâncias identificadas (GERSHENZON; DUDAREVA, 2007). O crescente interesse destes compostos é atribuído à gama de propriedades biológicas, tais como efeito antitumoral, antimicrobiano, antifúngico, antiviral, anti-hiperglicêmico, analgésico, anti-inflamatório e atividades antiparasitárias (PADUCH et al., 2007). Dentre os terpenos que podem estar presentes na composição dos óleos essenciais, o timol e o carvacrol são monoterpenos aromáticos com diversas atividades biológicas. Carvacrol e timol são os constituintes principais dos OEs de várias plantas, tais como *Thymusvulgaris L.* (Lamiaceae), *Origanium compactum* (Labiatae), *Acalypha phleoides* (Euphorbiaceae), *Ocimum basilicum L.* e *Lippia sidoides* (Verbenaceae) (PEIXOTO-NEVES et al., 2010; ALMEIDA, 2015).

A atividade anti-helmíntica e carrapaticida de terpenos, principalmente carvacrol e timol, já fora relatada em diversos estudos (MONTEIRO et al., 2009; CHAGAS et al., 2012;

CRUZ, 2013; LOPES, 2015; ANDRE, 2016; ANDRE, 2017; FERREIRA, 2016), e capazes de reduzir a quantidade de ovos de nematoides nas fezes de animais (ANDRE, 2016; ANDRE, 2017); BORTOLUZZI et al., 2021; ANDRE et al., 2017; CETIN et al., 2010; DOLAN et al., 2009; KOC et al., 2013; COSTA-JÚNIOR et al., 2016; SENRA et al., 2013).

O gênero *Ocimum* compreende mais de 50 espécies, das quais *Ocimum basilicum*, pertencente à família Lamiaceae (Figura 3), popularmente conhecido alfavaca ou manjericão de folha larga, possui elevado valor econômico. Esta planta é encontrada em locais como Ásia tropical, África, América central e América do sul. Trata-se de uma erva aromática e terapêutica amplamente utilizada na medicina popular para combater dores de cabeça, tosse, distúrbios renais e como agente antiespasmódico (ZAKARIA et al., 2008).

Adicionalmente diversas outras atividades já foram relatadas para *O. basilicum*, como atividade antisséptica, antibacteriana, anti-inflamatória, antimicrobiana, antioxidante e parasiticida (ALMEIDA et al. 2007; GÜLÇIN et al., 2007; MARTINEZ-VELAZQUEZ et al., 2011; CASTRO et al., 2017; BRUIN et al., 2017). Diferentes cultivares de *O. basilicum* foram identificados e sua classificação é feita de acordo com a concentração de seus diferentes componentes químicos. As cultivares de *O. basilicum* apresentam óleos essenciais com linalol, metil chavicol, citral e eugenol como constituintes principais, em concentrações variáveis (VIEIRA; SIMON, 2000; PASCUAL-VILLALOBOS; BALLESTA-ACOSTA, 2003; SAJJADI, 2006; MARTINS et al., 2010; OTTAI et al., 2012).

Figura 3 - *Ocimum basilicum L* (manjericão).
Fonte: UFRJ- Vanessa Ribeiro Affonso

Diante do cenário apresentado sobre a necessidade de denvolvimento de novos produtos contra nematoides e carrapatos e levando-se em consideração que a composição de produtos naturais varia entre diferentes cultivares, este estudo foi desenvolvido para responder se diferentes cultivares de *O. basilicum* teriam diferentes potenciais anti-helmínticos, em decorrência de sua variada composição, e se, um shampoo contendo o terpeno carvacrol seria efetivo contra larvas de *Rhipicephalus microplus* e *R. sanguineus*.

3. OBJETIVOS

3.1 Objetivo Geral

Estudar a ação de óleos essenciais e terpenos como estratégia de controle de carrapatos e nematoides.

3.2 Objetivos específicos

Avaliar a ação de óleos essenciais de diferentes cultivares de *Ocimum basilicum* L. e das combinações entre seus componentes majoritários sobre *Haemonchus contortus.*

Desenvolver um shampoo contendo o terpeno carvacrol efetivo sobre larvas de *Rhipicephalus microplus* e *R. sanguineus*.

CAPÍTULO 1

Essential oils from *Ocimum basilicum* cultivars: analysis of their composition and determination of the effect of the major compounds on *Haemonchus contortus* eggs

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Essential oils from *Ocimum basilicum* cultivars: analysis of their composition and determination of the effect of the major compounds on *Haemonchus contortus* eggs

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Abstract

The continuous use of synthetic anthelmintics against gastrointestinal nematodes (GINs) has resulted in the increased resistance, which is why alternative methods are being sought, such as the use of natural products. Plant essential oils (EOs) have been considered as potential products for the control of GINs. However, the chemical composition and, consequently, the biological activity of EOs vary in different plant cultivars. The aim of this study was to evaluate the anthelmintic activity of EOs from cultivars of *Ocimum basilicum* L. and that of their major constituents against *Haemonchus contortus*. The EOs from 16 cultivars as well the pure compound linalool, methyl chavicol, citral and eugenol were used in the assessment of the inhibition of *H. contortus* egg hatch. In addition, the composition of three cultivars was simulated using a combination of the two major compounds from each. The EOs from different cultivars showed mean Inhibition Concentration (IC_{50}) varying from 0.56 to 2.22 mg/mL. The cultivar with the highest egg-hatch inhibition, napoletano, is constituted mainly of linalool and methyl chavicol. Among the individual compounds tested, citral was the most effective (IC_{50} 0.30 mg/mL). The best combination of compounds was obtained with 11% eugenol plus 64% linalool (IC_{50} 0.44 mg/mL), simulating the Italian Large Leaf (Richters) cultivar. We conclude that different cultivars of *O. basilicum* show different anthelmintic potential, with cultivars containing linalool and methyl chavicol being the most promising; and that citral or methyl chavicol isolated should also be considered for the development of new anthelmintic formulations.

1. Introduction

Gastrointestinal nematodes (GINs) have very important economically negative effects on several animal production systems (Nieuwhof & Bishop, 2005; Lane et al., 2015). The nematode *Haemonchus contortus* is one of the most relevant GINs that infects small ruminants around the world (Rodríguez et al., 2015). The control of this nematode is performed mainly with syn- thetic anthelmintics. However, the increased resistance of this parasite to anthelmintics has major economic impacts on livestock worldwide (Kotze et al., 2014; Albuquerque et al., 2017). The development of natural-based formulations is being considered as an alternative. Natural products can be used to control strains of *H. contortus* that are resistant to synthetic compounds (Andre et al., 2016; Garcia-Bustos et al., 2019). Among these products, plant essential oils (EOs) and their major compounds, terpenoid and phenylpropanoid, have shown promising anthelmintic effects (Katiki et al., 2012; Castilho et al., 2017; Ferreira et al., 2018). However, the yield and composition in terms of bioactive volatile compounds depend on genetic, environmental and agronomic factors (Yang et al., 2018).

The plant *Ocimum basilicum* L., popularly known as basil, is native to Asia and grows spontaneously in tropical and sub-tropical regions (Khair et al., 2012). The *O. basilicum* EOs present compounds of interest to the food, cosmetic and also pharmaceutical industries, with a production higher than 40 tons annually (Lawrence, 1992; Telci et al., 2006). The *O. basilicum* EOs have been shown to exhibit several biological activities (Govindarajan et al., 2013; El-Soud et al., 2015; Silva et al., 2015; Güez et al., 2017), including action against *H. contortus* (Castro et al., 2017).

The distinction among numerous basil varieties is largely based on their EO composition, which is of the utmost importance to biological activities and consumers' preference (Kiferle et al., 2019). Several cultivars of *O. basilicum* present EOs with linalool, methyl chavicol (estra- gol), citral and eugenol as its main constituents, in variable concentrations (Vieira & Simon, 2000; Pascual-Villalobos & Ballesta-Acosta, 2003; Sajjadi, 2006; Martins et al., 2010; Ottai et al., 2012). These compounds have been shown to have anthelmintic activity, isolated or in a mixture, and they are also present, in different concentrations, in several other EOs (Katiki et al., 2017; Ferreira et al., 2018; Macedo et al., 2019). The standardization of efficient cultivars or the com- bination of natural compounds is extremally important to human and veterinary pharmaceutical industries.

Considering that different cultivars of the same plant species may have different EO compositions, with different bioactivity, the objective of this study was to evaluate the action of EOs obtained from different cultivars of *O. basilicum*, as well as combinations of their major constituents, on *H. contortus*.

2. Materials and methods

2.1. Plant material and EOs

EOs from 15 commercial cultivars and one experimental hybrid from the Basil Genetic Breeding Program of Universidade Federal de Sergipe were evaluated. The following 15 commercial cultivars were used: Anise, Napoletano, Genovese, Ararat, Edwina, Dark Opal, Italian Large Leaf (Richters), Magical Michael, Mrs Burns, Nufar F1, Purple Ruffles (Richters Herbs, Goodwood, ON, Canada), Italian Large Leaf (Isla), Italian Large Red Leaf, Limoncino (Isla Sementes, Porto Alegre, RS, Brazil) and Maria Bonita (Blank et al., 2007), and the experimental hybrid Genovese × Maria Bonita. All EOs used were obtained from the study of Pinto et al. (2019). The cultivars were planted and collected simultaneously during the rainy season (April–June 2016), and EOs were extracted and analysed according to Pinto et al. (2019).

2.2. Parasitological procedures

The *H. contortus* strain used in the present study was isolated from a goat naturally infected, as described in Silva et al. (2021). Third larvae stage (L3) of *Haemonchus contortus* (n = 2000 L3/animal) was used to experimentally infect a donor sheep confirmed to be parasite-free, with five successive negative faecal egg counts (Robert & O'sullivan, 1950) performed in three- day intervals. After 30 days, the infection was confirmed by faecal egg count, faecal culture and L3 identification (Robert & O'sullivan, 1950; Van Wyk & Mayhew, 2013). Through previous in vitro tests, the *H. contortus* strain used was confirmed to be resistant to benzimidazoles and susceptible to levamisole.

The nematode eggs were recovered from faeces, according to Silva et al. (2021), and stored in a 15 mL conical tube (eggs primary solution). The total number of eggs collected was estimated in three samples of 20 mL of the primary solution, and then a solution of 1000 eggs/mL was prepared. The experimental procedures were performed according to the guidelines of the Animal Ethics Committee (CEUA) of the Federal University of Maranhão, and were approved under the protocol number 23115018061/2011-01.

2.3. Egg-hatching assay

The eggs were added to a saturated sodium chloride solution and centrifuged (1350 g) for three minutes. The floating eggs were collected (Coles et al., 1992), washed three times and re-suspended in distilled water. A suspension of 100 eggs/well was placed in a 96-well sterile plate. The EOs from all cultivars and commercial samples of their major constituents linalool, methyl chavicol, citral and eugenol purchased from Sigma-Aldrich (St Louis, MO, US), were individu- ally diluted in 3% Tween in different concentrations (7.0, 4.9, 3.4, 2.4, 1.7, 1.2, 0.8, 0.6, 0.4 and 0.3 mg/mL). Each samples test was performed in quadruplicate (n = 4), using at least six concentra- tions. The negative control was performed with 3% Tween. The eggs were incubated for 48 h at 27°C. Eggs and first-stage larvae were counted under an inverted microscope at 40× magnification.

2.4. Compound combinations

Linalool, methyl chavicol, citral and eugenol (Sigma-Aldrich) were used to simulate the composition of three cultivars using the two major compounds of each. Cultivars with low and intermediate IC_{50} (concentration required to inhibit 50% of hatching) and different major compounds, were selected. The efficacy of compounds in combination to simulate Genovese (57% linalool and 27% methyl chavicol), Mrs Burns (38% linalool and 49% cit- ral) and Italian Large Leaf (Richters) cultivars (64% linalool and 11% eugenol) was assessed in an egg-hatching assay. To complete each mixture to 100% of composition, olive oil was used. The isolated compounds and their mixtures were diluted in 3% Tween in decreasing concentrations (3.4, 2.4, 1.7, 1.2, 0.8, 0.6, 0.4 and 0.3 mg/mL). The tests of each compound were performed in quadruplicate using at least six of the above-described concentra- tions. The negative control was performed with 3% Tween in olive oil, at 25 mg/mL. The egg-hatching assays were performed as described above.

2.5. Statistical analysis

The results were used to determine the IC**50** with respective 95% confidence intervals using GraphPad Prism 8.0 software (GraphPad Inc, San Diego, CA, US). The data were initially transformed into Log (X), normalized and then non-linear regression was applied to obtain the IC_{50} values. The differences among the IC_{50} were assessed using the F test (GraphPad Inc). Linear regres- sion was applied to compare the IC_{50} values from isolated com- pounds, their combinations and cultivars, for which the percentages of the four major constituents are listed (GraphPad Inc).

3. Results

The EOs from different cultivars showed differences in the IC_{50} (table 1). This difference reached up to 3.96-fold, between the Napoletano cultivar, which presented the highest efficacy (IC_{50} 0.56 mg/mL), and the cultivars with the lowest efficacy such as Purple Ruffles and Italian Large Red Leaf (IC_{50} 2.22 mg/mL) (table 1).

The anthelmintic activity of the major EO constituents – linalool, methyl chavicol, eugenol and citral – was also assessed. Citral was the most effective compound (IC_{50} 0.30 mg/mL) (table 2). Two of the three assessed combinations – eugenol + linalool and methyl chavicol + linalool – showed higher efficacy than their isolated compounds. However, the combination of citral + linalool is less effective than citral alone, and more effective than only linalool.

The best result was obtained with the combination of 11% eugenol plus 64% linalool (IC_{50} 0.30 mg/mL), simulating the Italian Large Leaf (Richters) cultivar (table 2). This Compound combination was 2.7 times more effective than EOs from the cultivar. On the other hand, the combination of 38% linalool and 49% citral was 1.4 times more effective than EOs from the cultivar Mrs Burns. The other combination used in the present study – 57% linalool and 27% methyl chavicol – did not differ statistically from the EO of the Genovese cultivar.

A negative correlation was observed at increase the concentration of citral in cultivars, compounds isolated and its combinations decreasing the IC_{50} value ($P = 0.03$). No other correlation was found.

Table 1. Major compounds (%) from essential oils of cultivars and hybrid of *Ocimum basilicum* and concentrations required for achieving 50% inhibition of egg hatching in *Haemonchus contortus* (IC_{50}) with respective 95% confidence intervals (95% CI).

Cultivar	Major compound (%)				IC_{50}	95% CI	R^2
	Linaloo l	Methyl chavicol	Eugenol	Citra l			
Napoletano	26	54	0	0	0.569	0.49–0.63	0.86
Genovese	57	27	0	0	0.62^{b}	0.60–0.63	0.98
Ararat	16	68	0	0	0.86^{c}	0.82–0.92	0.96
Mrs Burns	38	0	0	49	0.97^{d}	0.91–1.05	0.95
Dark Opal	55	0	0	0	1.09^{e}	1.05–1.14	0.97
Limoncino	9	0	0	50	1.18^{f}	1.13–1.22	0.95
Italian Large Leaf (Richters)	64	0	11	0	1.19^{g}	1.13–1.26	0.96
Magical Michael	64	0	20	0	1.54^{h}	1.48–1.68	0.95
Edwina	73	0	6	0	$1.66^{h,i}$	1.57–1.75	0.97
Italian Large Leaf (Isla)	61	0	8	0	1.69^{i}	1.56–1.85	0.92
Genovese x Maria Bonita	68	0	0	20	1.72^{j}	1.69–1.77	0.99
Anise	0	81	0	0	1.77^{i}	1.65–1.89	0.94
Nufar F1	66	12	0	0	2.11^{k}	2.02–2.22	0.97
Maria Bonita	78	0	0	0	2.13^{k}	2.05–2.22	0.98
Purple Ruffles	18	57	0	0	2.22^{k}	2.08–2.36	0.95
Italian Large Red Leaf	64	0	13	0	2.22^{k}	2.11–2.34	0.97

Chemical composition from Pinto et al. (2019).

R^2, regression coefficient. The R2 value quantifies goodness-of-fit at the non-linear regression curve performed to estimate the IC50. Different superscript letters in the IC_{50} column indicate significant differences ($P < 0.05$).

Table 2. Inhibition concentrations required for achieving 50% of egg hatching in *Haemonchus contortus* (IC_{50}) with respective 95% confidence intervals (95% CI) from major compounds and their combinations simulating cultivars of *Ocimum basilicum*.

Compounds	IC_{50}	95% CI	R^2
Citral	0.30^{a}	0.29–0.32	0.98
Methyl chavicol	0.66^{c}	0.65–0.68	0.98
Eugenol	1.39^{e}	1.33–1.45	0.97
Linalool	1.75^{e}	1.65–1.86	0.94
Eugenol + linalool[1]	0.44^{b}	0.37–0.54	0.71
Methyl chavicol + linalool[2]	0.65^{d}	0.63–0.68	0.97
Citral + linalool[3]	0.69^{d}	0.65–0.75	0.94

R2, regression coefficient. The R2 value quantifies goodness-of-fit at the non-linear regression curve performed to estimate the IC50; all combinations were used with olive oil to complete 100% composition; among the different treatments, IC50 values with the same superscript letter are statistically equivalent ($P < 0.05$).

[1] 11% eugenol and 64% linalool, simulating the EO from Italian Large Leaf (Richters) cultivar.

[2] 27% methyl chavicol and 57% linalool, simulating the EO from Genovese cultivar.

[3] 49% citral and 38% linalool, simulating the EO from Mrs Burns cultivar.

4. Discussion

The EO of *O. basilicum* has several biological activities, such as antifungal (El-Soud et al., 2015), antimicrobial (Lang & Buchbauer, 2012), antiprotozoal (Almeida et al., 2007; Santoro et al., 2007), insecticidal (Rodríguez-González et al., 2019), acaricidal (Martinez-Velazquez et al., 2011) and anthelmintic (Castro et al., 2017). However, there are several basil cultivars with considerably different EO composition (Sharopov et al., 2016). This is the first study to show a statistical difference in the inhibition of *H. contortus* egg hatch – up to 3.96 times – among EOs from cultivars of the same plant species (table 1).

The egg-hatch test used in the present study has been developed as a phenotypic diagnostic of resistant nematodes for the benzimidazoles, looking at the eggs that fail to hatch (Lacey et al., 1987; FAO, 2004). The benzimidazoles inhibit embryonation and hatching by interfering with microtubules' formation (Mandelkow & Mandelkow, 1990; Coles et al., 1992). Additionally, natural compounds altered the egg's surface and increased benzimidazole activity (Silva et al., 2021). Therefore, the rationale for using egg-hatch assay in the present study was to use it as a model to search for new compounds against nematode infection, and not to target specific use in nematode eggs.

Inhibition of *H. contortus* egg hatch was previously demonstrated by the EO of one *O. basilicum* cultivar and associated with methyl chavicol and linalool as major compounds of the EO tested (Castro et al., 2017). In the present study, the EOs from Napoletano, Genovese and Ararat cultivars showed the highest anthelmintic activity, and they also contain methyl chavicol and linalool, as major compounds (table 1). However, the EOs from Nufar F1 and Purple Ruffles cultivars exhibited low efficacy against *H. contortus* while having a similar chemical composition with methyl chavicol and linalool as major compounds. Despite methyl chavicol showing a relatively good efficacy in inhibiting *H. contortus* egg hatch, Anise cultivar, which possesses 81% methyl chavicol, does not present good efficacy when compared to other cultivars with low amounts of this compound. Interestingly, the hybrid cultivar Genovese + Maria Bonita presented an intermediate anthelmintic effect when compared with separate Genovese and Maria Bonita cultivars.

Citral, a natural combination of the isomers neral and geranial, has been shown to be effective against several nematodes, including *H. contortus*, both isolated and as the major compound of EO (Hierro et al., 2006; Macedo et al., 2019). A negative correlation between the citral concentration and efficacy was found when the results of all EO cultivars were analysed (P = 0.03), whereas isolated citral showed the best activity when tested alone (table 2). The composition of EOs extracted from basil varies considerably. It can be classified into four, five or seven chemical groups or chemotypes according to the main components and the statistical analysis performed (Martins et al., 2010; Liber et al., 2011; Giachino et al., 2014; Pinto et al., 2019). The variability of chemical composition from different chemotypes has been found in diverse regions of the world (Hassanpouraghdam et al., 2010). Differences in EO efficacy from the same vegetal species with different chemical compositions against parasites have been reported (Peixoto et al., 2015; Costa-Júnior et al., 2016; Lima et al., 2016). However, the efficacy could not be correlated with the chemotype or the EO's main compound, and seems to be associated with a blend of compounds (Cruz et al., 2013; Soares et al., 2016).

The combinations of the components eugenol + linalool and methyl chavicol + linalool showed more efficacy than the isolated compounds (table 2), demonstrating that the combined compounds potentialized egg-hatch inhibition. Linalool represents the main component of many species of *Ocimum*, and is considered responsible for biological activities, representing reasons for its relevance (Ravid et al., 1997).

Despite the benefits of using *O. basilicum* EOs in human and animal health, the present study has considerable importance for the bioprospection of pure or combinations of natural compounds to control ruminant nematodes. Our results clearly show differences in the bioactivity of EOs from different *O. basilicum* cultivars, related to the citral concentration. Additionally, the combinations using linalool and other compounds showed higher inhibition of *H. contortus* eggs than linalool alone, demonstrating the potential use of these compounds for the development of products for nematode control.

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and insti- tutional guides on the care and use of laboratory animals.

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CAPÍTULO 2

In vitro assessment of the acaricidal activity of a carvacrol shampoo on tick larvae

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In vitro assessment of the acaricidal activity of a carvacrol shampoo on tick larvae

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Abstract

Ticks are a widely distributed arthropod of veterinary importance. Resistance of ticks to synthetic acaricides has become widespread, warranting the development of new drugs for tick management. Carvacrol is a volatile monoterpene, with promising results against various species of ticks; however, to be used for therapeutic pur- poses, carvacrol must be included in a formulation that makes its application feasible. This study aims to develop a formulation of a carvacrol-containing shampoo that is effective against two species of ticks: *Rhipicephalus sanguineus* and *R. microplus*. Shampoo sensory characteristics and pH were evaluated at 37, 25 and 5 °C, for a maximum of 15 days. The shampoo remained stable at 25 and 5 °C. The efficacy of the carvacrol-containing formulation against two species of ticks was assessed by the larval immersion test. Mortality of both tick species was significantly higher for the carvacrol shampoo than for a carvacrol hydroalcoholic solution. In conclusion, the carvacrol-containing shampoo showed larvicidal efficacy on ticks.

1. Introduction

The brown dog tick, *Rhipicephalus sanguineus* sensu lato, is one of the most widely distributed tick species globally and preferentially parasitizes dogs, but may also be found feeding on other hosts, including humans (Dantas-Torres, 2008). The management of *R. sanguineus* is mostly based on the use of synthetic chemical acaricides. However, the intensive use of these compounds has led to the selection of acaricide-resistant tick strains (Borges et al., 2007; Rodriguez-Vivas et al., 2017; Becker et al., 2019). Consequently, there is a need for the development of alternative approaches for tick management, and some plant-based compounds have been evaluated (Ellse and Wall, 2013).

Carvacrol is a volatile plant monoterpene which is currently classified as GRAS (Generally Recognized As Safe) and approved for use in human food (EAFUS, 2006; Hyldgaard et al., 2012; European Parliament and Council, 1996). Importantly, carvacrol has shown promising results when used against various species of ticks, including *R. sanguineus* (Araújo et al., 2016; Novato et al., 2015; Tabari et al., 2017). Natural or synthetic chemical substances can be included in pesticide formulations in order to make their application feasible (York, 2016). Thus, effectiveness, stability, and ease of application are among the criteria that these formulations must satisfy (Díaz et al., 2019; Ferreira et al., 2017). For the development of an acaricide formulation containing carvacrol, its low solubility in water must be considered, and, for example, the use of colloidal distribution systems, may be required (Ryu et al., 2018). Because acaricides are typically applied topically (Dantas-Torres, 2008), shampoo formulations emerge as viable alternatives, having already shown good efficiency in the delivery of other acaricides (Franc and Cadiergues, 1999; Heukelbach et al., 2006; Schuele et al., 2008).

The current study aimed to formulate a shampoo containing carva- crol against the brown dog tick *R. sanguineus* and the cattle tick *Rhipicephalus microplus*, used here as model organism. The cattle tick *R. microplus* is an excellent model for testing acaricide formulations, due to its ease of maintenance in experimental animals and the large numbers of ticks that can be obtained for testing, when compared to other tick species. Even though it is uncommon to use shampoos in cattle, we tested the acaricide formulation on these two species as a proof of concept, and because it is of the utmost importance to test whether the acaricide formulation is tick species-specific.

2. Materials and methods

2.1. Shampoo formulation

The carvacrol shampoo was formulated at room temperature with the following raw materials: 14.0 g sodium lauryl ether sulfate, 1.0 g 30% cocamidopropyl betaine, and 0.5 g lauryl glucoside as surfactants; 0.75 g carboxymethyl cellulose as gelling agent; 0.2 g methylparaben as preservative; 10% citric acid (q.s.) as acidulant; 3.0 g carvacrol (W224502, Sigma-Aldrich, St. Louis, MO, USA), and ultrapure water (q. s. 100 g) as base solution. The surfactants and carvacrol were miXed until completely homogenized. Next, citric acid was added to adjust the pH to 5.0. The carboxymethyl cellulose and methylparaben (previously solubilized in water at 100 ◦C) were then added. Finally, the mass of formulation was adjusted to 100 g with ultrapure water. At each addition, the formulation was completely homogenized with a glass rod. A shampoo formulation without carvacrol was also prepared.

2.1. Sensory evaluation and pH stability

Sensory evaluation and pH stability tests were performed in triplicate, at 37   2 °C, 25   2 °C or 5   2 °C, without direct light exposure, using 100 mL of shampoo sealed hermetically in amber glass flasks. The results were recorded after 1, 7, and 15 days of preparation. The sensory evaluation tests consisted of judging any changes in color, odor, and appearance and results were ranked in three categories: normal, without alteration; slightly modified; and intensely modified (ANVISA, 2004). The pH was measured with universal pH indicator strips (gradation 1.0, range 0–14). The accuracy of the indicator strips was confirmed by testing them against buffer solutions of known pH.

2.2. Tick collection and maintenance

Naturally detached engorged R. sanguineus and R. microplus females were obtained from artificially-infested New Zealand rabbits and calves, respectively, and maintained at 27   1 °C, 80% humidity (Biological Oxygen Demand) until oviposition was completed. Eggs were collected and incubated for hatching. Larvae aged 14–21 days were used in larval immersion tests. The experimental procedures were approved by the Federal University of Maranhão (UFMA) ethics committee under protocol number 23115.005443/2017–51.

2.3. Larval immersion test

The larval immersion test was performed according to Klafke et al. (2006). Carvacrol shampoo and the shampoo without carvacrol were prepared and immediately diluted in water to be used in the assay. A carvacrol hydroalcoholic solution (3.0 g carvacrol diluted in 50% ethanol solution, q.s. 100 g) was also used. Water, 50% ethanol, and the non-carvacrol shampoo were considered as negative controls. The formulation samples were diluted at a ratio of 1:16, 1:19, 1:23, and 1:47 in water. Approximately 500 larvae were immersed for 10 min in each treatment solution and then transferred to a filter paper to dry. Subsamples of approximately 100 larvae were transferred to a clean dry filter paper (8.5 × 7.5 cm) that was folded and closed with plastic clips. The packets were incubated at 27 ± 1 ◦C and relative humidity ≥80% for 24 h. After incubation, dead and live larvae were counted: immobile ticks were considered dead. Three independent repetitions of the experiment were conducted for each experimental group. The statistical analysis of mortality data from the larval immersion test was performed using GraphPad Prism 8.0 software (version 8, GraphPad Inc., San Diego, CA, USA). The mean values for each Treatment were compared by analysis of variance (ANOVA), followed by Tukey's test ($p < 0.05$) to compare differences between specific groups.

3. Results and discussion

In this study, the shampoo containing carvacrol exhibited a pearl-like color, the characteristic carvacrol odor, pH 5.0, and the same color at 5, 25 and 37 °C. After 1, 7, and 15 days of preparation, at 5 and 25 °C, it remained homogeneous, and was rated normal, without alteration. However, a phase separation occurred at 37 ◦C after 7 days and the shampoo was rated as slightly modified after 7 days and intensely modified after 15 days. The incorporation of carvacrol in formulations is important for the stability of the product, by preventing degradation and microbiological contamination, facilitating its application, and enhancing the effect of the active compound (Díaz et al., 2019; Ferreira et al., 2017).

The carvacrol-containing shampoo was highly effective against both tick species, leading to 100% mortality in *R. microplus* and *R. sanguineus* after treatment with 0.125% of carvacrol shampoo (1:23 dilution of the shampoo in water) and with 0.15% of carvacrol shampoo (1:19 dilution of the shampoo in water), respectively (Table 1). The carvacrol hydro-alcoholic solution had no efficacy against *R. sanguineus* at the tested concentrations and showed only low efficacy (21.6 2.5% mortality at 0.175%, 1:16 dilution ratio) against *R. microplus* at the highest concentration used (Table 1).

Table 1. Mortality (mean ± SD) of *Rhipicephalus sanguineus* and *Rhipicephalus microplus* larvae, treated with different amounts of the carvacrol shampoo and with the experimental controls.

Treatment	Dilution ratio	Carvacrol concentration (%)	Mortality (%)	
			R. sanguineus	*R. microplus*
Water	-	-	0.0 ± 0.0[a] 0.0 ± 0.0[a]	0.0 ± 0.0[a] 0.0 ± 0.0[a]
50% Ethanol	-	-	0.0 ± 0.0[a] 0.0 ± 0.0[a]	0.0 ± 0.0[a] 0.0 ± 0.0[a]
Non-carvacrol shampoo	1:16	-	0.0 ± 0.0[a] 0.0 ± 0.0[a]	0.0 ± 0.0[a] 0.0 ± 0.0[a]
	1:19	-	0.0 ± 0.0[a] 0.0 ± 0.0[a]	0.0 ± 0.0[a] 0.0 ± 0.0[a]
	1:23	-	0.0 ± 0.0[a] 0.0 ± 0.0[a]	0.0 ± 0.0[a] 0.0 ± 0.0[a]
	1:47	-	0.0 ± 0.0[a] 0.0 ± 0.0[a]	0.0 ± 0.0[a] 0.0 ± 0.0[a]
Carvacrol hydroalcoholic solution	1:16	0.175	0.0 ± 0.0[a] 0.0 ± 0.0[a]	21.6 ± 2.5[b]
	1:19	0.15	0.0 ± 0.0[a] 0.0 ± 0.0[a]	3.4 ± 1.5[a]
	1:23	0.125	0.0 ± 0.0[a] 0.0 ± 0.0[a]	16.6 ± 5.4[b]
	1:47	0.0625	0.0 ± 0.0[a] 0.0 ± 0.0[a]	0.0 ± 0.0[a] 0.0 ± 0.0[a]
Carvacrol shampoo	1:16	0.175	100.0 ± 0.0[c]	100.0 ± 0.0[d]
	1:19	0.15	100.0 ± 0.0[c]	100.0 ± 0.0[d]
	1:23	0.125	97.3 ± 1.4[b]	100.0 ± 0.0[d]
	1:47	0.0625	97.3 ± 1.8[b]	39.4 ± 5.7[c]

Mean values, followed by different letters in the same column, are significantly different ($p < 0.05$).

Carvacrol has been studied for several years as a bactericide, fungicide, acaricide, and insecticide because of the growing interest for active compounds that are safe for human and animal health and the environment and that exert weak selection pressure leading to resistance (Abbaszadeh et al., 2014; Araújo et al., 2016; Park et al., 2017; Ryu et al., 2018). Even though the acaricidal activity of carvacrol against ticks including *R. sanguineus* has already been demonstrated (Araújo et al., 2016; Costa-Júnior et al., 2016; Cruz et al., 2013; Novato et al., 2018; Senra et al., 2013a, 2013b), carvacrol-containing formulations have been poorly explored against ticks, especially *R. sanguineus* (Lima et al., 2017, 2019; Novato et al., 2019). The bioactivity of carvacrol, which is frequently diluted in ethanol for the larval immersion test against unengorged *Rhipicephalus* larvae (Coelho et al., 2020; Daemon et al., 2012; Scoralik et al., 2012), can be partly explained based on its interaction with the tick's surface. The cuticle, the outermost part of the integument covering ticks, is composed mainly of lipids, polyphenols, proteins, and chitin (Hackman and Filshie, 1982; Lees, 1947). Because of its liposolubility, carvacrol has been suggested to interact strongly with the cuticle.

The mortality rates found in the tests comparing the carvacrol- containing shampoo and the carvacrol hydroalcoholic solution (Table 1) suggest a possible synergistic effects of the components of the shampoo formulation. The intrinsic properties of some compounds may have acaricidal effect or contribute to it. For instance, carboxymethyl cellulose (at 0.1%) alone is capable of inhibiting larval hatching in engorged *R. microplus* females (de Mendonça et al., 2019). Similarly, high mortality rates of *R. sanguineus* were observed when glycerin, which also forms a film on the surfaces where it is applied, was used in formulations associated with the terpene thymol (Delmonte et al., 2017). The authors suggested that this effect may be attributable to the increased water loss through the cuticle or to the film produced, which causes occlusion of the gas exchange channels. Most water loss in ticks occurs through the cuticle and spiracles (Lees, 1947), and the lipid layer in the cuticle plays an important role in regulating this occurrence. The higher efficacy of carvacrol shampoo against ticks compared to hydroalcoholic solution may be explained by the use of surfactants in the former increasing the terpene efficacy.

This is a proof-of-concept study, in which only the in vitro efficacy of one shampoo formulation was tested. Nonetheless, given the high efficiency of the carvacrol shampoo, even at low concentrations, the data presented here provide considerable support for new studies including, the assessment of *in vivo* effectiveness, allergenicity, and potential to cause dermatitis, contributing to the validation of integrated tick management strategies. In conclusion, the carvacrol shampoo developed was effective against *R. sanguineus* and *R. microplus* larvae under an in vitro study.

Credit author statement

Anildes Iran Pereira Sousa, carried out the experiment, collected samples, and data, and performed laboratory analyses.

Glayane de Jesus Soares Castro, collected samples and data, performed laboratory analyses, and prepared the first draft of the manuscript.

Caio Pavão Tavares and Tássia Lopes do Vale, carried out the experiment, collected samples, and data, and performed laboratory analyses.

Livio Costa-Junior was responsible for conceptualization, funding acquisition, visualization, and writing - review & editing.

Alexandra Martins dos Santos Soares, was responsible for project administration, conceptualization, funding acquisition, supervision, visualization, and writing - review & editing.

Declaration of competing interest

The authors declare no conflict of interest related to this work.

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5. CONSIDERAÇÕES FINAIS

Concluimos que os óleos essenciais de diferentes cultivares de *Ocimum basilicum* aparesentam potencial anti-helmíntico, sendo as cultivares que apresentam linalol e metil chavicol as mais promissoras, e também, concluimos que o shampoo contendo carvacrol apresenta eficácia acaricida.

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