Monoterpenes modulating cytokines - A review

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ABSTRACT

Inflammatory response can be driven by cytokine production and is a pivotal target in the management of inflammatory diseases. Monoterpenes have shown that promising profile as agents which reduce the inflammatory process and also modulate the key chemical mediators of inflammation, such as pro and anti-inflammatory cytokines. The main interest focused on monoterpenes were to develop the analgesic and anti-inflammatory drugs. In this review, we summarized current knowledge on monoterpenes that produce anti-inflammatory effects by modulating the release of cytokines, as well as suggesting that which monoterpenoid molecules may be most effective in the treatment of inflammatory disease. Several different inflammatory markers were evaluated as a target of monoterpenes. The proinflammatory and anti-inflammatory cytokines were found TNF-α, IL-1β, IL-2, IL-5, IL-4, IL-6, IL-8, IL-10, IL-12 IL-13, IL-17A, IFNγ, TGF-β1 and IFN-γ. Our review found evidence that NF-κB and MAPK signaling are important pathways for the anti-inflammatory action of monoterpenes. We found 24 monoterpenes that modulate the production of cytokines, which appears to be the major pharmacological mechanism these compounds possess in relation to the attenuation of inflammatory response. Despite the compelling evidence supporting the anti-inflammatory effect of monoterpenes, further studies are necessary to fully explore their potential as anti-inflammatory compounds.

1. Introduction

The inflammatory process is a complex pathophysiological or natural biological response initiated by vascular tissues to defend against pathogens, cell damages or irritants (Nathan, 2002). A cascade of biochemical events occurs involving the regional vascular system, sensitization of the immune system and different types of cells found in the tissue involved (Ferrero-Miliani et al., 2007). Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. However, the outcome may be deleterious if it leads to chronic inflammation without resolution of the underlying injurious process (Medzhitov, 2010).

The events in inflammation are well defined, regardless of the initiating agent, with an increase in blood flow, vasodilation, increased cellular metabolism and protein extravasation fluids, with the release of soluble mediators. This process begins with the activation of phospholipase A_2, which degrades cell membrane lipids releasing arachidonic acid and eicosanoid inflammatory mediators, serotonin, histamine and cytokines (Dassoler M et al., 2005; Falcão, H et al., 2005; Ferrero-Miliani et al., 2007).

Cytokines participate in a wide range of biological processes; which includes embryonic development, disease pathogenesis, non-specific response to infection, and the progression of the degenerative aging processes (Dinarello, 2007; Ramesh et al., 2013). Today, the term

"cytokine" encompasses interferons, interleukins, chemokines, mesenchymal growth factors, the tumor necrosis factor family and adipokines (Dinarello, 2007). Cytokines are small secreted proteins released by cells and have a specific effect on the interactions and communications between cells (Uçeyler et al., 2011). Cytokines have been an emerging target for the treatment of diseases associated with inflammatory conditions such as neuropathic pain, fibromyalgia (paradoxically considered a non-inflammatory rheumatic syndrome), neurodegeneration, sepsis and others (Ramesh et al., 2013; Uçeyler et al., 2011).

A range of therapies exists for the treatment of inflammation-driven diseases, which can be summarized as non-steroidal anti-inflammatory drugs (NSAIDs), corticoids and steroidal-related drugs (Ward et al., 2008). Despite of these notable successes, there are still major unmet medical needs in the treatment of inflammatory diseases and the development of new anti-inflammatory drugs features, prominently in the research portfolios of most pharmaceutical and biotech companies (Dutra et al., 2016; Ward et al., 2008).

Natural products (NPs) continue to be an invaluable source of new chemical entities for the treatment of several diseases, including inflammatory disorders, which are still challenges in the modern medicine, with currently available drugs often not being effective (Dutra et al., 2016; Kondamudi et al., 2013; Li and Vederas, 2009; Suroowan and Mahomoodally, 2018). Flavour and fragrance components common to human diets that have been designated Generally Recognized as Safe (GRAS) by the US Food and Drug Administration (FDA), including terpenes (Juergens, 2014). Monoterpenes are the secondary metabolites of plants with two isoprene units (C_5H_8), have shown a promising profile as agents that reduce the inflammatory process and also modulate key chemical mediators of the inflammatory cascade, such as cytokines (de Cássia da Silveira e Sá et al., 2013; Juergens, 2014).

Thus, to evaluate the usefulness of monoterpenes as a tool to modulate pro and anti-inflammatory cytokines this review sought to search the literature for evidence of their use for this purpose, as well as to highlight the cytokines that may be most useful in this approach.

2. Methods

This present review report followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14].

Search Strategy for the Identification of Studies: A comprehensive literature search was performed in Embase, PubMed/Medline, Scopus, and Web of science databases for studies published up to July 2017 were selected. The standardized search strategy included the use of MeSH terms or text words related to Cytokine (Interferon, Chemokine, and interleukin); and monoterpene (isoprenoid, iridoid).

Inclusion and Exclusion Criteria: Inclusion criteria were established for the selection of the manuscript as followingly: 1) articles published in English; 2) with the keywords in the title, abstract or full text and 3) studies that had been isolated with monoterpenes. Articles with essential oils were excluded. Two independent researchers (JSSQ and SS) conducted the first stage of article selection. They were initially selected according to the title, then to the abstract and finally to the analysis of the issue within the full text. Possible disagreements were resolved by a consensus between the parties involved in the search. A manual revision was applied on the selected items attempt to identify and eliminate any drifting from the criteria set out above. We did not contact the investigators, nor did we try to identify unpublished data.

Data extraction: Data were extracted into a pre-defined standardized form containing, article information (first author, year and study location), methods (substances studied, animal model, strain, randomization, blinding procedures, cytokines assessed and outcomes) and results.

3. Cytokines

Cytokines are extracellular proteins with water-soluble mediators released by various cell types and features with dimensions between 8 and 30 kDa that have a fundamental role in communication between cells. They also play an important role in mediating the cross-talk between the nervous and immune systems (Haroon et al., 2012). A large number of cells produce cytokines in the injured area, including immune cells; they are also produced from the activation of protein kinases activated by mitogens. These polypeptides act through paracrine and autocrine mechanisms, i.e., acting on neighboring cells or on the very cells that produce them, respectively (Lin et al., 2000; Sommer and White, 2010).

In the absence of a unified classification system, cytokines were organized by numeric order of discovery as interleukins (numbered from 1 to 35), by functional bioactivity on cells (e.g., tumor necrosis factor [TNF], interferons [IFN], and chemokines), and by functional role in inflammatory response (pro-inflammatory or anti-inflammatory) (Raeburn et al., 2002; Sommer and White, 2010). Based on the functional profile of an immune response, cytokine production is broadly regulated by T helper 1 cells (Th1) which generally mediate a pro-inflammatory cellular immune response and T helper 2 cells (Th2) which enhance anti-inflammatory and humoral immune reactions (Hou et al., 2017). The inflammatory response can be driven by the cytokine production and is certainly a major target in the management of the inflammatory disease. However, hemodynamic homeostasis and metabolic disorders can occur systemically by the overproduction of pro-inflammatory cytokines and low production of anti-inflammatory cytokines (Curfs et al., 1997; Lin et al., 2000). Thus, the inflammatory response is directly influenced by the type of cytokines produced in the microenvironment of the event.

Cytokines contribute to restoring tissues after injury through a complex network of interactions able to suppress the inflammatory response. Interleukins (IL) 1, 2, 6, 7 and TNF are examples of cytokines that favor the continuation of inflammation; while IL-10 opposes many of the pro-inflammatory effects of IL-1β and TNF-α (Sommer and White, 2010). Interestingly, cytokines contribute to the status quo of rheumatic but non-inflammatory syndromes such as fibromyalgia (Rodriguez-Pintó et al., 2014). Thus, the anti-inflammatory cytokines are a series of regulatory molecules that can control the pro-inflammatory cytokine response (Verri et al., 2006).

Moreover, the imbalance between pro and anti-inflammatory cytokine production is present in various types of diseases. The use of substances able to induce anti-inflammatory cytokines could represent an important advance in the therapeutic treatment of a range of diseases. In this context, medicinal plants and their secondary metabolites found worldwide stand out as an interesting option for the discovery of new bioactive molecules, especially as an alternative to reduce the inflammatory process (de Cássia da Silveira e Sá et al., 2013). Natural products may, for example, be strong modulators of TNF-α production, a strategic cytokine for the control of neuropathic pain (Leung and Cahill, 2010; Paul et al., 2006). In this field of research, the essential oils (EOs) and their main compounds (monoterpenes) are noteworthy for exhibiting a wide range of bioactive new entities with appreciable anti-inflammatory profiles.

3.1. Toll like receptor signaling pathway

Under the inflammatory condition (insult or injury), toll-like receptors (TLRs) activate the proinflammatory cytokine profiles in macrophages thus disrupting the homeostatic regulation of the immune system. Macrophages are essential components of the innate and adaptive immune systems and play central roles in inflammation and host defense and tissue repair (Gordon and Taylor, 2005; Martinez et al., 2009).

Depending on the microenvironment these cells are functionally

classified into two major types: classically activated, proinflammatory M1 macrophages and alternatively activated M2 macrophages (Ginhoux and Jung, 2014; Sica and Mantovani, 2012). M1 macrophages are induced by Th1 cytokines such as IFNγ and tumor necrosis factor α (TNF-α) or lipopolysaccharide (LPS) and are potent cells that typically attack microorganisms and tumor cells, express inducible nitric oxide synthase (iNOS) and the majority of TLRs (Gordon and Martinez, 2010). By contrast, M2 macrophages are induced by Th2 cytokines (IL-4, IL-13, IL-10, and TGF-βs), and are characterized by efficient phagocytosis of dead cells and strong scavenger receptor expression with resolution of inflammation, tissue remodelling, fibrosis and tumor progression (Wynn et al., 2013).

Previous studies demonstrated that TLR2 and TLR4 are closely related to systemic inflammatory response (Fresno et al., 2011; Könner and Brüning, 2011). TLRs, of which there are 10 types in humans and 12 in mice, contain adaptor proteins, the recruitment of which is followed by a signaling pathway activating NF-κB, AP-1, STAT-1, and IRFs, which mediate proinflammatory cytokine release (Kondo et al., 2012; Roy et al., 2016; Zhu et al., 2010).

3.2. NF-κB and MAPK signaling pathway

NF-kappa-B is a master nuclear transcription factor in the regulation of the inflammatory response (Lin et al., 2014). It is found in almost all cell types and involved in numerous biological processes such as inflammation, immunity, differentiation, cell growth, tumorigenesis and apoptosis (Jackson et al., 2003). NF-κB is regulated by binding with inhibitory molecules such as IκBα.

NF-κB subunits p65 dissociate from their inhibitory protein IκBα and translocate from the cytoplasm to the nucleus where they influence the expression of proinflammatory cytokines (e.g., TNF-α, IL-1β, IL-6, IL-8) (Hayden and Ghosh, 2012; Lawrence, 2009; Prasad, 2014). Preventing NF-κB nuclear translocation can, therefore, act as a potential therapeutic target.

The transcription factor Nrf2 is largely responsible for the basal and inducible expression of proteins involved in oxidative stress response, cellular protection and drug metabolism, and inhibits the expression of inflammatory cytokines, such as IL-6 and IL-1β. In addition Nrf2 is associated with NF-κB-mediated transcription of proinflammatory cytokine genes (Kobayashi et al., 2016). Saccani et al. (2002) proposed that p38 MAPK regulates the activation of NF-kB.

The mitogen-activated protein kinases (MAPK) signaling pathway consists of a family of serine/threonine kinases that are activated by several stimuli, including inflammatory factors (Kyriakis and Avruch, 2012). MAPK proteins control fundamental cellular processes, such as proliferation, differentiation, metabolism, inflammation and apoptosis (Kyriakis and Avruch, 2012; Sabio and Davis, 2014). Four subfamilies of the MAPK signaling pathway are described in mammalian cells: extracellular signal-regulated kinase ½ (ERK1/2); p38 MAPK; c-Jun amino terminal kinase (SAP/JNK); and ERK5. Disruption in the MAPK signaling pathway is associated with several human diseases, including inflammatory disorders (Culbert et al., 2006; Gurgis et al., 2014).

MAPK and NF-kB can collaborate synergistically to induce proinflammatory cytokine gene products(Craig et al., 2000). Therefore, treatments aimed at the inhibition of NF-kB and MAPKs may have potential therapeutic advantages in curing inflammatory diseases.

4. Monoterpenes

Monoterpenes consist of two isoprene units, which are formed by 5-carbons (C_5) joined in a head-to-tail fashion (Fig. 1). The biochemically active isoprene units were identified as the diphosphate (pyrophosphate) esters dimethylallyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP) (Dewick, n.d.).

Terpenes are a large class of organic chemical compounds of natural origin. This class of secondary metabolites comprises about 90% of EO

components and a variety of other compounds (Bakkali et al., 2008). Monoterpenes are the main active ingredients of essential oils with a number of biological activities, such as anti-cancer, antimicrobial, antioxidant, antiviral, analgesic and anti-inflammatory effects (Brito et al., 2012; Guimarães et al., 2013; Kozioł et al., 2014; Quintans et al., 2013; Santos et al., 2015; Siqueira-Lima et al., 2014; Aumeeruddy-Elalfi et al., 2018). Some studies report that monoterpenes are promising in relation to the modulation of cytokines because their lipophilic characteristics favor their absorption and rapid action (Spelman et al., 2006). Monoterpenes have also been acknowledged to stimulate an increase in anti-inflammatory cytokines, such as IL-10 (Held et al., 2007; M. da S. Lima et al., 2013). In fact, monoterpenes have become a subject of interest in relation to the development of analgesic and anti-inflammatory drugs with an increasing number of new patent applications (de Cássia da Silveira e Sá et al., 2013; Guimarães et al., 2015, 2014; Pina et al., 2017).

Monoterpenes are classified into four different types, namely: acyclic (hydrocarbons, alcohols, aldehydes, or esters, especially acetates), monocyclic, bicyclic and iridoid glycosides. Some chemical structures of representative monoterpenes are presented in Fig. 2.

4.1. Acyclic monoterpenes

(−)-Linalool (**1**) is a monoterpene alcohol commonly found as a major volatile component in EOs of several aromatic plants such as bergamot, jasmine, and lavender with already described anti-inflammatory and antinociceptive properties. Six of the studies in the review examined the use of linalool compounds in the management of pro-inflammatory cytokines (Table 2). Deepa and Anuradha (Deepa and Venkatraman Anuradha, 2013); Quintans-Júnior et al. (2013), Wu et al. (2014), Li et al. (2014); Sabogal-Guaqueta et al. (Sabogal-Guáqueta et al., 2016) revealed that 10–40 mg/kg of linalool taken orally reduced the pro-inflammatory cytokines TNF-α, IL-1β, IL-6, which had been increased by different inflammatory inducers. Furthermore, 25 mg/kg (p.o.) of linalool is able to reduce the proinflammatory mediator IL-1β in the brain of triple transgenic Alzheimer mice(Sabogal-Guáqueta et al., 2016). It is feasible to propose that linalool might have central and peripheral anti-inflammatory action.

To shed some light on some of the molecular mechanisms underlying linalool's anti-inflammatory mechanism, different authors proposed that linalool modulates important pathways that regulate the release of anti-inflammatory and proinflammatory cytokines in dose dependent manners. In this context, evidence shows that linalool acts in NF-κB activation and its translocation into the nucleus (Deepa and Venkatraman Anuradha, 2013; Li et al., 2014) reduces Nrf-2 activity (Li et al., 2014; Wu et al., 2014) and modulates p38MAPK activity (Sabogal-Guáqueta et al., 2016).

Fig. 3 summarizes some effects of linalool that modulate oxidative stress as well as the levels of some important cytokines in the inflammatory process and tissue repair or protection. Linalool significantly prevents UVB-mediated 8-deoxy guanosine formation (oxidative DNA damage) rather than UVB induced cyclobutane pyrimidine (CPD) formation, which might be due to its ability to prevent UVB-induced ROS formation and restore the oxidative imbalance of cells. This has been reflected in UVB-induced overexpression of MAPK and NF-κB signaling and IL-1β levels (Gunaseelan et al., 2017). In addition, a docking study suggested that linalool binds to the GST enzyme (a critical antioxidant and detoxification system) which modulates oxidative stress and the production of inflammatory cytokines, such as IL-1β, TNF-α as well as NF-κB signaling (Babu et al., 2012; Polosukhin et al., 2014). Finally, linalool, complexed or non-complexed with β-CD, decreases TNF-α levels in animals with carrageenan-induced paw edema (Quintans-Júnior et al., 2013). Therefore, the findings described in Fig. 3 reinforce the hypothesis that monoterpenes may be promising sources of new drugs in relation to the management of the inflammatory process or as protectors of tissue damage.
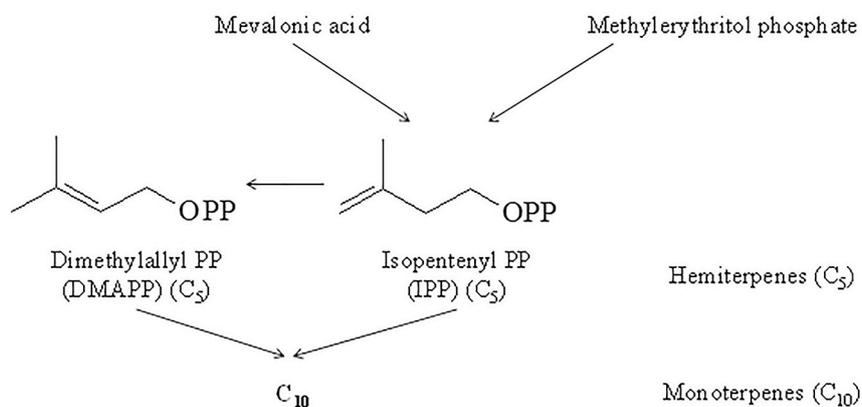
Fig. 1. Schematic of biosynthesis of monoterpenes.(Dewick, n.d.)

Geraniol (Ge−OH) (**2**) is an acyclic monoterpene alcohol, a component of the EO extracted from lemongrass, roses, and other aromatic plants. Several biological activities of Ge−OH have shown it to be a highly active antitumoral, antimicrobial compound, with antioxidant and anti-inflammatory properties (Ahmad et al., 2011; Khan et al., 2013; Thapa et al., 2012). The present review also suggested that higher oral doses and enema administration of Ge−OH strongly reduces dysbiosis and systemic inflammation in dextran sulfate sodium-treated mice by significantly decreasing plasma levels of IL-1β, IL-17, IFN-γ, and TNF-α (De Fazio et al., 2016). Also, oral administration of geraniol at doses of 50 and 100 mg/kg body weight ameliorates acute experimental murine colitis by inhibiting the pro-inflammatory cytokines TNF-α, IL-1β and IL-6 and NF-κB signaling (Medicherla et al., 2015).

Citronellol (CT) (**3**) is an acyclic monoterpene constituent of essential oils of several aromatic plant species, such as *Cymbopogon citratus,* (Abegaz et al., 1983), *Elalfi et al. (2016a)*, *Lippia alba* ,(Tavares et al., 2005) and *C. winterianus*(Quintans-Júnior et al., 2008). CT has been reported to have antidiabetic (Srinivasan and Muruganathan, 2016), cardiovascular (Santos et al., 2011), anticonvulsant (de Sousa et al., 2006a) and antinociceptive effects (Brito et al., 2013). This monoterpene exhibits potent anti-inflammatory capabilities, as demonstrated by mitigation of COX-2 expression and NF-κB activation on lipopolysaccharide (LPS)-induced inflammation in the mouse macrophage cell line RAW 264.7 (Su et al., 2010). Brito et al. (2012) reported that CT (25–100 mg/kg, ip) significantly suppressed the increase of TNF-α in carrageenan-induced pleurisy.

Another acyclic monoterpene of interest is citral (**4**) (composed by the isomers neral and geranial) which is a major active compound in lemongrass oil and has been reported to have antibacterial, anti-cancer and anti-inflammatory effects (Bachiega and Sforcin, 2011; Katsukawa et al., 2010; Zarai et al., 2011). Citral was found to inhibit cytokine production in LPS stimulated murine peritoneal macrophages (Bachiega and Sforcin, 2011). Studies showed that citral inhibited COX-2 expression in LPS stimulated U937 cells(Katsukawa et al., 2010). Furthermore, citral was found to have a protective effect on focal segmental glomerulosclerosis (FSGS) in mice (Yang et al., 2013) by inhibiting the secretion levels of IL-6, TNF-α, and IL-1β by the administration of citral in renal inflammation. Similarly, citral inhibits LPS-induced acute lung injury by activating peroxisome proliferator activated receptor-γ (PPAR-γ) and when compared to control group, LPS instillation dramatically increased TNF-α, IL-6 and IL-1β expression. However, TNF-α, IL-6 and IL-1β production induced by LPS were downregulated by citral in a dose-dependent manner (Shen et al., 2015).

4.2. Monocyclic monoterpenes

Carvacrol (**5**) is a phenolic monoterpene abundantly present in the essential oils produced by aromatic plants, including thyme and oregano (Baser, 2008; Elalfi et al., 2015). Carvacrol is probably one of the most studied terpenes that modulate cytokines and the inflammatory process (Suntres et al., 2015). It has been approved by the Federal Drug Administration for use in food and is included in the Council of Europe list of chemical flavorings permitted in alcoholic beverages, baked goods, chewing gum, condiment relish, frozen dairy, gelatin pudding, nonalcoholic beverages, and soft candy (De Vincenzi et al., 2004; Ultee et al., 1999).

Several studies have indicated the potential of this monoterpene as an antioxidant and anti-inflammatory (Guimarães et al., 2015, 2012; 2010; Suntres et al., 2015). The anti-inflammatory action of carvacrol is probably produced by the inhibition of mediators such as PGE$_2$, IL-1β and TNF-α (Guimarães et al., 2012). Given the key role of cytokines in the inflammation process (M. da S. Lima et al., 2013) a study evaluated the effect of carvacrol on cytokine modulation and its anti-inflammatory effects. The authors demonstrated that carvacrol is able to stimulate IL-10 production and reduce the local levels of IL-1β and PGE$_2$. The contribution of IL-10 in the anti-inflammatory effect of carvacrol was corroborated using IL-10 knockout mice. Moreover (Landa et al., 2009) it was shown that carvacrol inhibits the enzyme COX-2 and is an activator of PPAR-α and PPAR-γ (Hotta et al., 2010).

Thirteen other studies have determined the effects of carvacrol on levels of pro-inflammatory cytokines in several animal models (Table 2). Feng and Jia (2014), and Kara et al. (2015) experimentally proved that carvacrol at doses of 20, 40, and 80 mg/kg also significantly reduced TNF-α, IL-1β and IL-6 in LPS induced inflammation, and in acute lung injury induced by lipopolysaccharide in mice. Arigesavan and Sudhandiran (2015) reported that 50 mg/kg of carvacrol controls the IL-1β in colon rectal cells. To examine the effects of carvacrol on the inflammatory responses in rats with permanent focal cerebral ischemia, Li et al. (Z. Li et al., 2016b) investigated the levels of TNF-α and IL-1β and showed that carvacrol treatment prevented middle cerebral artery occlusion (MCAO), and reduced TNF-α and IL-1β levels in a dose dependent manner. Recently, some studies have demonstrated that complex molecular targets and mechanisms are implicated in the pharmacological properties of carvacrol. In this regard, carvacrol can alter the activity of several signaling cascades, which could be associated with compound anti-inflammatory actions, including the NF-κB signaling pathway (Z. Li et al., 2016b), the MAPK cascade (ERK, SAP/JNK and p38[MAPK]) (Cui et al., 2015) and TLR2 and TLR4 production (Cho et al., 2012) (Fig. 3).

Carvacrol inhibits NF-κB activation (Z. Li et al., 2016b), with this effect possibly being related to downregulated phosphorylated/activated NF-κB upstream signaling (Cui et al., 2015). MAPK response is modulated by many physiological and pathological signals, and this pathway is downstream of several membrane receptors, including the toll-like receptor family (TLRs) (Wu et al., 2017). Therefore, we propose that carvacrol might block activation of the TLR-mediated signaling
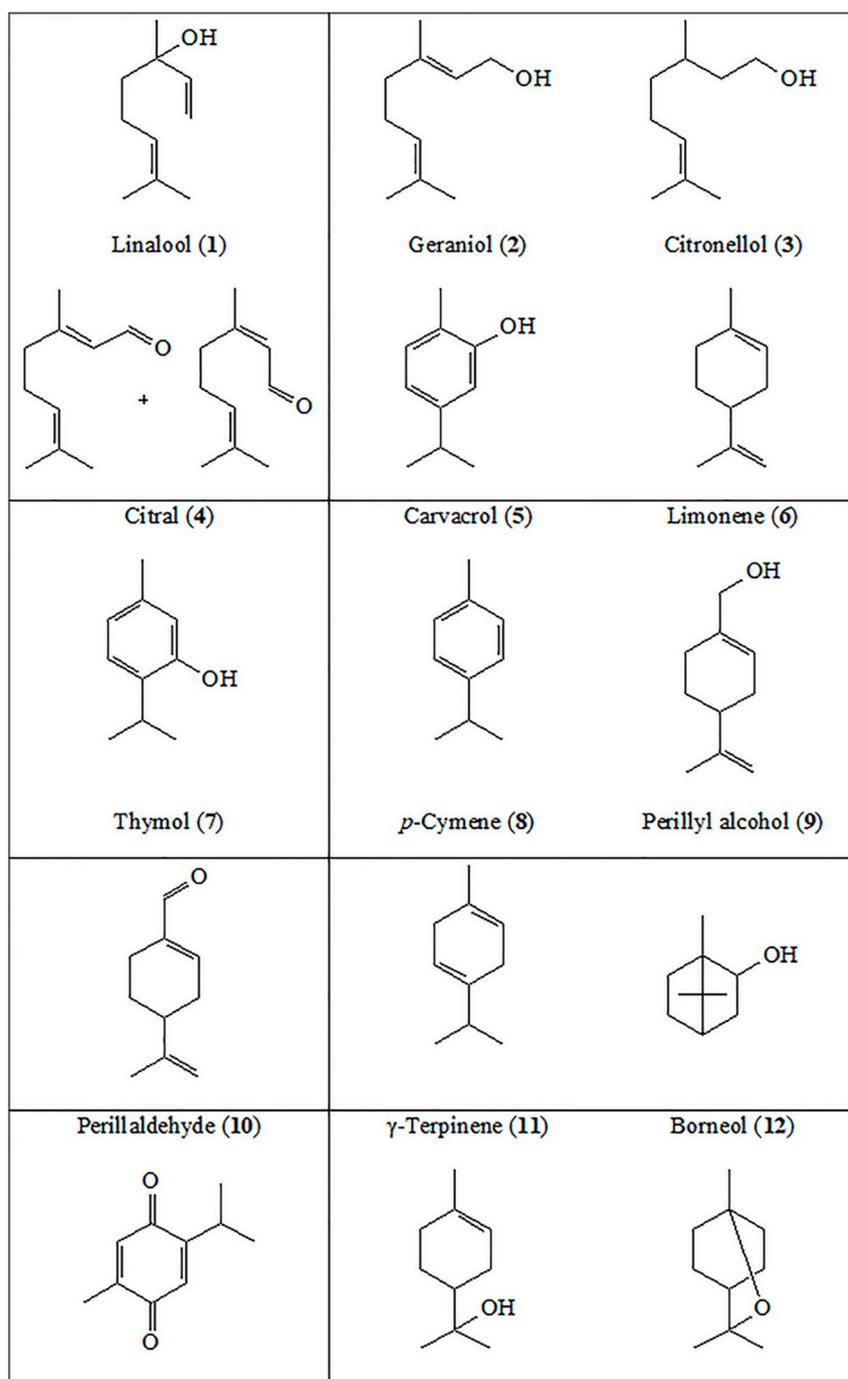
Fig. 2. Chemical structures of representative monoterpenes.

pathway. This would cause decreased MAPK phosphorylation and consequently inhibit the NF-κB nuclear translocation, thereby leading to a decrease in proinflammatory cytokines and chemokines, reducing inflammation. Thus, treatment that blocks the TLR-mediated signaling pathways may be an effective approach to treating inflammatory disease (Fig. 4).

Limonene (6) is a naturally occurring substance derived from several *Citrus* oils (Sun, 2007) plants of the *Lippia* genus (Verbenaceae) (do Vale et al., 2002) and *Cannabis* oils (Russo, 2011). This terpene is listed as generally recognized as safe (GRAS) in the US, FDA Code of Federal Regulations as a flavoring agent, and can be found in common food items such as fruit juices, soft drinks, baked goods, ice cream, and pudding (Nazaroff and Weschler, 2004; Sun, 2007; Zhao et al., 2009). Limonene is directly absorbed in the gastrointestinal tract of both

humans and animals when administered orally and rapidly disperses to different tissues (detectable in serum, liver, lung, kidney, and many other tissues) and quickly undergoes the metabolization processes for hydroxylation and carboxylation.[108]. Moreover, *D*-limonene has long been known to suppress tumor growth (Miller et al., 2011).

In the present review, three studies (Table 2) about the anti-inflammatory effect of this natural compound in different *in vivo* models were included. D'Alessio et al., (d'Alessio et al., 2014), observed that a subcutaneous treatment with 10 mg/kg of *D*-limonene or its metabolite perillyl alcohol (PA) altered the levels of the proinflammatory cytokines TNF-α, IL-1β and IL-6 in the model of 12-*O*-Tetradecanoylphorbol-13-Acetate (TPA)-induced dermatitis. Furthermore, Hansen et al. (2016), showed that limonene (40 ppm via inhalation) attenuates allergic lung inflammation by reduction of IL-5 levels. This interleukin is recognized

Table 1
Characteristics of studies of anti-inflammatory cytokines.

ACYCLIC MONOTERPENES

Authors, year, Country	Substance/Chemical group	Animals (Strain/Sex)	Dose (route)	Model	Sample	Evaluation	Cytokines	R	B
De Fazio et al. (2016), Italy [73]	Geraniol Compound (2) Fig. 2	Male C57BL/6 mice	30 and 120 mg/kg (p.o.)	(DSS)-induced colitis mouse model.	Plasma	IA	↓ (IL-10)	Y	N

MONOCYCLIC MONOTERPENES

Authors, year, Country	Substance/Chemical group	Animals (Strain/Sex)	Dose (route)	Model	Sample	Evaluation	Cytokines	R	B
Trinh et al. (2011), Korea [151]	α-Terpineol	Mice (IRC/F)	10% v/v (topic)	Vaginosis and vulvovaginal candidiasis	Vaginal tissue	ELISA	↑ (IL-10)	N	N
Rozza et al. (2014). Brazil [286]	Menthol	Rats (Wistar/M)	50 mg/kg (p.o.)	Ethanol-induced gastric ulcers	Gastric mucosal	ELISA	↑ (IL-10)	N	N
Lima et al., 2013a, Brazil [58]	Carvacrol Compound (5) Fig. 2	Mice (Swiss/M)	50–100 mg/kg (i.p.)	CFA-induced inflammation	Skin tissue	ELISA RT-PCR	↑ (IL-10)	N	N
Zhong et al. (2013), China [121]	p-Cymene Compound (8) Fig. 2	Mice (C57BL/6/M)	53–214 mg/kg (i.p.)	LPS-induced inflammation	Serum sample	ELISA	↑ (IL-10)	Y	N
Juhás et al. (2008), Slovak Republic [148]	Thymoquinone	Mice (ICR/M)	0.09%, 0.18% (suppl diet)	TNBS-induced colitis	Colon tissue	RT-PCR	⊠ IL-10	Y	N
Juhás et al. (2008), Slovak Republic [148]	Borneol Compound (12) Fig. 2	Mice (ICR/M)	0.09%, 0.18% (suppl diet)	TNBS-induced colitis	Colon tissue	RT-PCR	⊠ IL-10	Y	N

BICYCLIC MONOTERPENES

Authors, year, Country	Substance/Chemical group	Animals (Strain/Sex)	Dose (route)	Model	Sample	Evaluation	Cytokines	R	B
Bastos et al., Brazil, (2011) [280]	1,8-Cineole	Pigs (guinea/M)	1 mg/mL (Inhalation)	Ovalbumin - Challenged	BALF	ELISA	↑ (IL-10)	N	N
Trinh et al. (2011), Korea [151]	1,8-Cineole	Mice (IRC/F)	10% v/v (topic)	Vaginosis and vulvovaginal candidiasis	Vaginal tissue	ELISA	↑ (IL-10)	N	N
Lima et al. (2013b), Brazil [164]	1,8-Cineole	Mice (Swiss/M)	100–400 mg/kg (p.o.)	Cerulein-induced acute pancreatitis	Serum sample	ELISA	↑ (IL-10)	N	N
Zhao et al. (2014), China [162]	1,8-Cineole	Mice (ICR/M)	10–100 mg/kg (p.o.)	(LPS)-induced ALI	Lung tissues	ELISA	↑ (IL-10)	Y	N
Siveen and Kuttan, (2011), India [308]	Thujone	Mice (Balb/c/-)	1 (i.p)	EAC cells-induced tumor	Serum sample	ELISA	↑ (IL-2 and IFN-γ)	N	N

IRIDOID GLYCOSIDES

Authors, year, Country	Substance/Chemical group	Animals (Strain/Sex)	Dose (route)	Model	Sample	Evaluation	Cytokines	R	B
Xiaofeng et al. (2012). China [230]	Geniposide	Mice (Balb/c/M)	20–80 mg/kg (i.p.)	LPS-induced ALI	BALF	ELISA	↑ (IL-10)	Y	N
Liao et al. (2014), China [307]	Geniposide	Mice (C57BL6J/M)	100 mg/kg (p.o.)	HFD-induced atherosclerosis	Serum	ELISA	↑ (IL-10, TGF-β1)	N	N
Dai et al. (2014). China [234]	Geniposide	Rats (SD/M)	30–120 mg/kg (p.o.)	FCA- induced arthritis	PBL	ELISA	↑ (IL-4, TGF-β1)	Y	Y
Fu et al. (2014), China [211]	Catalpol	Mice (BALBc/M)	2.5–10 mg/kg (i.p.)	LPS – induced ALI	BALF	ELISA	↑ (IL-10)	Y	N
Zhou et al. (2015), China [295]	Catalpol	Mice (C57BL6J/M)	100 mg/kg (p.o.)	HFD-induced insulin resistance	Epididymal adipose tissue	ELISA	↑ (IL-10)	Y	N
Giner et al. (2013), Spain [301]	Oleuropein	Mice (C57BL/6/F)	0.25% (suppl diet)	DSS-Induced Chronic Colitis	Colon tissue	ELISA	↑ (IL-10)	Y	N
Caglayan et al. (2015), Turkey [252]	Oleuropein	Rat (Wistar/M)	20 mg/kg (p.o.)	BPDO-induced pancreatitis	Serum sample	ELISA	⊠ (IL-10)	Y	N
Wang et al. (2013), China [190]	Paeoniflorin	Mice (Kun Ming/M)	35–140 mg/kg (p.o.)	Allergic contact dermatitis	Blood sample	ELISA	↑ (IL-4, IL-10)	Y	N
Zhang et al. (2015a, 2015b), China [199]	Paeoniflorin	Mice (transgenic and WT/M)	5 mg/kg (i.p.)	APP and PS1 double transgenic	Brain tissue	ELISA	↑ (IL-4, IL-10)	Y	N
Saravanan et al. (2014a), (2014b), India [263]	Swertiamarin	Rat (S-D/F)	2–10 mg/kg (p.o.)	Adjuvant induced arthritis	Serum	ELISA	↑ (IL-4, IL-10)	N	Y

Abbreviations: Animals- Homozygous triple transgenic AD model (3xTg-AD) and no transgenic (Non-Tg) mice, Sprague–Dawley (SD), amyloidprecursor protein (APP) and presenilin 1 (PS1) double transgenic model Alzheimer's disease (AD), wild-type (WT), New Zealand White (NZW). **Model –** Lipopolysaccharide (LPS), High-fat diet (HFD), 2,4,6-trinitrobenzene sulfonic acid (TNBS), Freund's complete adjuvant (FCA), mesenteric lymph node lymphocytes (MLNL) and peripheral blood lymphocytes (PBL), chronic constriction injury (CCI) and lumbar 5 spinal nerve ligation (L5 SNL), amyloid precursor protein (APP) and presenilin 1 (PS1), Dextran Sodium Sulfate (DSS), bilepancreatic duct obstruction (BPDO), Ovalbumin (OVA), acute lung injury (ALI). **Evaluation** - enzyme-linked immunosorbent assay (ELISA), Immunoassay (IA).

Table 2
Characteristics of studies of pro-inflammatory cytokines.

ACYCLIC MONOTERPENES

Authors, year, Country	Substance/ Chemical group	Animals (Strain/Sex)	Dose (mg/kg) (route)	Model	Sample	Evaluation	Cytokines	R	B
Deepa and Anuradha, 2011, India [62]	Linalool Compound (1) Fig. 2	Rat (Wistar/M)	25 (p.o.)	Diabetes-induced Nephropathic changes	Plasm/kidney tissue	ELISA/PCR	↓ (TNF-α, IL-6)	N	N
Quintans-Júnior et al. (2013), Brazil [63]	Linalool	Mice (Swiss/M)	20 or 40 (p.o.)	Antinociceptive effect	Peritoneal fluid	ELISA	↓ (TNF-α)	Y	N
Wu et al. (2014), China [64]	Linalool	Mice (C57BL6/M)	25 (p.o.)	Lung inflammation induced by Pasteurella multocida	Lung	ELISA	↓ (TNF-α, IL-6)	N	N
Li et al. (2014), China [65]	Linalool	Mice	10, 20, 40	LPS/GalN-induced acute liver injury	Serum	ELISA	↓ (TNF-α, IL-6)	Y	N
		(BALBc/M)	(i.p.)		Liver tissue				
Sabogal-Guáqueta et al., 2016, Colombia [66]	Linalool	Mice (3xTg-AD, Non-Tg/-)	25 (p.o.)	Triple transgenic Alzheimer's mice	Brain tissue	ELISA	↓ (IL-1β)	Y	N
Marcuzzi et al. (2011), Italy [266]	Geraniol Compound (2) Fig. 2	Mice (BALBc/M)	100 (i.p.)	Mevalonate kinase deficiency	Serum	ELISA	↓ (TNF-α, IL-1β, IL-6)	Y	N
Medicherla et al. (2015), India [74]	Geraniol	Mice (BALBc/M)	50, 100 (p.o.)	Acute experimental colitis	Colon tissue	ELISA	↓ (TNF-α, IL-1β, IL-6)	Y	N
De Fazio et al. (2016) Italy [73]	Geraniol	Mice (C57BL6/M)	30, 120 (p.o.)	(DSS)-induced colitis mouse model.	Plasma	Immune assay	↓(TNF-α, IL-1β, IL-6, IL-17, IFN-γ)	Y	N
Brito et al. (2012), Brazil [81]	Citronellol Compound (3) Fig. 2	Mice (Swiss/M)	25–100 (i.p.)	Carrageenan-induced pleurisy	Pleural lavage	ELISA	↓ (TNF-α)	Y	Y
Yang et al. (2013), Taiwan [86]	Citral Compound (4) Fig. 2	Mice (BALB/c M)	200 (p.o)	Renal inflammation	Renal tissues	ELISA	↓ (TNF-α, IL-1β, IL-6)	N	N
Shen et al. (2015), China [87]	Citral	Mice (BALBc/M)	40 (i.p.)	(LPS)-induced acute lung injury	BALF	ELISA	↓ (TNF-α, IL-1β, IL-6)	Y	N

MONOCYCLIC MONOTERPENES

Authors, year, Country	Substance/ Chemical group	Animals (Strain/Sex)	Dose (route)	Model	Sample	Evaluation	Cytokines	R	B
Trinh et al. (2011) Korea [151]	α-Terpineol	Mice (IRC/F)	10% v/v (topic)	Vaginosis and vulvovaginal candidiasis	Vaginal tissue	ELISA	↓ (TNF-α, IL-1β, IL-6)	N	N
Ramalho et al., (2015) Brazil [138]	γ-Terpinene Compound (11) Fig. 2	Mice (Swiss/F)	25 (p.o.)	Carrageenan-induced peritonitis	Peritoneal lavage	ELISA	↓ (TNF-α, IL-1β) ⊠ IL-6	N	N
Xue et al. (2015) China [267]	L-Menthone	Mice (ICR/M)	15, 30 (p.o.)	UCMS	Hippocampus samples	ELISA	↓ (TNF-α, IL-1β, IL-6)	Y	Y
Rozza et al. (2014) Brazil [268]	Menthol	Rats (Wistar/M)	50 (p.o.)	Ethanol-induced gastric ulcers	Gastric mucosal	ELISA	↓ (TNF-α, IL-6)	N	N
Cho et al. (2012) Korea [101]	Carvacrol Compound (5) Fig. 2	Mice (C57BL/M)	0.1% (suppl diet)	HFD-induced obesity	Visceral adipose tissue	RT-PCR	↓ (TNF-α, INF− α)	N	N
Guimarães et al. (2012), Brazil [92]	Carvacrol	Mice (Swiss/M)	25, 50, 100 (i.p.)	Carrageenan-induced pleurisy	Pleural lavage	ELISA	↓ TNF-α	Y	N
Lima (2013), Brazil [58]	Carvacrol	Mice (Swiss/M)	50,100 (i.p.)	CFA-induced inflammation	Skin paw tissue	ELISA RT-PCR	⊠ TNF-α ↓ IL-1β	N	N
Aristatile et al. (2013), India [269]	Carvacrol	Rats (Wistar/M)	20 (p.o.)	D-GalN-induced hepatotoxic	Liver tissue	RT-PCR W.Blot	↓ (TNF-α, IL-6)	N	N
Deng et al. (2013a, 2013b), China [270]	Carvacrol	Rats (Wistar/M)	25, 50, 100 (i.p)	Streptozotocin-induced diabetic	Cerebral cortex Hippocampus	ELISA	↓ (TNF-α, IL-1β)	Y	N
Celik et al. (2013), Turkey [271]	Carvacrol	Rats (Wistar/M)	73 (i.p)	Methotrexate induced toxicity	Sciatic nerve	ELISA	↓ (TNF-α, IL-1β)	Y	N
Mahtaj et al. (2014), Iran [272]	Carvacrol	Pig (Guinea/M,F)	60–240 µg/mL (drinking water)	Cigarette Smoke-Induced COPD	Serum samples	ELISA	↓ IL-8	Y	N
Feng and Jia (2014), China [96]	Carvacrol	Mice (BALBc/M)	20, 40, 80 (i.p)	LPS-induced ALI	BALF	ELISA	↓ (TNF-α, IL-1β, IL-6)	Y	N
Kara et al. (2015), Turkey [97]	Carvacrol	Rats (SD/F)	20, 40, 80 (p.o.)	LPS-induced Sepses	Serum samples	ELISA	↓ (TNF-α, IL-6)	N	N
Arigesavan and Sudhandiran (2015), India [98]	Carvacrol	Rat (SD/M)	50 10, 20, 40 (p.o.)	DMH/DSS-induced colitis associated Colon cancer	Colonic tissue	IHC	↓ IL-1β	N	N
Li et al. (2016a, 2016b), China [99]	Carvacrol	Rats (SD/M)	10, 20, 40 (i.p.)	MCAO	Cortical tissues	ELISA	↓(TNF-α, IL-1β)	Y	N
Zhou et al. (2014), China [116]	Thymol	Mice (BALBc/ F)	4, 8, 16 (p.o.)	OVA-induced asthma	BALF	ELISA	↓(IL-4, IL-5, IL-13)	N	N

(*continued on next page*)

Table 2 (*continued*)

ACYCLIC MONOTERPENES

Authors, year, Country	Substance/ Chemical group	Animals (Strain/Sex)	Dose (mg/kg) (route)	Model	Sample	Evaluation	Cytokines	R	B
Deng et al. (2015), China [273]	Thymol Compound (7) Fig. 2	Mice (ICR/M)	15, 30 (p.o.)	CUMS	Hippocampus	RT-PCR	↓(TNF-α, IL-1β, IL-6)	Y	N
Nagoor Meeran et al., 2015, India [117]	Thymol	Rats (Wistar/M)	7.5 (p.o.)	ISO induced MI	Heart tissue	RT-PCR	↓(TNF-α, IL-1β, IL-6)	N	N
Xie et al., 2012, China [274]	*p*-Cymene Compound (8) Fig. 2	Mice (BALB/c/ M)	25, 50, 100 (i.p.)	LPS-Induced ALI	BALF	ELISA	↓ (TNF-α, IL-1β, IL-6)	Y	N
Zhong et al. (2013), China [121]	*p*-Cymene	Mice (C57BL/6/F)	53, 107, 214 (i.p.)	LPS-induced inflammation	Serum sample	ELISA	↓ (TNF-α, IL-1β)	Y	N
Chen et al. (2014a, 2014b). China [275]	*p*-Cymene	Mice (BALB/c/F)	5, 10 (i.p.)	LPS-Induced ALI	BALF	ELISA	↓ (TNF-α, IL-1β, IL-6)	Y	N
de Santana et al. (2015), Brazil [122]	*p*-Cymene	Mice (Swiss/M)	25, 50, 100 (i.p.)	Carrageenan-induced pleurisy	Pleural lavage	ELISA	↓ TNF-α	N	N
Nonato et al. (2012), Brazil [276]	Rose oxide	Mice (Swiss/M)	100 (i.p.)	CFA-induced paw inflammation	Skin tissues	ELISA	⊠TNF-α, ↓IL-1β	N	N
Juhás et al. (2008), Slovak Republic [148]	Thymoquinone	Mice (ICR/M)	75 (suppl diet)	TNBS-induced colitis	Colon tissue	RT-PCR	⊠ (TNF-α, IL-1β, IL-6)	Y	N
Juhás et al. (2008), Slovak Republic [148]	Borneol Compound (12) Fig. 2	Mice (ICR/M)	135, 270 (suppl diet)	TNBS-induced colitis	Colon tissue	RT-PCR	⊠TNF-α, ↓ (IL-1β, IL-6)	Y	N
Kong et al. (2014). China [147]	Borneol	Rat (Wistar/M)	1, 2, 3 (i.v.)	Focal ischemia reperfusion	Brain tissue	IHC	↓TNF-α, ⊠ IL-1β	Y	N
Siqueira et al. (2016) Brazil [277]	α-Phellandrene	Mice (Swiss/M)	50 (p.o.)	Carrageenan-induced peritonitis	Peritoneal lavage	ELISA	↓ (TNF-α, IL-6)	N	N
d'Alessio et al. (2014), France [110]	*D*-Limonene	Mice (HS1/F)	10 (s.c.)	TPA-induced dermatitis	Serum sample	Bio-Plex	↓ (TNF-α, IL-6) ⊠ IL-1β	N	Y
Rehman et al., 2014, India [113]	D-limonene	Rat (Wistar/M)	5%, 10% (suppl diet)	Doxorubicin induced inflammation	Serum sample	ELISA	↓TNF-α	N	N
Hansen et al. (2016), Denmark [111]	Limonene Compound (6) Fig. 2	Mice (BALBcJ/F)	40 ppm (via inhalation)	OVA-induced allergic airway inflammation	Lung tissues	Flow cytometer	⊠ (TNF-α, IFN− γ, IL-10) ↓ IL-5	Y	N
Khan et al. (2011), India [126]	Perillyl alcohol Compound (9) Fig. 2	Rats (Wistar/M)	50, 100 (p.o.)	Ethanol induced acute hepatotoxicity	Liver Tissue	ELISA	↓ TNF-α	Y	N
d'Alessio et al. (2014), France [110]	Perillyl alcohol	Mice (HS1/F)	10 (s.c.)	TPA-induced dermatitis	Serum sample	Bio-Plex	↓ (TNF-α, IL-6) ⊠ IL-1β	N	Y
Imamura et al. (2014), Japan [132]	Perillyl alcohol	Mice (BALB/c/M)	75 (i.p.)	OVA-induced allergic airway inflammation	BALF	ELISA	↓ IL-13	N	N
Tabassum et al. (2015), India [133]	Perillyl alcohol	Rats (Wistar/M)	100 (p.o.)	MCAO	Frontal cortex hippocampus	–	↓ (TNF-α, IL-1β, IL-6)	Y	Y
Xu et al. (2014), China [136]	Perillaldehyde Compound (10) Fig. 2	Rats (SD/M)	18, 36 (i.g.)	MCAO	Serum	ELISA	↓ (TNF-α, IL-1β, IL-6)	Y	N
Ji et al. (2014), China [137]	Perillaldehyde	Mice (ICR/M)	60, 120 (p.o.)	LPS-induced depressive-like behaviour and inflammation	Serum prefrontal cortex	ELISA RT-PCR	↓ (TNF-α, IL-6)	Y	Y
Shih et al. (2012). Taiwan [278]	β-Thujaplicin	Mice (ICR/M)	7, 14, 21 (p.o.)	LPS-induced inflammation	Serum	ELISA	↓ TNF-α	N	N

BICYCLIC MONOTERPENES

Authors, year, Country	Substance/ Chemical group	Animals (Strain/Sex)	Dose (route)	Model	Sample	Evaluation	Cytokines	R	B
Bae et al. (2012), South Korea [180]	α-Pinene	Mice (C57BL/6/F)	5, 25, 50 (p.o.)	Cerulein-induced acute pancreatitis	Pancreas tissue	RT-PCR	↓(TNF-α, IL-1β, IL-6)	Y	N
Nam et al. (2014). Republic Korea [181]	α-Pinene	Mice (BALBc/ F)	0.1, 1,10 (p.o.)	OVA-induced allergic rhinitis	Nasal mucosa	ELISA	↓ (TNF-α, IL-6) ⊠IL-1β	N	N
Santos et al. (2001) Brazil [279]	1,8-Cineole	Mice (Swiss/M)	400 (p.o.)	GalN/LPS-induced shock	Serum sample	ELISA	↓ (TNF-α)	N	N
Bastos et al, (2011) Brazil [280]	1,8-Cineole	Pigs (guinea/M)	1 mg/mL (Inhalation)	Ovalbumin-Challenged	BALF	ELISA	↓ (TNF-α, IL-1β)	N	N
Lima et al. (2013b) Brazil [164]	1,8-Cineole	Mice (Swiss/M)	100–400 (p.o.)	Cerulein-induced acute pancreatitis	Serum sample	ELISA	↓ (TNF-α, IL-1β, IL-6)	N	N
Zhao et al. (2014) China [162]	1,8-Cineole	Mice (ICR/M)	10–100 (p.o.)	LPS-induced ALI	Lung tissues	ELISA	↓ (TNF-α, IL-1β)	Y	N

Table 2 (*continued*)

ACYCLIC MONOTERPENES

Authors, year, Country	Substance/ Chemical group	Animals (Strain/Sex)	Dose (mg/kg) (route)	Model	Sample	Evaluation	Cytokines	R	B
Li et al. (2016a, 2016b) China [281]	1,8-Cineole	Mice (BALB/c,*)	30, 60, 120 (p.o)	Influenza-Virus-Induced Pneumonia	Nasal lavage fluids Lung tissues	ELISA	↓ (IL-4, IL-5, IL-10) ↓(TNF-α,IL-1β, IL-6, IFN-γ)	Y	N
Lee et al. (2016) South Korea [282]	1,8-Cineole	Mice (BALBc/F)	10 mg/mL (Inhalation)	Der-p-induced Allergic Asthma	BALF	ELISA	↓ (IL-4, IL-13, IL-17)	N	N
Kim et al. (2015a, 2015b, 2015c) Republic of Korea [283]	1,8-Cineole	Mice (BALBc/M)	200, 400 (i.p.)	LPS-induced ALI	BALF	ELISA	↓ (TNF-α, IL-6)	Y	N
Chen et al. (2014a, 2014b) China [284]	Bornyl acetate	Mice (BALBc/M)	25, 50, 100 (i.p.)	LPS-induced ALI	BALF	ELISA	↓ (TNF-α, IL-1β, IL-6)	Y	N
Babu et al. (2012) India [68]	Myrtenal	Rat (Wistar/M)	230 (p.o.)	DEN–PB-induced hepatocarcinogenesis	Liver tissue	Immunoblot	↓ TNF-α	N	N
Silva et al. (2014) Brazil [175]	Myrtenol	Mice (Swiss/M)	75 (i.p.)	carrageenan-induced peritonitis	Peritoneal exudates	ELISA	⊠ TNF-α, ↓ IL-1β	Y	N

IRIDOID GLYCOSIDES

Authors, year, Country	Substance/ Chemical group	Animals (Strain/Sex)	Dose (route)	Model	Sample	Evaluation	Cytokines	R	B
Kim et al. (2010), Republic of Korea [285]	Genipin	Mice (ICR/M)	100 (i.p.)	GalN/LPS-induced liver failure	Serum sample	ELISA	↓ (TNF-α)	Y	N
Kim et al. (2012), Republic of Korea [242]	Genipin	Mice (ICR/M)	2.5 (i.v.)	Cecal ligation and puncture	Serum sample	ELISA	↓(TNF-α, IL-1β, IL-6)	Y	N
Li et al. (2012), Taiwan [243]	Genipin	Mice (Transgenic/F)	100 (i.p.)	LPS-induced inflammation	Serum sample	ELISA	↓(TNF-α, IL-1β)	Y	N
Cho et al. (2016), Republic of Korea [246]	Genipin	Mice (ICR/M)	2.5 (i.v.)	Cecal ligation and puncture	Serum Sample	ELISA	↓ (TNF-α, IL-6)	Y	N
Zhang et al. (2016a, 2016b), China [247]	Genipin	Mice (Balb/c/M)	1, 2.5, 5 (i.v.)	LPS-induced acute lung injury	BALF	ELISA	↓(TNF-α, IL-1β, IL-6)	Y	N
Zheng et al. (2010). China [224]	Geniposide	Mice (KM/M,F)	40 (i.v.)	LPS-induced sepse	Serum sample	ELISA	↓ (TNF-α, IL-6)	Y	N
Ma et al. (2011), China [286]	Geniposide	Rats (SD/M)	25–100 (diet)	Nonalcoholic steatohepatitis	Liver	RT-PCR	↓ TNF-α	Y	N
Xiaofeng et al. (2012). China [230]	Geniposide	Mice (Balb/c/M)	20–80 (i.p.)	LPS-induced ALI	BALF	ELISA	↓ (TNF-α, IL-6)	Y	N
Deng et al. (2013a, 2013b). China [232]	Geniposide	Mice (BALBc/F)	80 (i.p.)	Ova-induced airway inflammation	BALF	ELISA	↓ (IL-4, IL-5, IL-13)	Y	N
Song et al. (2014), China [287]	Geniposide	Mice (BALBc/M,F)	5,10 (3x/d) (i.p.)	LPS mastitis	mammary gland tissues	ELISA	↓(TNF-α, IL-1β, IL-6)	N	N
Dai et al. (2014). China [234]	Geniposide	Rats (SD/M)	30–120 (p.o.)	FCA- induced arthritis	PBL	ELISA	↓ (IL-6, IL-17)	Y	Y
Lv et al. (2015). China [233]	Geniposide	Mice (APP/PS1/M)	25 (p.o.)	APP/PS1 model Alzheimer disease	Brain tissue	ELISA	↓ (TNF-α, IL-1β)	Y	N
Xu et al. (2017), China [288]	Geniposide	Rats (SD/M)	25, 50 (p.o.)	TNBS-induced experimental colitis	Colon tissue	ELISA	↓(TNF-α, IL-1β, IL-6)	Y	N
Kondo et al. (1994). Japan [289]	Gentiopicroside	mice (ICR/M)	30, 60 (p.o.)	BCG/LPS-induced Hepatitis	Serum sample	IA	↓ TNF-α	N	N
Lian et al. (2010), China [290]	Gentiopicroside	Mice (C57BL/6/M)	40, 80 (p.o.)	GalN/LPS - induced hepatic failure	Serum sample	IA	↓ TNF-α	N	N
Lv et al. (2015), China [233]	Gentiopicroside	Rats (SD/M)	100, 400 (p.o.)	Acute pancreatitis	Pancreas tissue	RIA	↓ (TNF-α, IL-1β)	N	N
Kim et al. (2013). Republic Korea [291]	Geniposidic acid	Mice (ICR/M)	50 (i.p.)	GalN/LPS - induced hepatic failure	Serum sample	ELISA	↓ (TNF-α, IL-6)	N	N
Zhang et al. (2013). China [208]	Catalpol	Mice (KM/M,F)	2.5–10 (s.c.)	*D*-galactose induced brain aging	Brain tissue	ELISA	↓ (TNF-α, IL-1β)	Y	N
Xiao et al. (2014), China [292]	Catalpol	Rat (SD/M)	50 (p.o)	STC-induced pancreatitis	Serum sample	ELISA RT-PCR	↓(TNF-α, IL-1β, IL-6)	Y	N
Wang et al. (2014a, 2014b), China [293]	Catalpol	Rat (S-D/M)	25, 125 (i.p.)	CCI	Spinal cord	Western blot	↓(TNF-α, IL-1β, IL-6)	N	Y
Fu et al. (2014), China [211]	Catalpol	Mice (BALBc/M)	2.5–10 (i.p.)	LPS – induced ALI	BALF	ELISA	↓(TNF-α, IL-1β, IL-6, IL-4)	Y	N

Table 2 (*continued*)

ACYCLIC MONOTERPENES

Authors, year, Country	Substance/Chemical group	Animals (Strain/Sex)	Dose (mg/kg) (route)	Model	Sample	Evaluation	Cytokines	R	B
Liu et al. (2016), China [294]	Catalpol	Rabbit (NZW/M)	5 (p.o.)	Hypercholesterolemia-induced atherosclerosis	Serum sample	ELISA	↓ (TNF-α, IL-6)	Y	N
Zhou et al. (2015), China [295]	Catalpol	Mice (C57BL6J/M)	100 (p.o.)	HFD-induced insulin resistance	Epididymal adipose tissue	RT-PCR	↓(TNF-α, IL-1β, IL-6)	Y	N
Chen et al. (2017), China [296]	Catalpol	Mice (BALBc/M)	5, 10 (i.p.)	OVA-induced asthma	Peripheral blood BALF	ELISA	↓ (IL-4, IL-5)	Y	N
Lee et al., 2016, China [297]	Catalpol	Rabbit (NZW/M)	5 (p.o.)	Diabetic atherosclerosis	Plasma	ELISA	↓ TNF-α	Y	N
Wang et al. (2014a, 2014b), China [298]	Monotropein	Rats (KM/-)	25–100 (p.o.)	Osteoarthritis	Synovial fluid	ELISA	↓ (TNF-α, IL-1β)	N	N
Zhang et al. (2016a, 2016b). China [299]	Monotropein	Mice (C57/BL6/F)	40, 80 (p.o.)	Ovariectomy induced osteoporosis	Serum sample	ELISA	↓ (IL-1β, IL-6)	Y	N
Impellizzeri et al. (2011a, 2011b), Italy [253]	Oleuropein	Mice (CD/M)	100 μM/kg (i.p.)	Carrageenan-induced pleurisy	Pleural exudates	ELISA	↓(TNF-α, IL-1β)	Y	N
Giner et al. (2011), Spain [249]	Oleuropein	Mice (BALB/c/F)	1% (suppl diet)	DSS-Induced Chronic Colitis	Colon tissue	ELISA	↓(TNF-α, IL-1β, IL-6)	Y	N
Impellizzeri et al. (2011a, 2011b), Italy [248]	Oleuropein	Mice (DBA/1J/M)	20, 40 μg/kg (i.p.)	Collagen-induced arthritis	Serum sample	ELISA	↓(TNF-α, IL-1β, IL-6)	N	N
Giner et al. (2013), Spain [301]	Oleuropein	Mice (C57BL/6/F)	0.25% (suppl diet)	DSS-Induced Chronic Colitis	Colon tissue	ELISA	↓ (IL-1β, IL-6)	Y	N
Andreadou et al. (2014), Greece [250]	Oleuropein	Rat (Wistar/M)	166, 333 (i.p.)	Doxorubicin-induced cardiomyopathy	Myocardial tissue	ELISA	↓(IL-6)	Y	N
Janahmadi et al., 2014, Iran [251]	Oleuropein	Rat (SD/M)	20, 30 (p.o.)	Myocardial Infarction	Serum sample	ELISA	↓(TNF-α, IL-1β)	Y	N
Caglayan et al. (2015), Turkey [252]	Oleuropein	Rat (Wistar/M)	20 (p.o.)	BPDO-induced pancreatitis	Serum sample	ELISA	⊠ (TNF-α, IL-6)	Y	N
Giner et al. (2016), Spain [254]	Oleuropein	Mice (C57BL/6/F)	50, 100 (driking water)	AOM/DSS-induced colorectal cancer	Colon tissue	ELISA	↓(TNF-α, IL-6, IFN-γ, IL-17)	Y	N
Liu et al. (2006), China [302]	Paeoniflorin	Mice (BALBc/M)	25, 50 (i.v.)	BCG/LPS induced liver injury	Liver tissue	RT-PCR	↓ (TNF-α, IL-6)	Y	N
Li et al. (2010), China [196]	Paeoniflorin	Mice (BALBc/F)	30 (p.o.)	*S. japonicum* cercariae infection	Liver tissue	ELISA	↓ (IL-13)	Y	N
Tang et al. (2010), Taiwan [200]	Paeoniflorin	Rat (S-D/M)	20 (i.v.)	Cerebral Infarct Induced by Ischemia-Reperfusion Injured	Brain sections	Immunostain	↓ (TNF-α, IL-1β)	Y	Y
Zhou et al. (2011), China [201]	Paeoniflorin	Mice (ICR/M)	100 (i.p.)	LPS-Induced ALI	BALF Lung tissue	ELISA RT-PCR	↓ (TNF-α, IL-1β)	Y	N
Guo et al. (2012). China [300]	Paeoniflorin	Rat (SD/M)	10 (i.p.)	MCAO	Serum sample Brain	ELISA RT-PCR	↓ (TNF-α, IL-1β)	Y	Y
Chen et al. (2012), China [303]	Paeoniflorin	Rat (Wistar/M)	20 (p.o.)	DMN-induced liver fibrosis	Serum sample	ELISA	↓ (TNF-α, IL-1β)	Y	N
Wang et al. (2013), China [190]	Paeoniflorin	Mice (KM/M)	70,140 (p.o.)	Allergic contact dermatitis	Blood sample	ELISA	↓ (IL-2, IL-17)	Y	N
Zhang et al. (2014), China [202]	Paeoniflorin	Mice (C57BL/6/F)	50 (p.o.)	DSS-induced colitis	Colon segments	ELISA RT-PCR	↓(TNF-α, INF-γ,IL-6)	Y	N
Chen et al. (2015a, 2015b), China [203]	Paeoniflorin	Rat (SD/-)	5–20 (i.v.)	Acute myocardial infarction	Serum sample	ELISA	↓(TNF-α, IL-1β, IL-6)	Y	N
Chen et al. (2015a, 2015b), China [203]	Paeoniflorin	Mice (C57BL/6/)	50 (i.v.)	Concanavalin A-induced hepatitis	Serum sample Liver tissue	ELISA RT-PCR	↓(TNF-α, INF-γ, IL-6)	Y	N
Zhang et al. (2015a, 2015b), China [199]	Paeoniflorin	Mice (APP/PS1 and WT/M)	5 (i.p.)	APP/PS1 model Alzheimer disease	Brain tissue	ELISA	↓(TNF-α, IL-1β)	Y	N
Sun et al., (2015a, 2015b), China [198]	Paeoniflorin	Mice (BALBc/M)	10–50 (p.o.)	OVA-induced asthma	BALF	ELISA	↓(IL-5, IL-13, IL-17)	Y	N
Shen et al. (2015), China [204]	Paeoniflorin	Mice (BALBc/F)	150–300 (i.p.)	Imiquimod-induced psoriasis	Skin tissue	RT-PCR	↓(TNF-α, IL-1β, IL-6)	N	N
Ya et al. (2010), China [304]	Cornel	Rat (SD/M)	60,180 (p.o.)	MCAO	Brain tissue	ELISA	↓ (TNF-α, IL-1β)	Y	N
Kim et al. (2015a, 2015b, 2015c), South Korea [244]	Loganin	Mice (C57BL/6/F)	10–100 (p.o.)	Cerulein-induced pancreatitis	Pancreas tissue Serum sample	RT-PCR ELISA	↓ (TNF-α, IL-1β)	Y	N
Song et al. (2015), Republic of Korea [305]	Piscroside C	Mice (C57BL/6N/M)	15, 30 (p.o.)	cigarette smoke/LPS induced COPD	BALF	ELISA	↓ (TNF-α, IL-6)	N	N
Saravanan et al. (2014a), (2014b), India [263]	Swertiamarin	Rat (SD/F)	2–10 (p.o.)	Adjuvant induced arthritis	Serum	ELISA	↓(TNF-α, IL-1β, IL-6)	N	Y

Table 2 (*continued*)

ACYCLIC MONOTERPENES

| Authors, year, Country	Substance/ Chemical group	Animals (Strain/Sex)	Dose (mg/kg) (route)	Model	Sample	Evaluation	Cytokines	R	B
Wang et al. (2015), China [306]	Incarvillateine monoterpene alkaloid	Mice (C57/BL6/M)	20 (i.p.)	CFA-induced inflammation and pain	Hindpaw tissue	ELISA	↓ IL-1β	N	N

Abbreviations: Animals- Homozygous triple transgenic AD model (3xTg-AD) and no transgenic (Non-Tg) mice, Sprague–Dawley (SD), amyloid precursor protein (APP) and presenilin 1 (PS1) double transgenic model Alzheimer's disease (AD), wild-type (WT), New Zealand White (NZW). **Model -** LPS = Lipopolysaccharide, D-GalN = D-galactosamine, D-galactosamine/lipopolysaccharide (GalN/LPS) Unpredictable chronic mild stress (UCMS), High-fat diet (HFD), 2,4,6-trinitrobenzene sulfonic acid (TNBS), *Dermatophagoides pteronyssinus* (Der p); diethylnitrosamine-phenobarbital (DEN–PB) induced hepatocarcinogenesis, dimethylhydrazine (DMH), Chronic obstructive pulmonary disease (COPD), chronic unpredictable mild stress (CUMS), Middle cerebral artery occlusion (MCAO), Freund's complete adjuvant (FCA), mesenteric lymph node lymphocytes (MLNL) and peripheral blood lymphocytes (PBL), chronic constriction injury (CCI) and lumbar 5 spinal nerve ligation (L5 SNL), amyloid precursor protein (APP) and presenilin 1 (PS1), Dimethylnitrosamine (DMN), middle cerebral artery occlusion (MCAO), DXR-induced cardiomyopathy (DXR-CM), Dextran Sodium Sulfate (DSS), bilepancreatic duct obstruction (BPDO), Ovalbumin (OVA), tetradecanoylphorbol-13-acetate (TPA), acute lung injury (ALI), Azoxymethane (AOM), sodium taurocholate (STC), Bacillus Calmette-Guerin (BCG). **Evaluation** - immunohistochemistry (IHC), enzyme-linked immunosorbent assay (ELISA), Immunoassay (IA), Radioimmunoassay (RIA).

as an important maturation and differentiation factor for eosinophils in rodents and humans. Over-expression of IL-5 increases the amount of eosinophil cells and antibody levels *in vivo*. Lower IL-5 production, therefore, supported the anti-inflammatory effects of limonene. In agreement with other authors, Ku and Lin (2013), suggested that the limonene anti-inflammatory and T-helper cell (Th)-2-stimulating effect could be mainly due to promotion of anti-inflammatory IL-10 secretion.

Examining the complexity of molecules' anti-inflammatory properties, Rehman et al. (2014), showed that limonene knocks out TNF-α expression in a doxorubicin-induced inflammation model and that this effect is related to NF-κB downregulation. Additionally, the anti-inflammatory effect produced by limonene was associated with repression of COX-2 and iNOS enzymes, as well as decreased PGE$_2$ levels (Rehman et al., 2014). In line with these findings, d'Alessio et al., (d'Alessio et al., 2014), reported that *D*-limonene is able to control the increase of TNF-α serum levels after 2,5,6-trinitrobenzene sulfonic acid-induced colitis by decreasing NF-κB activation. These findings support the anti-inflammatory action of this terpene as an active process affecting cell-signaling pathways.

Therefore, these data suggest that *D*-limonene modulates the pro-
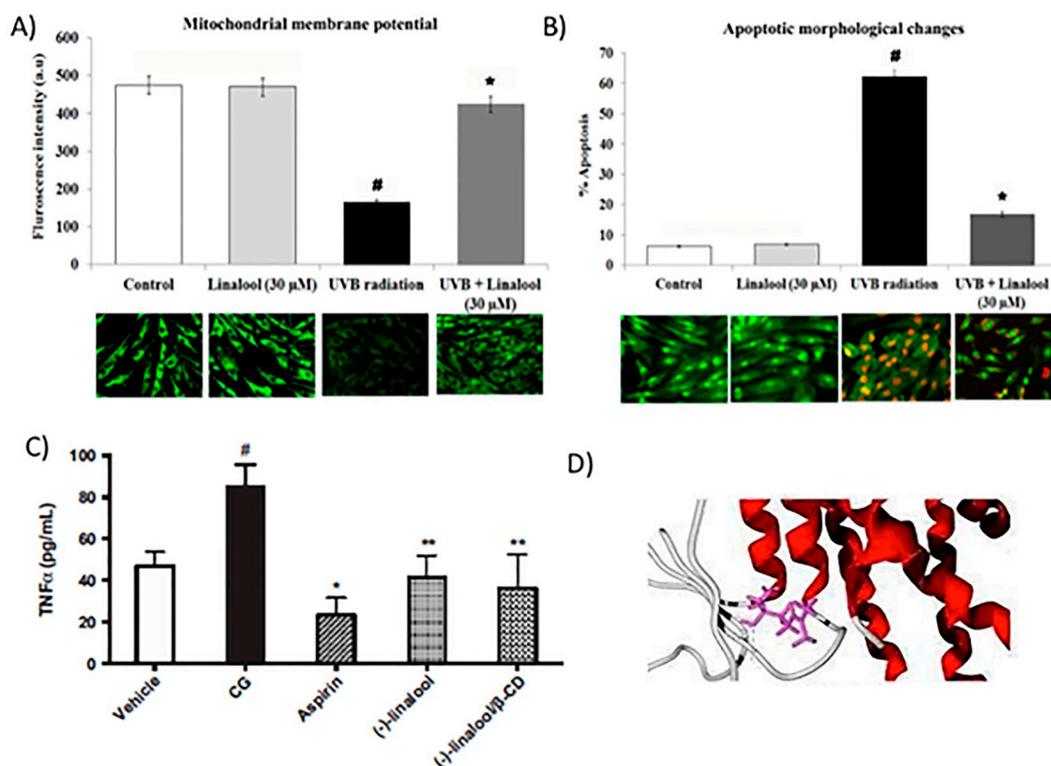
Fig. 3. A) and **B)** Linalool protects against UVB-induced apoptosis in HDFa cells. Linalool protects against UVB induced alteration of mitochondrial membrane potential in HDFa cells, and against UVB induced apoptotic morphological changes, measured by AO/EtBr staining, respectively. Fluorescence microscopic images (20X) recorded using fluorescence microscope (Cell Imaging Station, Life Technologies) (Adapted from Gunaseelan) (Gunaseelan et al., 2017). **C).** Effect of linalool, linalool/βCD or aspirin on leucocyte migration into the peritoneal cavity induced by carrageenan (CG) in mice and determination of TNF-α levels (Adapted from Quintans-Júnior) (Quintans-Júnior et al., 2013). **D)** Docking view showing hydrogen bond interaction of linalool with glutathione S-transferases (GST) enzyme (Adapted from Babu et al., 2012).
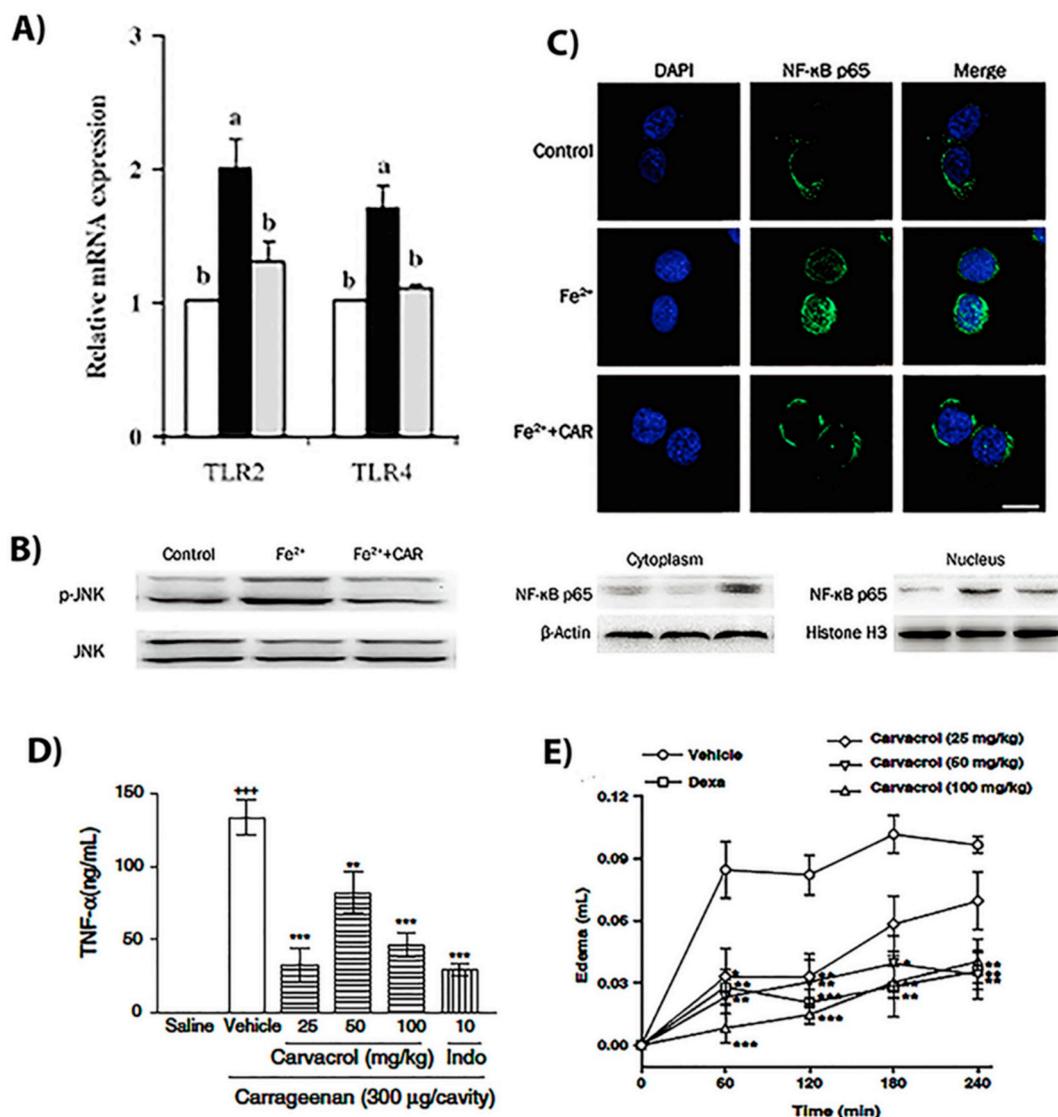
Fig. 4. A) Carvacrol attenuates the release of cytokines in visceral adipose tissues by inhibiting the TLR2-and TLR4-mediated pathways (Adapted from Soomin et al., 2012). B) and C) Carvacrol prevents the inflammatory response via inhibition of NF-κB nuclear translocation (Adapted from Cui et al., 2015) D) Effect of carvacrol or indomethacin on TNFα levels in carrageenan pleurisy model (adapted from Guimarães et al., 2012). E) Carvacrol presented antiedematogenic activity on CG-induced mouse paw edema (adapted from Guimarães et al., 2012).

inflammatory or anti-inflammatory production of cytokines and decreases some key inflammatory mediators (e.g. PGE₂). Furthermore, it is indeed possible that decreased activation of NF-κB could be responsible for cytokine misregulation and lower expression of inflammatory genes, including iNOS and COX-2. This effect could be contributing to limonene's anti-inflammatory action. However, additional studies will be necessary to further characterize the potential role of limonene as an anti-inflammatory molecule with pharmacological properties to treat inflammatory disease.

Thymol (2-isopropyl-5-methylphenol) (**7**), a naturally occurring monocyclic phenolic compound derived from *Thymus vulgaris* (Lamiaceae), has been widely used in medicine for its antimicrobial, antiseptic and wound-healing properties (Aeschbach et al., 1994; Shapiro and Guggenheim, 1995). We found three studies (Table 2) which discussed this monoterpene in different *in vivo* models. An allergic airway inflammation in ovalbumin (OVA)-induced mouse asthma study was conducted by Zhou et al. (2014) which found that pretreatment with thymol (16 mg/kg) reduced the levels of IL-4, IL-5, and IL-13 in a dose-dependent manner in BALF (bronchoalveolar lavage fluids) of OVA-challenged mice. Meeran et al., (Nagoor Meeran et al., 2015),

reported that thymol attenuates inflammation in isoproterenol induced myocardial infarcted rats by inhibiting the release of lysosomal enzymes and downregulating the expression of pro-inflammatory cytokines including TNF-α, IL-1β, IL-6.

p-Cymene (**8**) is a naturally occurring aromatic organic compound present in *Cinnamon* essential oil (Santana et al., 2011; Siani et al., 1999). The analgesic and anti-inflammatory properties of *p*-cymene have been previously described by our group. *p*-Cymene demonstrated promising analgesic action in an animal model of orofacial pain, modulating neurogenic and inflammatory pain (Bonjardim et al., 2012; Santana et al., 2011). We found four studies that described the action of *p*-cymene in several animal models modulating cytokines (Table 2). Zhong et al. (2013) used LPS as an inflammation agent in rodents and *p*-cymene exhibited a significant anti-inflammatory effect on the regulation of cytokine expression. Pre-treatment with *p*-cymene decreased the release of TNF-α, IL-1β, and IL-6, and significantly increased the release of IL-10 in *in vivo* tests. It was also confirmed through an *in vitro* approach. In addition, Quintans et al. (2013), developed an inclusion complex containing *p*-cymene and β-cyclodextrin and reported increased bioavailability for this terpenoid when compared with non-

complexed *p*-cymene, and the ability to produce consistent and long-lasting analgesic and anti-inflammatory effects. These effects appear to be related to the ability of *p*-cymene to reduce TNF-α and involve the descending pain-inhibitory mechanism through opioid system activation (de Santana et al., 2015).

Perillyl alcohol (PA) (**9**) is a monoterpene found in the essential oil of several plant species like mint, cherries, citrus fruit, lavender and lemon grass (Crowell, 1999). This terpene can be biocatalyticly produced from limonene using *Mycobacterium* sp (van Beilen et al., 2005). PA exhibits antioxidant and anti-inflammatory pharmacological properties (Jahangir and Sultana, 2007; Khan et al., 2011). Furthermore, it has been considered as a strong candidate for the treatment of cancer. Phase-I clinical trials for the treatment of refractory solid tumors have already taken place with satisfactory results (Hudes et al., 2000; Ripple et al., 1998). PA has also been tested for prostate cancer in phase-II clinical trials(Liu et al., 2003). and for colon and ovarian cancer (Bailey et al., 2002; Meadows et al., 2002). This monoterpene has neuroprotective effects, which may be applicable in the preventive treatment of stroke (Imamura et al., 2014). PA was assessed by Imamura et al. (2014) in allergen-induced inflammation in a murine model of asthma. In this test, PA significantly down-regulated the production of IL-5, IL-10, and IL-17, but IFN-γ was not affected. The anti-inflammatory effect of PA does not seem to involve an increase in the expression of anti-inflammatory cytokines. Recently, Tabassum et al. (2015), showed in an ischemia/reperfusion injury model that PA acts on the inflammation by inhibiting the expression of IL-1β, IL-6, TNF-α, NOS-2 COX-2 and NF-κβ (Tabassum et al., 2015).

Perillaldehyde (PAH) (**10**) is a major component in EO extracted from Perilla frutescens, and has been found to exhibit antimicrobial (Duelund et al., 2012), anticancer (Elegbede et al., 2003) and vasodilator effects (Duelund et al., 2012). Detection of IL-1β, TNF-α and IL-6 concentrations in rats with MCAO was significantly increased compared to sham animals. However, pretreatment with PAH (18, 36 mg/kg) significantly attenuated ischemia/reperfusion injury-induced upregulation of pro-inflammatory cytokine levels (Xu et al., 2014). Similarly, LPS (0.5 mg/kg, 24 h) significantly increased the levels of IL-6 in the prefrontal cortex versus the control group, but PAH treatments (60 and 120 mg/kg) produced a significant reduction of IL-6 concentration in the prefrontal cortex *vs* the LPS-induced mice model (Ji et al., 2014).

Two recent studies conducted by Ramalho et al., (Ramalho et al., 2016, 2015), demonstrated the effects of γ-terpinene (**11**) (a monoterpene present in the essential oils of several plants, including those from the *Eucalyptus* genus.) against pro-inflammatory mediators. They reported that γ-terpinene in LPS-induced production of cytokines by murine peritoneal macrophages induced a significant inhibition of pro-inflammatory cytokines, such as IL-1β and IL-6, and equally enhanced the production of IL-10. These effects were followed by increased levels of COX-2, as well as the production of PGE$_2$. Interestingly, COX-2 inhibition by nimesulide abolished the potentiating effect of γ-terpinene on interleukin-10 production (Ramalho et al., 2015).

Another terpene found in our survey with widespread use in clinical practice and of interest in the management of cytokine production was borneol (**12**). This monocyclic monoterpene possesses a pungent, bitter taste and fragrant odor, and is synthesized from turpentine oil or camphor. It has been used as an analgesic, antioxidant and anti-inflammatory in pharmaceutical formulations (Almeida et al., 2013; Dantas et al., 2016; Wang et al., 2017). It is also found in various plants, such as sage (*Salvia officinalis*), valerian (*Valeriana officinalis*), chamomile (*Matricaria chamomilla*), rosemary (*Rosmarinus officinalis*), and lavender (*Lavandula officinalis*) (Bhatia et al., 2008; Elalfi et al., 2015). It has been reported that borneol can improve neural cell energy metabolism and consequently reduce brain tissue damage in ischemic cerebral regions (He et al., 2006; Zhao et al., 2006). Recently, Zhang et al. (2017), reported that borneol enhanced blood–brain barrier permeability, improving the delivery of drugs to the brain, which is extremely interesting for association with drugs that act on the central nervous

system (CNS). Moreover, Kong et al. (2014), examined the effects of borneol on intracerebral inflammatory response after focal ischemia reperfusion in rats. The administration of 1–3 mg/kg (i.v) of borneol was reported to decrease the number of TNF-α positive cells, and leucocyte infiltration in the brains of rats. In addition, no statistically significant difference was observed in IL-1β expression in the borneol experimental groups. Furthermore, dietary administration of borneol at concentrations of 0.09 and 0.18% were reported to possibly suppress IL-6 and IL-1β mRNA levels in TNBS (2,4,6-trinitrobenzene sulfonic acid)-induced colitis in mice, however, no changes were observed in TNF-α (Juhás et al., 2008).

The anti-inflammatory profile of thymoquinone (TQ) (**13**), another acyclic monoterpene, was studied by Juhás (Juhás et al., 2008). They demonstrated that no changes were observed in TNFα, IL-6 and IL-1β mRNA levels in TNBS-induced colitis in mice treated with 0.05% thymoquinone added to commercial standard lab rodent chow. However, there is increasing evidence to suggest that TQ has anti-inflammatory properties, for example TQ had protective effects on sepsis due its ability to inhibit the elevation of pro-inflammatory mediators such as TNF-α, IL-1β and IL-6 triggered by sepsis., (Ozer et al., 2017). These findings are corroborated by Tekeoglu et al. (2006), who described the anti-inflammatory effects of TQ on experimentally-induced arthritis in rats, which equally reduced levels of TNF-α and IL-1β plasma in the rodents.

Trinh (Trinh et al., 2011) evaluated the effect of α-terpineol (**14**) (TPN), a monoterpene found in essential oils from various plant species, such as *Ravensara aromatica* and *Eucalyptus globulus*, which are popularly used in aromatherapy, perfumery, cosmetics and household products (Craveiro et al., 1981; de Sousa, 2011; Franchome and Penoel D., 1995; Elalfi. et al., 2016b). It was shown that this monoterpene alcohol was able to inhibit the expressions of pro-inflammatory cytokines and increase the expression of the anti-inflammatory cytokine IL-10. Moreover, TPN was able to reduce the COX-2 and iNOS levels and decrease the activation of NF-κB. These findings are consistent with previous pharmacological findings in relation to TPN, which attributed it with antimicrobial, anti-spasmodic, anti-convulsant and immunostimulant effects (de Sousa et al., 2006b; Franchome and Penoel, 1995; Hassan et al., 2010; Lee et al., 1997; Williams and Barry, 1991). Moreover, Trinh, (Trinh et al., 2011), also described the inhibition of the expression of proinflammatory cytokines and the reduced activation of NF-κB in lipopolysaccharide-stimulated peritoneal macrophages. Corroborating the anti-inflammatory and analgesic profiles of TPN, it has been shown to inhibit the production of proinflammatory cytokines (such as TNF-α) and modulate the central descending pain-inhibitory mechanism (de Oliveira et al., 2012; Oliveira et al., 2016; Quintans-Júnior et al., 2011).

4.3. Bicyclic monoterpenes

Eucalyptol (1,8-cineole [synonym]) (**15**) is a natural bicyclic monoterpene comprising the majority of the volatile oil in many plants, particularly in *Eucalyptus* spp. Some reports suggest that eucalyptol possesses analgesic and/or anti-inflammatory properties (Elaissi et al., 2012; Guimarães et al., 2013; Zhao et al., 2014). Lima et al. (2013), evaluated the antioxidant and anti-inflammatory properties of eucalyptol against cerulein-induced acute pancreatitis and found that cerulein increased serum levels of amylase and lipase, and the pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6). Interestingly, pretreatment with eucalyptol reduced the production of these enzymes and inflammatory mediators and the level of IL-10 was enhanced. Moreover, these effects can also be associated with the inhibition of nuclear NF-κB p65 translocation via IκBα, resulting in decreased levels of proinflammatory NF-κB target genes, which may broaden the range of the clinical applications for this natural compound in the treatment of inflammatory diseases (Greiner et al., 2013). These data suggest that eucalyptol produces an anti-inflammatory effect by decreasing TNF-α,

IL-1β, and IL-6 through inhibition of the NF-κB pathway.

The key to the anti-inflammatory effect of eucalyptol may be related to the enhancement of IL-10, as described by Trinh (Trinh et al., 2011). This study suggested that eucalyptol in an animal model of bacterial vaginosis (a chronic infection caused by the disturbance of the natural vaginal flora, resulting in an increase in vaginal pH, foul-smelling secretions and the presence of intense inflammation) was able to ameliorate IL-10 levels and contribute to reducing the inflammatory process (Amsel et al., 1983; Hawes et al., 1996).

Other anti-inflammatory molecules that have produced promising effects on the modulation of cytokine production are myrtenal (16) and myrtenol (17), two monoterpenes which differ in their functional group. Myrtenal is found in the essential oil of *Artemisia annua* L. (Asteraceae) (Ahmad and Misra, 1994) or *Glycyrrhiza glabra* L. (Fabaceae) (Kameoka and Nakai, n.d.). Myrtenal has been shown to have a range of properties including anti-acetylcholinesterase (Kaufmann et al., 2011) and antioxidant effects (Babu et al., 2012) and has been used against some diseases including cancer (Lingaiah et al., 2013). In addition, the present review suggested that myrtenal is able to reduce TNF-α immunocontent in carcinogen-induced hepatocellular carcinoma in rats, suggesting an anti-inflammatory activity by myrtenal.

Moreover, myrtenol, a bioactive compound of many medicinal plants such as *Rhodiola rosea* L., *Paeonia lactiflora* Pall, *Cyperus rotundus*. L. and *Tanacetum vulgare* L., has exhibited an anti-inflammatory effect (Evstatieva et al., 2010; Mockute and Judzentiene, 2003; Ngan et al., 2012). Myrtenol has shown anti-inflammatory action in chronic and acute protocols with the reduction of inflammatory mediators seeming to be the key to these effects (Gomes et al., 2017; Silva et al., 2014). Silva (Silva et al., 2014) suggested that myrtenol modulates acute inflammation through the inhibition of the release of cytokines such as IL-1β.

α-Pinene (18), a bicyclic monoterpene from the EOs of coniferous trees and many other plants has anti-inflammatory and antimicrobial profiles (Hong et al., 2004; Lee et al., 2009). However, there have been few studies of the anti-inflammatory features of α-pinene. Kim et al. (D.-S. Kim et al., 2015a) suggested that α-pinene suppresses IL-6 and TNF-α release in a dose dependent manner in a protocol using LPS-stimulated macrophages, with the monoterpene significantly inhibiting PGE$_2$ production, and COX-2 and iNOS protein expression.

In addition, other articles support the pharmacological evidence which shows that the anti-inflammatory effect are related to TNF-α, IL-1β, and IL-6 inhibition during acute pancreatitis (Bae et al., 2012; Nam et al., 2014). A significant reduction in the levels of inflammatory cytokine such as TNF-α and IL-6 were induced by α-pinene in an oval-bumin-sensitized allergic rhinitis animal model, however, no change was observed in IL-1β levels in the same model (Nam et al., 2014).

Interestingly, the key to the anti-inflammatory effect of this monoterpene may be related to downregulated ERK and JNK phosphorylation (D.-S. Kim et al., 2015a) and inhibited NF-κB activity (D.-S. Kim et al., 2015a; Nam et al., 2014). Our review corroborates the evidence that α-pinene may be a promising anti-inflammatory agent and suggests that it may be useful in the clinical management of inflammatory illness.

4.4. Iridoid glycosides

The iridane skeleton found in iridoids is monoterpenoid in origin and contains a cyclopentane ring which is usually fused to a six-membered oxygen heterocycle. The iridoid system arises from geraniol by a type of folding, which is different from that already encountered with monoterpenoids (Dewick, n.d.). Iridoids are found in a wide variety of plants, especially in species belonging to the Apocynaceae, Lamiaceae, Loganiaceae, Rubiaceae, Scrophulariaceae and Verbenaceae families (Viljoen et al., 2012). They are associated with a wide range of health benefits, such as antibacterial, anticancer, anticoagulant, antifungal, anti-inflammatory, antioxidative, antiprotozoal, hepatoprotective and

neuroprotective activities (Dinda et al., 2007). Moreover, iridoids exhibit promising anti-inflammatory activity for a wide spectrum of inflammatory disorders and are an interesting class of compounds for possible clinical use (Viljoen et al., 2012).

Paeoniflorin (PF) (19) is an iridoid glucoside and is the main bioactive components (more than 90%) of the *Paeonia lactiflora* root (Sun et al., 2008). PF has been used for 2000 years in traditional Chinese medicine for the treatment of autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and Sjogren's syndrome. PF equally attenuates gynecological problems, cramp, pain, giddiness and allergic diseases (He and Dai, 2011). Species from the *Paeonia* genus have been clinically used to treat painful or inflammatory disorders in China, specifically due the presence of PF (Zheng and Wei, 2005). PF has been shown to reduce the production of inflammatory cytokines including VEGF, MMPs, TNF-α, IFN-γ and IL-1 induced by adjuvant arthritis (Zheng and Wei, 2005). Moreover, PF is reported to decrease the expression of intercellular adhesion of molecule-1 and 3-nitrotyrosine proteins in a type 1 diabetes animal model (Zhang et al., 2009). Some mechanisms found in this review showed that PF reduces the activation of Th1 and Th17 cells and decreases TNF-α, IFN-γ and IL-2 expression in rheumatoid arthritis patients and in animal models. Consistently, PF inhibits dendritic cell maturation and reduces IL-12 production mice (Shi et al., 2014; Wu et al., 2007).

Scientific findings on the anti-inflammatory effects of PF are common, especially in the Chinese scientific literature; we highlight two interesting studies using different animal models to consider the action of PF on anti-inflammatory cytokines. Wang et al. (2013), demonstrated in rats that PF attenuates the degree of allergic contact dermatitis. The purpose of this study was to evaluate the effects of PF on inflammatory and immune responses towards thymocytes and splenocytes and the mechanisms by which PF regulates Dinitrochlorobenzene (DNCB) in relation to the redox-linked mechanism induced by skin inflammation mouse model. Interestingly, it was found that PF could significantly increase the production of the anti-inflammatory cytokines IL-4 and IL-10.

IL-4 is produced by mast cells, Th2 lymphocytes and NKT cells (Cicuttini et al., 1995; Kronenberg, 2005; Vervoordeldonk and Tak, 2002) and inhibits the production of inflammatory cytokines such as IFN-γ, TNF-α, IL-15, and IL-1, and enhances IL-1Ra production. Moreover, IL-4 regulates a multitude of immune functions including immunoglobulin isotype switching, class-II MHC expression by B-cells and the differentiation fate of certain T-cell subsets (Brown, 2008). TGF-β is a pleiotropic cytokine that in combination with IL-4 promotes the activation of T-cells to produce IL-10 (Cho et al., 2012; Dardalhon et al., 2008). It is secreted by a variety of immune cells and, similarly to IL-10, it is present at a high level in the synovial fluid (Vervoordeldonk and Tak, 2002).

Li et al. (2010) examined the effects of PF on experimental hepatic fibrosis (a complex clinical state in patients with hepatitis) induced by infection in mice. The authors reported that PF inhibited the deposition of collagens I and III, as well the levels of hydroxyproline in the livers of mice contaminated with *S. japonicum* eggs. Additionally, the elevated levels of IL-13 and IL-13Rα2 in the infected mice were significantly suppressed by PF treatment. Considering the immunomodulatory effect of IL-13 on IgE synthesis on chemokine production, Li et al. (2009), demonstrated the involvement of low levels of IL-13 as a mechanism for the decline in liver fibrosis. IL-13 is homologous to IL-4 and IL-10 and is produced by NK and T-cells (Vervoordeldonk and Tak, 2002). It is worth mentioning that IL-13 and its receptors have been proposed as attractive therapeutic targets for the treatment of allergic diseases (J. Sun et al., 2015a).

Recently, Zhang et al.(H.-R. Zhang et al., 2015a) suggested that PF may regulate neuroprotective effects in amyloid precursor protein (APP) and presenilin 1 (PS1) double transgenic (APP/PS1) mice via inhibiting neuroinflammation mediated by the GSK-3β and NF-κB signaling pathways and the nucleotide-binding domain-like receptor

protein 3 inflammasome. The pretreatment of mice with PF produced a significant inhibition of TNF-α and IL-1β levels, and significantly up-regulated IL-10 and IL4 levels in the cortex and hippocampus. Thus, these findings suggest that the beneficial effects of PF treatment were associated with a modulation of inflammatory responses in APP/PS1 mice.

Moreover, the findings suggested that PF can impair the capacity of allergic contact dermatitis and inhibit neuroinflammation by improving the production of the anti-inflammatory cytokines. IL-10 and TGF-β are the most commonly studied immunosuppressive cytokines; they induce the proliferation of Treg cells, e.g., IL-10-producing T-cells and CD4$^+$ CD25$^+$ Foxp3$^+$ T-cells. IL-10 is produced by activated B− and T-cells, monocytes and macrophages, (Cicuttini et al., 1995). The role of increased IL-10 in the course of acute inflammation is to control the degree of inflammation and stop the process. In many acute cases of inflammation, this mechanism is enough to inhibit inflammation (Vervoordeldonk and Tak, 2002).

Additionally, PF can also normalize the Bacillus Calmétte-Guérin (BCG) plus LPS induced liver injury, CFA-induced arthritis, DSS-induced colitis, acute myocardial infarction, concanavalin A-induced hepatitis, OVA-induced asthma and imiquimod-induced psoriasis by significant down regulation of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-12, IL-5, IL-13, IL-17 and INF-γ as reported in recent studies, (C. C. Chen et al., 2015a; J. Sun et al., 2015a; Y. Sun et al., 2015b; Tang et al., 2010; Zhang et al., 2014; Zhou et al., 2011). The cytokines TNF-α, IL-1β, and IL-6 are associated with a variety of pathological reactions and organ dysfunction, and they are upregulated after LPS challenge and contribute to septic shock (Dinarello, 1984). Clinical studies in patients with meningitis found a positive correlation between high levels of plasma TNF-α and mortality (Waage et al., 1987). IL-6 levels have been assessed in several diseases. In patients with severe burns, plasma IL-6 correlates significantly with body temperature, which supports the concept that IL-6 is an endogenous pyrogen. In sepsis patients, the reported levels of IL-6 were much higher (Zhong et al., 2013). Based on the evidence from these and other studies, we highlight the strong evidence that PF is a crucial monoterpenoid which is able to modulate cytokine production and is especially important in relation to the control of inflammatory processes.

Catalpol (20) is a nutraceutical substance already used in food supplementation for neurodegenerative disorders and plays a vital role in the regulation of anti-inflammatory and pro-inflammatory cytokine levels. This iridoid is the main bioactive compound in the dried root of *Rehmannia glutinosa,* and has been found to have broad and diverse pharmacological activities that include neuroprotection, alleviation of cognitive deficits and diabetic encephalopathy (Jiang et al., 2015). Catalpol potentially attenuates inflammation-related neurodegenerative diseases and offers protection against cerebral and cardiac ischemia/reperfusion injury, as well as hepatoprotection and radioprotection (Chen et al., 2013; Fu et al., 2014; Huang et al., 2013; Liu et al., 2014; Wang et al., 2010; Zhang et al., 2013, 2007). In addition, Dong and Chen (2013), reported that catalpol reduces the kidney weight index, improves kidney function and pathological change, reducing the tissue level of angiotensin II, TGF-1, connective tissue growth factor, fibronectin, and collagen type IV. Catalpol can also down-regulate the mRNA expressions of TGF-1 and CTGF in the renal cortex and lower blood glucose concentrations in diabetic rats with nephropathy.

The therapeutic profile of catalpol appears to be related in nephrogenic diabetes with TGF-1, which is a major mediator in the development of this complication, since the high glucose concentrations up-regulate the expression of TGF-1 (Reeves and Andreoli, 2000, 2000; Ziyadeh et al., 1994). It stimulated the synthesis of ECM in the glomeruli through the TGF-1/Smad cell signaling pathway (Lan, 2012). TGF-1 mRNA expression and protein levels are increased in the glomeruli in various experimental animal diabetic models (Nakamura et al., 1993). Catalpol significantly attenuated the increase in TGF-1

protein concentrations in the renal cortex and down-regulated the expression of corresponding mRNA.

Fu et al. (2014), investigated the role of catalpol in LPS induced acute lung injury in rodents, and showed an inhibition of the ratio of wet lung to dry lung (W/D ratio), myeloperoxidase activity of lung samples, and the amounts of inflammatory cells and TNF-α, IL-6, IL-4 and IL-1β in bronchoalveolar lavage fluid (BALF) induced by LPS. Moreover, the production of IL-10 in BALF was also up-regulated by catalpol. Corroborating this data, in an *in vitro* approach, catalpol inhibited TNF-α, IL-6, IL-4 and IL-1β production and up-regulated IL-10 expression in LPS-stimulated alveolar macrophages. In addition, it is known that the activation of the NF-κB pathway has been considered as a dominant transcription factor responsible for inflammation. Because NF-κB is a key transcription factor, activated by several cellular signal transduction pathways associated with the regulation of cell survival, expression of proinflammatory cytokines and enzymes, these findings suggest that inhibition of inflammation by catalpol may be related to inactivation of the NF-kB pathway (Baldwin, 2001; Cheong et al., 2011).

Geniposide (GE) (21), another iridoid glycoside and the main bioactive compound found in fruits of the *Gardenia jasminoides*, is widely used in traditional Chinese medicine and has been considered clinically effective as a hemostatic agent and is effective in treating injuries to muscles, joints, and tendons (Wang et al., 2015). Its pharmacological actions, such as its antioxidant, antihypertensive, antiangiogenic, hypolipidemic and anti-septic properties, as well as its application in neurodegenerative disorders (such as Alzheimer's disease [AD]) have already been described in the scientific literature (Higashino et al., 2014; Park et al., 2003; Uddin et al., 2014; Y. Zhang et al., 2015b; Zheng et al., 2010). The anti-inflammatory effect of GE has been demonstrated in various pre-clinical studies. In paw edema induced by carrageenan, GE reduced the inflammatory process, also producing inhibition of vascular permeability induced by acetic acid, by downregulating the expression of Toll-like receptor 4 (TLR4) up-regulated by lipopolysaccharide (LPS) in primary mouse macrophages and mouse models (Fu et al., 2012; Koo et al., 2006).

This anti-inflammatory profile was also corroborated by Xiaofeng et al. (2012), who demonstrated in an animal model of pulmonary inflammation induced by LPS, that GE reduced levels of IL-6 and TNF-α, and increased levels of IL-10. The ability of GE to enhance IL-10 production was previously described in a lung inflammatory process induced by LPS (Cribbs et al., 2010), so IL-10 appears to be a kind of wildcard cytokine in the management of inflammation promoted by GE (Y. Deng et al., 2013b).

GE was also assessed by Lv et al. (2015), in an experimental model of AD and it was found that this iridoid suppresses the production of pro-inflammatory mediators depending on the RAGE (Receptor for advanced glycation end products) mediated signaling pathway in APP/PS1 mice. The effects of GE in this model do not seem to be related to the increased production of anti-inflammatory cytokines, but to reduce levels of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6.

The effect of GE also extends to chronic models of inflammation, in which it was able to inhibit the inflammatory response in a model of rheumatoid arthritis (RA) (Dai et al., 2014). RA is a chronic inflammatory autoimmune disease characterized by joint pain, swelling and stiffness, as well as deformity and serious functional damage (Firestein, 2003). It is believed that uncontrolled production of CD4$^+$ T-cells and Th17 regulatory T-cells (Tregs) are related to the development of RA (Wang et al., 2012). According to Dai et al. (2014), this is possibly because of the action of immune cells and an increase in the effects of Treg cells, reducing the synthesis of cytokines IL-17 and IL-6 and their pro-inflammatory effects, but mostly because of the increase in the formation of the anti-inflammatory cytokine TGF-β1. The production of anti-inflammatory cytokines may antagonize the deleterious effects of pro-inflammatory cytokines, modifying the severity of inflammation (Cribbs et al., 2010). Moreover, using the same model of RA, Chen

et al., (J.-Y. Chen et al., 2015b), reported that GE-treated rodents increased the production of IL-10 and reduced IL-1, IL-6 and TNF-α, so corroborating the hypothesis that GE may represent a potential anti-inflammatory agent due to its significant enhancement of cytokine production thereby down-regulating the inflammatory process.

Gardenia jasminoides (Rubiaceae) fruits accumulate iridoid compounds, such as genipin (**22**) which has been used as a coloring (blue) agent in the food industry (Fujikawa et al., 1987). Similarly to other iridoids, genipin also possesses a variety of pharmacological activities, including anti-microbial, hepatoprotective, and neurotrophic effects (Yamamoto et al., 2000; Yamazaki and Chiba, 2008). An anti-topical inflammatory profile of genipin has also been reported (Koo et al., 2006, 2004). This anti-inflammatory effect is related to the capacity of genipin to control pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IFN-γ, IL-2 and IL-1 which has been demonstrated in various pharmacological models including cecal ligation and puncture, LPS-induced acute systemic inflammation, hypertension-induced renal damage and sepsis induced liver injury model (Cho et al., 2016; M.-J. Kim et al., 2015c; Kim et al., 2012; Li et al., 2012; Yu et al., 2016).

Zhang et al., (A. Zhang et al., 2016a), demonstrated that the NF-κB and NLRP3 signaling pathways were inhibited in rodents pretreated with genipin in LPS-induced acute lung injury. It is already well established that genipin is able to produce a marked reduction in the levels of inflammatory cytokines such as TNF-α, IL-1β and IL-6 which have been significantly increased in BALF 7 h after LPS stimulation. Li et al. (2012), corroborated this finding, demonstrating that genipin can reduce the levels of IL-1β and TNF-α in the sera and organs of rodents.

Oleuropein (**23**) is a glycosylated seco-iridoid obtained from *Olea europaea* L., and has been shown to produce antioxidant, anti-atherosclerotic, and anti-inflammatory activities (Impellizzeri et al., 2011b). Several studies have reported that oleuropein can attenuate the levels of pro-inflammatory cytokines in various experimental models such as carrageenan-induced pleurisy, DSS (dextran sulfate sodium)-induced chronic colitis (Giner et al., 2011), doxorubicin-induced cardiomyopathy (Andreadou et al., 2014), myocardial infarction (Janahmadi et al., 2015) and BPDO (bile-pancreatic duct obstruction)-induced pancreatitis (Caglayan et al., 2015). Impellizzeri et al. (2011a), showed that oleuropein significantly attenuated the release of TNF-α and IL-1β in the pleural exudates in a carrageenan-induced pleurisy model. Oleuropein has been shown to be beneficial in controlling colorectal cancer by chemopreventive action, with oleuropein producing a significant reduction in pro-inflammatory cytokines (IL-6, IFN−γ, TNF-α and IL-17) in the colon cells (Giner et al., 2016).

Swertiamarin (**24**) is a secoiridoid glycoside found in the plants of the *Swertia* genus, and is an abundant component of many *Swertia* species, such as *Swertia mileensis*, *Swertia japonica* and *Swertia chirata* (Kshirsagar et al., 2016; Suryawanshi et al., 2006). This secoiridoid has been shown to have important and extensive pharmacological activities, including antibacterial (Kumarasamy et al., 2003), hepatoprotective, antioxidant (Jaishree and Badami, 2010), antihyperlipidemic (Vaidya et al., 2009), anticholinergic, antinociceptive, anti-inflammatory (Jaishree et al., 2009), antiedematogenic and antispastic properties (Vaijanathappa and Badami, 2009).

Recently, Saravanan et al. (2014a,b) evaluated the immunomodulatory activity of swertiamarin isolated from *Enicostema axillare* and showed the anti-inflammatory action of this compound; pretreatment with swertiamarin significantly reduced the release of TNF-α and IL-1β in sheep red blood cells. In *in vitro* studies, the treatment with swertiamarin increased mRNA and protein levels of the Th2-mediated cytokines IL-10 and IL-4 and decreased the levels of Th1-mediated cytokine IFN-γ. In general, Th1 cells which produce mainly IL-2 and IFN-γ effect immunity against intracellular pathogens, while Th2 cells producing mainly IL-4, IL-5, IL-10, IL-and 13 are responsible for the elimination of extracellular pathogens. The modulation of these targets in the swertiamarin treatment suggested its immunosuppressive activity resulted from increasing Th2-mediated anti-inflammatory

cytokines (IL-10 and IL-4) and inducing a humoral immune response.

5. FPR modulation by essential oil

The formyl peptide receptors (FPRs) are chemotactic G protein-coupled receptors which help to control the inflammation, as well as participating in the processes of many pathophysiologic conditions (Dahlgren et al., 2016; Filepa et al., 2018). FPRs were originally discovered as receptors that bind highly conserved N-formyl methionine-containing protein and peptide sequences of bacterial and mitochondrial origin, (Schiffmann et al., 1975), which represent major pro-inflammatory products. Earlier investigations conducted into the expression of FPRs in human cells and tissues showed the immunoreactivity of FPR was observed in hepatocytes, fibroblasts, astrocytes, neurons of the autonomic nervous system, lung and lung carcinoma cells, thyroid, adrenal glands, heart, the tunica media of coronary arteries, endothelial cells, uterus, ovary, testis, placenta, kidney, stomach and colon (Migeotte et al., 2006; Devosse et al., 2009; Shao et al., 2011; Prevete et al., 2015). Recent studies reported that some essential oil components of medicinal plants and products were able to modulate some of these neutrophil functional responses (Schepetkin et al., 2015, 2016). These authors also studied that plant essential oils as a source of novel therapeutics that might be developed to modulate innate immune responses and also enhance defense against microbial infection or control excessive inflammation (Schepetkin et al., 2016). Especially, α-pinene, β-pinene, and terpinen-4-ol, common monoterpenes found in Ferula oils which directly activate $[Ca^{2+}]_i$ flux in human neutrophils. In addition, essential oils from Citrus aurantium (bergamot) stimulated ROS production in human neutrophils (Cosentino et al., 2014). Eosinophil migration was inhibited by essential oils from Syzygium cumini and Psidium guajava, which have relatively high levels of β-pinene (Siani et al., 2013). Recently, new chemotactic For-Met-Leu-Phe-OMe (fMLF-OMe) analogues have been synthesized as innovative drugs that act as agonists or/and antagonists of FPRs (Mollica et al., 2006; Torino et al., 2009; Giordano et al., 2004).They can be based on the pharmacophoric groups commonly found in terpenes and other natural products associated with the modulation of inflammatory mediators by tune-up of neutrophil function (Dorward et al., 2015; He and Ye, 2017).

6. Cytokines as targets for the development of drugs

Since the first scientific evidence describing the large number of cytokines and their functional roles and involvement in molecular mechanism of various diseases or disorders researchers have targeted cytokines. (Isaacs and Lindenmann, 1957), Despite this, there is still a lack of drugs that are selective in relation to specific cytokines. This paradoxical hiatus has encouraged clinical researchers to seek solid evidence of the cytokine/disease relationship (Hur et al., 2012). Moreover, T helper Th1 and Th2 cytokines have been shown to playan important role in the mechanism of inflammation, pain, allergic and infectious processes and transplantation rejection (Gandhi et al., 2018).

Several studies and patent applications have shown a trend in the search for new drugs that act on specific cytokines that participate in crucial stages in certain diseases or clinical conditions (Jin and Dong, 2013; Oliveira et al., 2017; Bevivino and Monteleone, 2018). Cytokine therapy emerged from the need to enhance immunity for tumors using the lymphocyte activator and proliferative factor, interleukin-2 (IL-2) (Rider et al., 2016). Based on its therapeutic effectiveness in pre-clinical studies, cancer patients with renal cell carcinoma (RCC) and melanoma were treated with high doses of IL-2, but the results were double-edged due to its high toxicity, despite showing good antitumor properties (Atkins et al., 1999). Another example is the TNF-α inhibitor etanercept (Enbrel®) which was the first biopharmaceutical on the market approved by U.S. F.D.A to treats chronic autoimmune and inflammatory diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis and

psoriatic arthritis (Rider et al., 2016). A further example is, Adalimumab (Humira®), a fully human monoclonal antibody against TNF-α, that can relieve symptoms of autoimmune diseases, reduce inflammation and inhibit chronic pain (Aitken et al., 2018). The TNF-α inhibitors, certolizumab and golimumab, were also approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and Crohn's disease unresponsive to regular medications (Rider et al., 2016).

Numerous studies have shown that IL-1 and TNF-α, prototypic proinflammatory cytokines, play a pivotal role in the mechanisms involved in inflammatory disorders and chronic diseases, such as rheumatoid arthritis, neuropathic pain (NP), sepsis and septic shock (Zanotti et al., 2002; Gabay, 2002). These reviews, which demonstrated the results of clinical trials with TNF-α inhibitors and a specific IL-1 inhibitor (IL-1 receptor antagonist [IL-1Ra]), are potentially highly significant in relation to the treatment of NP, sepsis and in septic shock management. Anakinra (Kinere®), a recombinant non-glycosylated form of IL-1Ra, which can be administered at home by subcutaneous injection, is clinically indicated for the treatment of rheumatoid arthritis, but has side-effects that include headaches, and it has been shown to increase levels of cholesterol in patient blood (Rider et al., 2016).

Although some drugs already available in the pharmaceutical market which act by modulating cytokines, new drugs are urgently needed for the management of intractable inflammatory diseases or to help improve the recovery of patients with greater effectiveness and safety. Natural products, such as flavonoids and terpenes, that act as anti-inflammatory agents, painkillers, anti-allergic substances, along with other pharmacological activities are often cytokine modulators, and can, therefore, be interesting substances for the control of clinical conditions that depend on the management of strategic cytokines (Hur et al., 2012; Gandhi et al., 2018). The pro-inflammatory cytokines TNF-α, IL-1β and IL-6, and a range of others, have been shown to be important cytokines modulated by natural products. (Paul et al., 2006). Recently, our group demonstrated the effect of terpenes on inflammatory response based on the modulation of two main cytokines: TNF-α and IL-1β (Souza et al., 2014). These cytokines were the main ones described in this review (see Table 1).

Interestingly, some drugs have been shown to be effective in the regulation of cytokine production (such as IL-2, IL-10, IL-27, IL-35, IL-37 and transforming growth factor-β, TGF-β) and, therefore, having a key role in the management of certain inflammatory-based clinical conditions (Banchereau et al., 2012). The production of IL-10, an important cytokine that exerts potent immunosuppressive activity by downregulating monocytic cell and T cell activation, has been modulated by several monoterpenes (i.e. carvacrol and gamma-terpinene) in inflammatory conditions (Lima et al., 2013; Ramalho et al., 2016). The ability of IL-10 to inhibit pro-inflammatory cytokine production and its immune suppressive action can generates a cascade of beneficial effects in relation to conditions such as dysfunctional pain, rheumatoid arthritis, inflammatory bowel disease, psoriasis, organ transplantation, and chronic hepatitis C (Asadullah et al., 2003). Therefore, monoterpenes that stimulate IL-10 are promising drugs for the treatment of intractable diseases or those for which there is not a large therapeutic arsenal available.

Additionally, natural products have been shown to be a source of new substances with immunosuppressive activity that can reduce cytokine production by targeting the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, a strategic route for the management of cancer and other difficult to treat diseases (O'Shea et al., 2005; Butturini et al., 2011). The JAK-STAT pathway plays a major role in the orchestration of the immune system, especially in relation to cytokine receptors. Despite this promising pharmacological profile, few studies have addressed this hypothesis of the mechanism of action at a molecular depth, meaning that treatments using this pathway remain little studied, particularly in relation to monoterpenes. This was corroborated by our review which shows an absence of studies with this approach (Table 1).

The future of new drugs that act on cytokines can be based on families of cytokines and their molecular pathways; natural products, such as monoterpenes, appear to be promising chemical entities with innovative mechanism of action for targeting different cytokines (Souza et al., 2014; Gandhi et al., 2018). In particular, monoterpenes which act on the cytokines TNF-α and IL-1β appear to be promising targets, as well as those that stimulate the production of anti-inflammatory cytokines such as IL-10, in the development of anti-inflammatory, analgesic and immunomodulator drugs. Thus, this review summarized the experimental evidence in order to highlight the major monoterpenes with the ability to modulate cytokines as a starting point for further clinical studies and the development of novel drugs.

7. Conclusion

For more than a decade, many researchers have studied the effects of different monoterpenes on modulating the inflammatory cascade through *in vivo* and *in vitro* assays. The chemical characteristics and pharmacological properties of monoterpenes have been of interest to researchers, laboratories and pharmaceutical companies, with their anti-inflammatory and analgesic effects being identified as the most essential due to their abilities to modulate cytokines, act on important neurotransmitter systems responsible for generating and transmitting pain and their antioxidant profiles (Guimarães et al., 2013; Oliveira et al., 2017; Pina et al., 2017). In this review, we summarized the current knowledge on monoterpenes that possess anti-inflammatory effects and are able to modulate the release of anti-inflammatory and pro-inflammatory cytokines, as well as suggesting which monoterpenoid molecules are the most important in terms of an effective approach to treating inflammatory disease.

This review described 24 monoterpenes that regulate cytokine release and the levels of others inflammatory mediators. Several different inflammatory markers were evaluated as a target of monoterpenes across the studies included within the review. The pro-inflammatory and anti-inflammatory cytokines found were TNF-α, IL-1β, IL-2, IL-5, IL-4, IL-6, IL-8, IL-10, IL-12 IL-13, IL-17A, IFNγ, TGF-β1 and IFN-γ. Given the numbers of cytokines measured in the studies, details are given in Tables 1 and 2.

In summary, the reduction of one or more pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-8 was observed in almost all the monoterpenes studied. Increased levels of the anti-inflammatory cytokine IL-10 was shown to play a prominent function in the anti-inflammatory effect of monoterpenes, with this characteristics being more prevalent in alcohol monocyclic monoterpenes, such as α-terpineol, menthol and carvacrol. Downregulated production of proinflammatory cytokines and mediators, and up-regulated release of anti-inflammatory cytokines serve as key mechanisms in the management of inflammatory responses. Several anti-inflammatory molecules against pro-inflammatory cytokines such as IL-6 and TNF-α have already entered clinical trials as a potential treatments for inflammatory disorders (Reinhart and Karzai, 2001).

Furthermore, our survey provides evidence that NF-κB signaling is one of the most important pathways for the anti-inflammatory action of monoterpenes. The transcription factor NF-κB plays an important role in inflammation progression. Upon activation of the inflammation processes, NF-κB induces the expression of many inflammatory genes, including COX-2 and iNOS which influences the expression of proinflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-8 which are crucial factors in the inflammatory process. Moreover, monoterpenes such as linalool, carvacrol, and *D*-limonene downregulate the NF-κB pathways, consequently inhibiting the expression of inflammatory mediators and suppressing the progression of inflammation.

In conclusion, the major pharmacological property of these 24 monoterpenes is ability to attenuate inflammatory response by modulating the production of cytokines. Despite the compelling evidence of the substantial anti-inflammatory effects of monoterpenes, the lack of

controlled clinical studies (phase II studies), potential toxicity and their short half-life means that further studies are necessary. Hopewe have provided a compelling and exciting insight into the current understanding of the intriguing properties of these monoterpenes and their possible role in new anti-inflammatory drugs.

Declarations of interest

None.

Transparency document

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References

Abegaz, B., Yohannes, P.G., Dieter, R.K., 1983. Constituents of the essential oil of Ethiopian cymbopogon citratus stapf. J. Nat. Prod. 46, 424–426.

Aeschbach, R., Löliger, J., Scott, B.C., Murcia, A., Butler, J., Halliwell, B., Aruoma, O.I., 1994. Antioxidant actions of thymol, carvacrol, 6-gingerol, zingerone and hydroxytyrosol. Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc. 32, 31–36.

Ahmad, A., Misra, L.N., 1994. Terpenoids from Artemisia annua and constituents of its essential oil. Phytochemistry. Int. J. Plant Biochem. 37, 183–186. https://doi.org/10.1016/0031-9422(94)85021-6.

Ahmad, S.T., Arjumand, W., Seth, A., Nafees, S., Rashid, S., Ali, N., Sultana, S., 2011. Preclinical renal cancer chemopreventive efficacy of geraniol by modulation of multiple molecular pathways. Toxicology 290, 69–81. https://doi.org/10.1016/j.tox.2011.08.020.

Aitken, D., Laslett, L.L., Pan, F., Haugen, I.K., Otahal, P., Bellamy, N., Bird, P., Jones, G.A., 2018. Randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand Osteoarthritis - the HUMOR trial. Osteoarthritis Cartilage 26, 880–887. https://doi.org/10.1016/j.joca.2018.02.899. Epub 2018 Mar 2.

Almeida, J.R.G. da S., Souza, G.R., Silva, J.C., Saraiva, S.R.G. de L., Júnior, R.G. de O., Quintans, J. de S.S., Barreto, R. de S.S., Bonjardim, L.R., Cavalcanti, S.C. de H., Quintans, L.J., 2013. Borneol, a bicyclic monoterpene alcohol, reduces nociceptive behavior and inflammatory response in mice. ScientificWorldJournal 2013, 808460. https://doi.org/10.1155/2013/808460.

Amsel, R., Totten, P.A., Spiegel, C.A., Chen, K.C., Eschenbach, D., Holmes, K.K., 1983. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am. J. Med. 74, 14–22.

Andreadou, I., Mikros, E., Ioannidis, K., Sigala, F., Naka, K., Kostidis, S., Farmakis, D., Tenta, R., Kavantzas, N., Bibli, S.-I., Gikas, E., Skaltsounis, L., Kremastinos, D.T., Iliodromitis, E.K., 2014. Oleuropein prevents doxorubicin-induced cardiomyopathy interfering with signaling molecules and cardiomyocyte metabolism. J. Mol. Cell. Cardiol. 69, 4–16. https://doi.org/10.1016/j.yjmcc.2014.01.007.

Arigesavan, K., Sudhandiran, G., 2015. Carvacrol exhibits anti-oxidant and anti-inflammatory effects against 1, 2-dimethyl hydrazine plus dextran sodium sulfate induced inflammation associated carcinogenicity in the colon of Fischer 344 rats. Biochem. Biophys. Res. Commun. 461, 314–320. https://doi.org/10.1016/j.bbrc.2015.04.030.

Aristatile, B., Al-Assaf, A.H., Pugalendi, K.V., 2013. Carvacrol suppresses the expression of inflammatory marker genes in D-galactosamine-hepatotoxic rats. Asian Pac. J. Trop. Med. 6, 205–211. https://doi.org/10.1016/S1995-7645 (13)60024-3.

Asadullah, K., Sterry, W., Volk, H.D., 2003. Interleukin-10 therapy - review of a new approach. Pharmacol. Rev. 55, 241–269.

Atkins, M.B., Lotze, M.T., Dutcher, J.P., et al., 1999. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J. Clin. Oncol. 17, 2105–2116.

Aumeeruddy-Elalfi, Z., Lall, N., Fibrich, B., Staden, A.B., Hosenally, M., Mahomoodally, M.F., 2018 Jan. Selected essential oils inhibit key physiological enzymes and possess intracellular and extracellular antimelanogenic properties in vitro. J. Food Drug Anal. 26 (1), 232–243. https://doi.org/10.1016/j.jfda.2017.03.002.

Babu, R.O., Moorkoth, D., Azeez, S., Eapen, S.J., 2012. Virtual screening and in vitro assay of potential drug like inhibitors from spices against Glutathione-S-Transferase of Meloidogyne incognita. Bioinformation 8, 319–325. https://doi.org/10.6026/97320630008319.

Bachiega, T.F., Sforcin, J.M., 2011. Lemongrass and citral effect on cytokines production by murine macrophages. J. Ethnopharmacol. 137, 909–913. https://doi.org/10.1016/j.jep.2011.07.021.

Bae, G.-S., Park, K.-C., Choi, S.B., Jo, I.-J., Choi, M.-O., Hong, S.-H., Song, K., Song, H.-J., Park, S.-J., 2012. Protective effects of alpha-pinene in mice with cerulein-induced acute pancreatitis. Life Sci. 91, 866–871. https://doi.org/10.1016/j.lfs.2012.08.035.

Bailey, H.H., Levy, D., Harris, L.S., Schink, J.C., Foss, F., Beatty, P., Wadler, S., 2002. A phase II trial of daily perillyl alcohol in patients with advanced ovarian cancer: eastern Cooperative Oncology Group Study E2E96. Gynecol. Oncol. 85, 464–468.

Bakkali, F., Averbeck, S., Averbeck, D., Idaomar, M., 2008. Biological effects of essential oils–a review. Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc. 46, 446–475. https://doi.org/10.1016/j.fct.2007.09.106.

Baldwin, A.S., 2001. Control of oncogenesis and cancer therapy resistance by the transcription factor NF-kappaB. J. Clin. Invest. 107, 241–246. https://doi.org/10.1172/JCI11991.

Banchereau, J., Pascual, V., O'Garra, A., 2012. From IL-2 to IL-37: the expanding spectrum of anti-inflammatory cytokines. Nat. Immunol. 13, 925–931. https://doi.org/10.1038/ni.2406.

Baser, K.H.C., 2008. Biological and pharmacological activities of carvacrol and carvacrol bearing essential oils. Curr. Pharmaceut. Des. 14, 3106–3119.

Bastos, V.P.D., Gomes, A.S., Lima, F.J.B., Brito, T.S., Soares, P.M.G., Pinho, J.P.M., Silva, C.S., Santos, A.A., Souza, M.H.L.P., Magalhães, P.J.C., 2011. Inhaled 1,8-cineole reduces inflammatory parameters in airways of ovalbumin-challenged Guinea pigs. Basic Clin. Pharmacol. Toxicol. 108, 34–39. https://doi.org/10.1111/j.1742-7843.2010.00622.x.

Bevivino, G., Monteleone, G., 2018. Advances in understanding the role of cytokines in inflammatory bowel disease. Expet Rev. Gastroenterol. Hepatol. 12, 907–915. https://doi.org/10.1080/17474124.2018.1503053.

Bhatia, S.P., McGinty, D., Letizia, C.S., Api, A.M., 2008. Fragrance material review on isoborneol. Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc. 46 (Suppl. 11), S182–S184. https://doi.org/10.1016/j.fct.2008.06.052.

Bonjardim, L.R., Cunha, E.S., Guimarães, A.G., Santana, M.F., Oliveira, M.G.B., Serafini, M.R., Araújo, A.A.S., Antoniolli, A.R., Cavalcanti, S.C.H., Santos, M.R.V., Quintans-Júnior, L.J., 2012. Evaluation of the anti-inflammatory and antinociceptive properties of p-cymene in mice. Z. Naturforschung C J. Biosci. 67, 15–21.

Brito, R.G., Guimarães, A.G., Quintans, J.S.S., Santos, M.R.V., De Sousa, D.P., Badaue-Passos, D., de Lucca, W., Brito, F.A., Barreto, E.O., Oliveira, A.P., Quintans, L.J., 2012. Citronellol, a monoterpene alcohol, reduces nociceptive and inflammatory activities in rodents. J. Nat. Med. 66, 637–644. https://doi.org/10.1007/s11418-012-0632-4.

Brito, R.G., Santos, P.L., Prado, D.S., Santana, M.T., Araújo, A.A.S., Bonjardim, L.R., Santos, M.R.V., de Lucca Júnior, W., Oliveira, A.P., Quintans-Júnior, L.J., 2013. Citronellol reduces orofacial nociceptive behaviour in mice - evidence of involvement of retrosplenial cortex and periaqueductal grey areas. Basic Clin. Pharmacol. Toxicol. 112, 215–221. https://doi.org/10.1111/bcpt.12018.

Brown, M.A., 2008. IL-4 production by T cells: you need a little to get a lot. J. Immunol. 181, 2941–2942 Baltim. Md 1950.

Butturini, E., Cavalieri, E., Carcereri de Prati, A., et al., 2011. Two Naturally Occurring Terpenes, Dehydrocostuslactone and Costunolide, Decrease Intracellular GSH Content and Inhibit STAT3 Activation. Srivastava RK, ed.. PloS One 6, e20174. https://doi.org/10.1371/journal.pone.0020174.

Caglayan, K., Güngör, B., Cinar, H., Avci, B., Gur, S., Arslan, N., 2015. Effects of oleuropein on serum inflammatory cytokines and histopathological changes in rats with pancreatitis. Adv. Clin. Exp. Med. Off. Organ Wroclaw Med. Univ. 24, 213–218.

Celik, F., Gocmez, C., Bozkurt, M., Kaplan, I., Kamasak, K., Akil, E., Dogan, E., Guzel, A., Uzar, E., 2013. Neuroprotective effects of carvacrol and pomegranate against methotrexate-induced toxicity in rats. Eur. Rev. Med. Pharmacol. Sci. 17, 2988–2993.

Chen, X., Liu, C., Lu, Y., Yang, Z., Lv, Z., Xu, Q., Pan, Q., Lu, L., 2012. Paeoniflorin regulates macrophage activation in dimethylnitrosamine-induced liver fibrosis in rats. BMC Complement Altern. Med. 12, 254. https://doi.org/10.1186/1472-6882-12-254.

Chen, C., Chen, Z., Xu, F., Zhu, C., Fang, F., Shu, S., Li, M., Ling, C., 2013. Radio-protective effect of catalpol in cultured cells and mice. J. Radiat. Res. 54, 76–82. https://doi.org/10.1093/jrr/rrs080.

Chen, L., Zhao, L., Zhang, C., Lan, Z., 2014a. Protective effect of p-cymene on lipopolysaccharide-induced acute lung injury in mice. Inflammation 37, 358–364. https://doi.org/10.1007/s10753-013-9747-3.

Chen, N., Sun, G., Yuan, X., Hou, J., Wu, Q., Soromou, L.W., Feng, H., 2014b. Inhibition of lung inflammatory responses by bornyl acetate is correlated with regulation of myeloperoxidase activity. J. Surg. Res. 186, 436–445. https://doi.org/10.1016/j.jss.2013.09.003.

Chen, C., Du, P., Wang, J., 2015a. Paeoniflorin ameliorates acute myocardial infarction of rats by inhibiting inflammation and inducible nitric oxide synthase signaling pathways. Mol. Med. Rep. 12, 3937–3943. https://doi.org/10.3892/mmr.2015.3870.

Chen, J.-Y., Wu, H., Li, H., Hu, S.-L., Dai, M., Chen, J., 2015b. Anti-inflammatory effects and pharmacokinetics study of geniposide on rats with adjuvant arthritis. Int. Immunopharm. 24, 102–109. https://doi.org/10.1016/j.intimp.2014.11.017.

Chen, Y., Zhang, Y., Xu, M., Luan, J., Piao, S., Chi, S., Wang, H., 2017. Catalpol alleviates ovalbumin-induced asthma in mice: reduced eosinophil infiltration in the lung. Int. Immunopharm. 43, 140–146. https://doi.org/10.1016/j.intimp.2016.12.011.

Cheong, M.-H., Lee, S.-R., Yoo, H.-S., Jeong, J.-W., Kim, G.-Y., Kim, W.-J., Jung, I.-C., Choi, Y.H., 2011. Anti-inflammatory effects of Polygala tenuifolia root through inhibition of NF-κB activation in lipopolysaccharide-induced BV2 microglial cells. J. Ethnopharmacol. 137, 1402–1408. https://doi.org/10.1016/j.jep.2011.08.008.

Cho, S., Choi, Y., Park, S., Park, T., 2012. Carvacrol prevents diet-induced obesity by modulating gene expressions involved in adipogenesis and inflammation in mice fed with high-fat diet. J. Nutr. Biochem. 23, 192–201. https://doi.org/10.1016/j.jnutbio.2010.11.016.

Cho, H.-I., Kim, S.-J., Choi, J.-W., Lee, S.-M., 2016. Genipin alleviates sepsis-induced liver

injury by restoring autophagy. Br. J. Pharmacol. 173, 980–991. https://doi.org/10.1111/bph.13397.

Cicuttini, F.M., Byron, K.A., Maher, D., Wootton, A.M., Muirden, K.D., Hamilton, J.A., 1995. Serum IL-4, IL-10 and IL-6 levels in inflammatory arthritis. Rheumatol. Int. 14, 201–206.

Cosentino, M., Luini, A., Bombelli, R., Corasaniti, M.T., Bagetta, G., Marino, F., 2014. The essential oil of bergamot stimulates reactive oxygen species production in human polymorphonuclear leukocytes. Phytother Res. 28, 1232–1239. https://doi.org/10.1002/ptr.5121.

Craig, R., Larkin, A., Mingo, A.M., Thuerauf, D.J., Andrews, C., McDonough, P.M., Glembotski, C.C., 2000. p38 MAPK and NF-kappa B collaborate to induce interleukin-6 gene expression and release. Evidence for a cytoprotective autocrine signaling pathway in a cardiac myocyte model system. J. Biol. Chem. 275, 23814–23824. https://doi.org/10.1074/jbc.M909695199.

Craveiro, A.A., Fernandes, A.G., Andrade, C.H.S., Matos, F.J.A., Alencar, J.W., Machado, M.I.L., 1981. Óleos essenciais de Plantas do Nordeste. pages 210.

Cribbs, S.K., Matthay, M.A., Martin, G.S., 2010. Stem cells in sepsis and acute lung injury. Crit. Care Med. 38, 2379–2385. https://doi.org/10.1097/CCM.0b013e3181f96f5f.

Crowell, P.L., 1999. Prevention and therapy of cancer by dietary monoterpenes. J. Nutr. 129, 775S–778S. https://doi.org/10.1093/jn/129.3.775S.

Cui, Z., Xie, Z., Wang, B., Zhong, Z., Chen, X., Sun, Y., Sun, Q., Yang, G., Bian, L., 2015. Carvacrol protects neuroblastoma SH-SY5Y cells against Fe(2+)-induced apoptosis by suppressing activation of MAPK/JNK-NF-κB signaling pathway. Acta Pharmacol. Sin. 36, 1426–1436. https://doi.org/10.1038/aps.2015.90.

Culbert, A.A., Skaper, S.D., Howlett, D.R., Evans, N.A., Facci, L., Soden, P.E., Seymour, Z.M., Guillot, F., Gaestel, M., Richardson, J.C., 2006. MAPK-activated protein kinase 2 deficiency in microglia inhibits pro-inflammatory mediator release and resultant neurotoxicity. Relevance to neuroinflammation in a transgenic mouse model of Alzheimer disease. J. Biol. Chem. 281, 23658–23667. https://doi.org/10.1074/jbc.M513646200.

Curfs, J.H., Meis, J.F., Hoogkamp-Korstanje, J.A., 1997. A primer on cytokines: sources, receptors, effects, and inducers. Clin. Microbiol. Rev. 10, 742–780.

d'Alessio, P.A., Mirshahi, M., Bisson, J.-F., Bene, M.C., 2014. Skin repair properties of d-Limonene and perillyl alcohol in murine models. Anti-Inflammatory Anti-Allergy Agents Med. Chem. 13, 29–35.

Dahlgren, C., Gabl, M., Holdfeldt, A., Winther, M., Forsman, H., 2016. Basic characteristics of the neutrophil receptors that recognize formylated peptides, a danger-associated molecular pattern generated by bacteria and mitochondria. Biochem. Pharmacol. 114, 29–39. https://doi.org/10.1016/j.bcp.2016.04.014.

Dai, M.-M., Wu, H., Li, H., Chen, J., Chen, J.-Y., Hu, S.-L., Shen, C., 2014. Effects and mechanisms of Geniposide on rats with adjuvant arthritis. Int. Immunopharm. 20, 46–53. https://doi.org/10.1016/j.intimp.2014.02.021.

Dantas, M.G.B., Reis, S.A.G.B., Damasceno, C.M.D., Rolim, L.A., Rolim-Neto, P.J., Carvalho, F.O., Quintans-Junior, L.J., Almeida, J.R.G. da S., 2016. Development and evaluation of stability of a gel formulation containing the monoterpene borneol. ScientificWorldJournal 2016, 7394685. https://doi.org/10.1155/2016/7394685.

Dardalhon, V., Awasthi, A., Kwon, H., Galileos, G., Gao, W., Sobel, R.A., Mitsdoerffer, M., Strom, T.B., Elyaman, W., Ho, I.-C., Khoury, S., Oukka, M., Kuchroo, V.K., 2008. IL-4 inhibits TGF-beta-induced Foxp3+ T cells and, together with TGF-beta, generates IL-9+ IL-10+ Foxp3(-) effector T cells. Nat. Immunol. 9, 1347–1355.

Dassoler, M., Schwanz, M., Busseto, F., Moreira, E.A., Gutierrez, L., 2005. Perfil fitoquímico e ensaio farmacológico de Averrhoa carambola L. (Oxalidaceae). J. Bras. Fitomedicina 2, 4–8.

de Cássia da Silveira e Sá, R., Andrade, L.N., de Sousa, D.P., 2013. A review on anti-inflammatory activity of monoterpenes. Mol. Basel Switz. 18, 1227–1254. https://doi.org/10.3390/molecules18011227.

De Fazio, L., Spisni, E., Cavazza, E., Strillacci, A., Candela, M., Centanni, M., Ricci, C., Rizzello, F., Campieri, M., Valerii, M., 2016. Dietary geraniol by oral or enema administration strongly reduces dysbiosis and systemic inflammation in dextran sulfate sodium-treated mice. Front. Pharmacol. 7, 38. https://doi.org/10.3389/fphar.2016.00038.

de Oliveira, M.G.B., Marques, R.B., de Santana, M.F., Santos, A.B.D., Brito, F.A., Barreto, E.O., De Sousa, D.P., Almeida, F.R.C., Badauê-Passos, D., Antoniolli, A.R., Quintans-Júnior, L.J., 2012. α-terpineol reduces mechanical hypernociception and inflammatory response. Basic Clin. Pharmacol. Toxicol. 111, 120–125. https://doi.org/10.1111/j.1742-7843.2012.00875.x.

de Santana, M.F., Guimarães, A.G., Chaves, D.O., Silva, J.C., Bonjardim, L.R., de Lucca Júnior, W., Ferro, J.N. de S., Barreto, E. de O., dos Santos, F.E., Soares, M.B.P., Villarreal, C.F., Quintans, J. de S.S., Quintans-Júnior, L.J., 2015. The anti-hyperalgesic and anti-inflammatory profiles of p-cymene: evidence for the involvement of opioid system and cytokines. Pharm. Biol. 53, 1583–1590. https://doi.org/10.3109/13880209.2014.993040.

de Sousa, D.P., 2011. Analgesic-like activity of essential oils constituents. Mol. Basel Switz. 16, 2233–2252. https://doi.org/10.3390/molecules16032233.

de Sousa, D.P., Gonçalves, J.C.R., Quintans-Júnior, L., Cruz, J.S., Araújo, D.A.M., de Almeida, R.N., 2006a. Study of anticonvulsant effect of citronellol, a monoterpene alcohol, in rodents. Neurosci. Lett. 401, 231–235. https://doi.org/10.1016/j.neulet.2006.03.030.

de Sousa, D.P., Gonçalves, J.C.R., Quintans-Júnior, L., Cruz, J.S., Araújo, D.A.M., de Almeida, R.N., 2006b. Study of anticonvulsant effect of citronellol, a monoterpene alcohol, in rodents. Neurosci. Lett. 401, 231–235. https://doi.org/10.1016/j.neulet.2006.03.030.

De Vincenzi, M., Stammati, A., De Vincenzi, A., Silano, M., 2004. Constituents of aromatic plants: carvacrol. Fitoterapia 75, 801–804. https://doi.org/10.1016/j.fitote.2004.05.002.

Deepa, B., Venkatraman Anuradha, C., 2013. Effects of linalool on inflammation, matrix

accumulation and podocyte loss in kidney of streptozotocin-induced diabetic rats. Toxicol. Mech. Methods 23, 223–234. https://doi.org/10.3109/15376516.2012.743638.

Deng, W., Lu, H., Teng, J., 2013a. Carvacrol attenuates diabetes-associated cognitive deficits in rats. J. Mol. Neurosci. MN 51, 813–819. https://doi.org/10.1007/s12031-013-0069-6.

Deng, Y., Guan, M., Xie, X., Yang, X., Xiang, H., Li, H., Zou, L., Wei, J., Wang, D., Deng, X., 2013b. Geniposide inhibits airway inflammation and hyperresponsiveness in a mouse model of asthma. Int. Immunopharm. 17, 561–567. https://doi.org/10.1016/j.intimp.2013.06.028.

Deng, X.-Y., Li, H.-Y., Chen, J.-J., Li, R.-P., Qu, R., Fu, Q., Ma, S.-P., 2015. Thymol produces an antidepressant-like effect in a chronic unpredictable mild stress model of depression in mice. Behav. Brain Res. 291, 12–19. https://doi.org/10.1016/j.bbr.2015.04.052.

Devosse, T., Guillabert, A., D'Haene, N., Berton, A., De Nadai, P., Noel, S., et al., 2009. Formyl peptide receptor-like 2 is expressed and functional in plasmacytoid dendritic cells, tissue-specific macrophage subpopulations, and eosinophils. J. Immunol. 182, 4974–4984. https://doi.org/10.4049/jimmunol.0803128.

Dewick P. M., n.d. Alkaloids. Medicinal Natural Products: a Biosynthetic Approach.

Dinarello, C.A., 1984. Interleukin-1 and the pathogenesis of the acute-phase response. N. Engl. J. Med. 311, 1413–1418. https://doi.org/10.1056/NEJM198411293112205.

Dinarello, C.A., 2007. Historical insights into cytokines. Eur. J. Immunol. 37 (Suppl. 1), S34–S45. https://doi.org/10.1002/eji.200737772.

Dinda, B., Debnath, S., Harigaya, Y., 2007. Naturally occurring secoiridoids and bioactivity of naturally occurring iridoids and secoiridoids. A review, part 2. Chem. Pharm. Bull. (Tokyo) 55, 689–728.

do Vale, T.G., Furtado, E.C., Santos, J.G., Viana, G.S.B., 2002. Central effects of citral, myrcene and limonene, constituents of essential oil chemotypes from Lippia alba (Mill.) n.e. Brown. Phytomedicine Int. J. Phytother. 9, 709–714.

Dong, Z., Chen, C.X., 2013. Effect of catalpol on diabetic nephropathy in rats. Phytomedicine Int. J. Phytother. Phytopharm. 20, 1023–1029. https://doi.org/10.1016/j.phymed.2013.04.007.

Dorward, D.A., Lucas, C.D., Chapman, G.B., Haslett, C., Dhaliwal, K., Rossi, A.G., 2015. The role of formylated peptides and formyl peptide receptor 1 in governing neutrophil function during acute inflammation. Am. J. Pathol. 185, 1172–1184. https://doi.org/10.1016/j.ajpath.2015.01.020.

Duelund, L., Amiot, A., Fillon, A., Mouritsen, O.G., 2012. Influence of the active compounds of Perilla frutescens leaves on lipid membranes. J. Nat. Prod. 75, 160–166. https://doi.org/10.1021/np200713q.

Dutra, F.L., Oliveira, M.M., Santos, R.S., Silva, W.S., Alviano, D.S., Vieira, D.P., Lopes, A.H., 2016. Effects of linalool and eugenol on the survival of Leishmania (L.) infantum chagasi within macrophages. Acta Trop. 164, 69–76. https://doi.org/10.1016/j.actatropica.2016.08.026.

Elaissi, A., Rouis, Z., Mabrouk, S., Salah, K.B.H., Aouni, M., Khouja, M.L., Farhat, F., Chemli, R., Harzallah-Skhiri, F., 2012. Correlation between chemical composition and antibacterial activity of essential oils from fifteen Eucalyptus species growing in the Korbous and Jbel Abderrahman arboreta (North East Tunisia). Mol. Basel Switz. 17, 3044–3057. https://doi.org/10.3390/molecules17033044.

Elalfi, A.Z., Fakim, A.G., Mahomoodally, M.F., 2015. Antimicrobial, antibiotic potentiating activity and phytochemical profile of essential oils from exotic and endemic medicinal plants of Mauritius. Ind. Crop. Prod. 71, 197–204.

Elalfi, A.Z., Fakim, A.G., Mahomoodally, M.F., 2016a. Chemical composition, antimicrobial and antibiotic potentiating activity of essential oils from 10 tropical medicinal plants from Mauritius. J. Herb. Med. 6, 88–95.

Elalfi, A.Z., Fakim, A.G., Mahomoodally, M.F., 2016b. Kinetic studies of tyrosinase inhibitory activity of 19 essential oils extracted from endemic and exotic medicinal plants. South Afr. J. Bot. 103, 89–94. https://doi.org/10.1016/j.sajb.2015.09.

Elegbede, J.A., Flores, R., Wang, R.C., 2003. Perillyl alcohol and perillaldehyde induced cell cycle arrest and cell death in BroTo and A549 cells cultured in vitro. Life Sci. 73, 2831–2840.

Evstatieva, L., Todorova, M., Antonova, D., Staneva, J., 2010. Chemical composition of the essential oils of Rhodiola rosea L. of three different origins. Pharmacogn. Mag. 6, 256–258. https://doi.org/10.4103/0973-1296.71782.

Falcão, H., Lima, I.O., Santos, V.L., Dantas, H.F., Diniz, M.F.F.M., Barbosa-Filho, J.M., Batista, L.M., 2005. Review of the plants with anti-inflammatory activity studied in Brazil. Br. J. Pharmacol. 15, 381–391.

Feng, X., Jia, A., 2014. Protective effect of carvacrol on acute lung injury induced by lipopolysaccharide in mice. Inflammation 37, 1091–1101. https://doi.org/10.1007/s10753-014-9833-1.

Ferrero-Miliani, L., Nielsen, O.H., Andersen, P.S., Girardin, S.E., 2007. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1beta generation. Clin. Exp. Immunol. 147, 227–235. https://doi.org/10.1111/j.1365-2249.2006.03261.x.

Filepa, J.G., Sekheri, M., Kebir, D.E., 2018. Targeting formyl peptide receptors to facilitate the resolution of inflammation. Eur. J. Pharmacol. 833, 339–348. https://doi.org/10.1016/j.ejphar.2018.06.025.

Firestein, G.S., 2003. Evolving concepts of rheumatoid arthritis. Nature 423, 356–361. https://doi.org/10.1038/nature01661.

Franchome, P., Penoel, D., 1995. L"Aromathérapie Exactement: Encyclopedie de l"Utilisation Thérapeutique des Huiles Essentielles. Roger Jollois Edition.

Fresno, M., Alvarez, R., Cuesta, N., 2011. Toll-like receptors, inflammation, metabolism and obesity. Arch. Physiol. Biochem. 117, 151–164. https://doi.org/10.3109/13813455.2011.562514.

Fu, Y., Liu, B., Liu, J., Liu, Z., Liang, D., Li, F., Li, D., Cao, Y., Zhang, X., Zhang, N., Yang, Z., 2012. Geniposide, from Gardenia jasminoides Ellis, inhibits the inflammatory response in the primary mouse macrophages and mouse models. Int. Immunopharm. 14, 792–798. https://doi.org/10.1016/j.intimp.2012.07.006.

Fu, K., Piao, T., Wang, M., Zhang, J., Jiang, J., Wang, X., Liu, H., 2014. Protective effect of catalpol on lipopolysaccharide-induced acute lung injury in mice. Int. Immunopharm. 23, 400–406. https://doi.org/10.1016/j.intimp.2014.07.011.

Fujikawa, S., Fukui, Y., Koga, K., Kumada, J., 1987. Brilliant skyblue pigment formation from gardenia fruits. J. Ferment. Technol. 65, 419–424. https://doi.org/10.1016/0385-6380(87)90138-5.

Gabay, C., 2002. Cytokine inhibitors in the treatment of rheumatoid arthritis. Expet Opin. Biol. Ther. 2, 135–149.

Gandhi, G.R., Neta, M.T.S.L., Sathiyabama, R.G., Quintans, J.S.S., de Oliveira, E.S.A.M., Araújo, A.A.S., Narain, N., Quintans-Júnior, L.J., Gurgel, R.Q., 2018. Flavonoids as Th1/Th2 cytokines immunomodulators: a systematic review of studies on animal models. Phytomedicine 44, 74–84.

Giner, E., Andújar, I., Recio, M.C., Ríos, J.L., Cerdá-Nicolás, J.M., Giner, R.M., 2011. Oleuropein ameliorates acute colitis in mice. J. Agric. Food Chem. 59, 12882–12892. https://doi.org/10.1021/jf203715m.

Giner, E., Recio, M.-C., Ríos, J.-L., Giner, R.-M., 2013. Oleuropein protects against dextran sodium sulfate-induced chronic colitis in mice. J. Nat. Prod. 76, 1113–1120. https://doi.org/10.1021/np400175b.

Giner, E., Recio, M.C., Ríos, J.L., Cerdá-Nicolás, J.M., Giner, R.M., 2016. Chemopreventive effect of oleuropein in colitis-associated colorectal cancer in c57bl/6 mice. Mol. Nutr. Food Res. 60, 242–255. https://doi.org/10.1002/mnfr.201500605.

Ginhoux, F., Jung, S., 2014. Monocytes and macrophages: developmental pathways and tissue homeostasis. Nat. Rev. Immunol. 14, 392–404. https://doi.org/10.1038/nri3671.

Giordano, C., Lucente, G., Mollica, A., Nalli, M., Pagani Zecchini, G., Paglialunga Paradisi, M., Gavuzzo, E., Mazza, F., Spisani, S., 2004. Hybrid < alpha > / < beta > 3-petides with proteinogenic side chains. Monosubstituted analogues of the chemotactic tripeptide For-Met-Leu-Phe-OMe. J. Pept. Sci. 10, 510–523. https://doi.org/10.1002/psc.562.

Gomes, B.S., Neto, B.P.S., Lopes, E.M., Cunha, F.V.M., Araújo, A.R., Wanderley, C.W.S., Wong, D.V.T., Júnior, R.C.P.L., Ribeiro, R.A., Sousa, D.P., Venes R Medeiros, J., Oliveira, R.C.M., Oliveira, F.A., 2017. Anti-inflammatory effect of the monoterpene myrtenol is dependent on the direct modulation of neutrophil migration and oxidative stress. Chem. Biol. Interact. 273, 73–81. https://doi.org/10.1016/j.cbi.2017.05.019.

Gordon, S., Martinez, F.O., 2010. Alternative activation of macrophages: mechanism and functions. Immunity 32, 593–604. https://doi.org/10.1016/j.immuni.2010.05.007.

Gordon, S., Taylor, P.R., 2005. Monocyte and macrophage heterogeneity. Nat. Rev. Immunol. 5, 953–964. https://doi.org/10.1038/nri1733.

Greiner, J.F.-W., Müller, J., Zeuner, M.-T., Hauser, S., Seidel, T., Klenke, C., Grunwald, L.-M., Schomann, T., Widera, D., Sudhoff, H., Kaltschmidt, B., Kaltschmidt, C., 2013. 1,8-Cineol inhibits nuclear translocation of NF-κB p65 and NF-κB-dependent transcriptional activity. Biochim. Biophys. Acta 1833, 2866–2878. https://doi.org/10.1016/j.bbamcr.2013.07.001.

Guimarães, A.G., Oliveira, G.F., Melo, M.S., Cavalcanti, S.C.H., Antoniolli, A.R., Bonjardim, L.R., Silva, F.A., Santos, J.P.A., Rocha, R.F., Moreira, J.C.F., Araújo, A.A.S., Gelain, D.P., Quintans-Júnior, L.J., 2010. Bioassay-guided evaluation of antioxidant and antinociceptive activities of carvacrol. Basic Clin. Pharmacol. Toxicol. 107, 949–957. https://doi.org/10.1111/j.1742-7843.2010.00609.x.

Guimarães, A.G., Xavier, M.A., de Santana, M.T., Camargo, E.A., Santos, C.A., Brito, F.A., Barreto, E.O., Cavalcanti, S.C.H., Antoniolli, A.R., Oliveira, R.C.M., Quintans-Júnior, L.J., 2012. Carvacrol attenuates mechanical hypernociception and inflammatory response. Naunyn-Schmiedeberg's Arch. Pharmacol. 385, 253–263. https://doi.org/10.1007/s00210-011-0715-x.

Guimarães, A.G., Quintans, J.S.S., Quintans, L.J., 2013. Monoterpenes with analgesic activity–a systematic review. Phytother. Res. PTR 27, 1–15. https://doi.org/10.1002/ptr.4686.

Guimarães, A.G., Serafini, M.R., Quintans-Júnior, L.J., 2014. Terpenes and derivatives as a new perspective for pain treatment: a patent review. Expert Opin. Ther. Pat. 24, 243–265. https://doi.org/10.1517/13543776.2014.870154.

Guimarães, A.G., Oliveira, M.A., Alves, R. dos S., Menezes, P. dos P., Serafini, M.R., Araújo, A.A. de S., Bezerra, D.P., Quintans Júnior, L.J., 2015. Encapsulation of carvacrol, a monoterpene present in the essential oil of oregano, with β-cyclodextrin, improves the pharmacological response on cancer pain experimental protocols. Chem. Biol. Interact. 227, 69–76. https://doi.org/10.1016/j.cbi.2014.12.020.

Gunaseelan, S., Balupillai, A., Govindasamy, K., Ramasamy, K., Muthusamy, G., Shanmugam, M., Thangaiyan, R., Robert, B.M., Prasad Nagarajan, R., Ponniresan, V.K., Rathinaraj, P., 2017. Linalool prevents oxidative stress activated protein kinases in single UVB-exposed human skin cells. PloS One 12, e0176699. https://doi.org/10.1371/journal.pone.0176699.

Guo, R.-B., Wang, G.-F., Zhao, A.-P., Gu, J., Sun, X.-L., Hu, G., 2012. Paeoniflorin protects against ischemia-induced brain damages in rats via inhibiting MAPKs/NF-κB-mediated inflammatory responses. PloS One 7, e49701. https://doi.org/10.1371/journal.pone.0049701.

Gurgis, F.M.S., Ziaziaris, W., Munoz, L., 2014. Mitogen-activated protein kinase-activated protein kinase 2 in neuroinflammation, heat shock protein 27 phosphorylation, and cell cycle: role and targeting. Mol. Pharmacol. 85, 345–356. https://doi.org/10.1124/mol.113.090365.

Hansen, J.S., Nørgaard, A.W., Koponen, I.K., Sørli, J.B., Paidi, M.D., Hansen, S.W.K., Clausen, P.A., Nielsen, G.D., Wolkoff, P., Larsen, S.T., 2016. Limonene and its ozone-initiated reaction products attenuate allergic lung inflammation in mice. J. Immunot. 13, 793–803. https://doi.org/10.1080/1547691X.2016.1195462.

Haroon, E., Raison, C.L., Miller, A.H., 2012. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 37,

137–162. https://doi.org/10.1038/npp.2011.205.

Hassan, S.B., Gali-Muhtasib, H., Göransson, H., Larsson, R., 2010. Alpha terpineol: a potential anticancer agent which acts through suppressing NF-kappaB signalling. Anticancer Res. 30, 1911–1919.

Hawes, S.E., Hillier, S.L., Benedetti, J., Stevens, C.E., Koutsky, L.A., Wolner-Hanssen, P., Holmes, K.K., 1996. Hydrogen peroxide-producing lactobacilli and acquisition of vaginal infections. J. Infect. Dis. 174, 1058–1063.

Hayden, M.S., Ghosh, S., 2012. NF-κB, the first quarter-century: remarkable progress and outstanding questions. Genes Dev. 26, 203–234. https://doi.org/10.1101/gad.183434.111.

He, D.-Y., Dai, S.-M., 2011. Anti-inflammatory and immunomodulatory effects of paeonia lactiflora pall., a traditional Chinese herbal medicine. Front. Pharmacol. 2, 10. https://doi.org/10.3389/fphar.2011.00010.

He, H.Q., Ye, R.D., 2017. The formyl peptide receptors: diversity of ligands and mechanism for recognition. Molecules 22https://doi.org/10.3390/molecules22030455. pii: E455.

He, X.J., Jian, L.Y., Liu, Y.L., 2006. Protective effects of borneol injection on experimental cerebral ischemia in mice. J. Xinxiang Med. Coll. 23 (1), 23–251.

Held, S., Schieberle, P., Somoza, V., 2007. Characterization of alpha-terpineol as an anti-inflammatory component of orange juice by in vitro studies using oral buccal cells. J. Agric. Food Chem. 55, 8040–8046. https://doi.org/10.1021/jf071691m.

Higashino, S., Sasaki, Y., Giddings, J.C., Hyodo, K., Sakata, S.F., Matsuda, K., Horikawa, Y., Yamamoto, J., 2014. Crocetin, a carotenoid from Gardenia jasminoides Ellis, protects against hypertension and cerebral thrombogenesis in stroke-prone spontaneously hypertensive rats. Phytother. Res. PTR 28, 1315–1319. https://doi.org/10.1002/ptr.5130.

Hong, E.-J., Na, K.-J., Choi, I.-G., Choi, K.-C., Jeung, E.-B., 2004. Antibacterial and antifungal effects of essential oils from coniferous trees. Biol. Pharm. Bull. 27, 863–866.

Hotta, M., Nakata, R., Katsukawa, M., Hori, K., Takahashi, S., Inoue, H., 2010. Carvacrol, a component of thyme oil, activates PPARalpha and gamma and suppresses COX-2 expression. J. Lipid Res. 51, 132–139. https://doi.org/10.1194/jlr.M900255-JLR200.

Hou, R., Garner, M., Holmes, C., Osmond, C., Teeling, J., Lau, L., Baldwin, D.S., 2017. Peripheral inflammatory cytokines and immune balance in Generalised Anxiety Disorder: case-controlled study. Brain Behav. Immun. 62, 212–218. https://doi.org/10.1016/j.bbi.2017.01.021.

Huang, C., Cui, Y., Ji, L., Zhang, W., Li, R., Ma, L., Xing, W., Zhou, H., Chen, B., Yu, J., Zhang, H., 2013. Catalpol decreases peroxynitrite formation and consequently exerts cardioprotective effects against ischemia/reperfusion insult. Pharm. Biol. 51, 463–473. https://doi.org/10.3109/13880209.2012.740052.

Hudes, G.R., Szarka, C.E., Adams, A., Ranganathan, S., McCauley, R.A., Weiner, L.M., Langer, C.J., Litwin, S., Yeslow, G., Halbert, T., Qian, M., Gallo, J.M., 2000. Phase I pharmacokinetic trial of perillyl alcohol (NSC 641066) in patients with refractory solid malignancies. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 6, 3071–3080.

Hur, S.J., Kang, S.H., Jung, H.S., Kim, S.C., Jeon, H.S., Kim, I.H., Lee, J.D., 2012. Review of natural products actions on cytokines in inflammatory bowel disease. Nutr. Res. 32, 801–816.

Imamura, M., Sasaki, O., Okunishi, K., Nakagome, K., Harada, H., Kawahata, K., Tanaka, R., Yamamoto, K., Dohi, M., 2014. Perillyl alcohol suppresses antigen-induced immune responses in the lung. Biochem. Biophys. Res. Commun. 443, 266–271. https://doi.org/10.1016/j.bbrc.2013.11.106.

Impellizzeri, D., Esposito, E., Mazzon, E., Paterniti, I., Di Paola, R., Bramanti, P., Morittu, V.M., Procopio, A., Britti, D., Cuzzocrea, S., 2011a. The effects of oleuropein aglycone, an olive oil compound, in a mouse model of carrageenan-induced pleurisy. Clin. Nutr. Edinb. Scotl. 30, 533–540. https://doi.org/10.1016/j.clnu.2011.02.004.

Impellizzeri, D., Esposito, E., Mazzon, E., Paterniti, I., Di Paola, R., Morittu, V.M., Procopio, A., Britti, D., Cuzzocrea, S., 2011b. Oleuropein aglycone, an olive oil compound, ameliorates development of arthritis caused by injection of collagen type II in mice. J. Pharmacol. Exp. Therapeut. 339, 859–869. https://doi.org/10.1124/jpet.111.182808.

Isaacs, A., Lindenmann, J., 1957. Virus interference: I. The interferon. Proc. R. Soc. Lond. B Biol. Sci. 147, 258–267.

Jackson, A.L., Bartz, S.R., Schelter, J., Kobayashi, S.V., Burchard, J., Mao, M., Li, B., Cavet, G., Linsley, P.S., 2003. Expression profiling reveals off-target gene regulation by RNAi. Nat. Biotechnol. 21, 635–637. https://doi.org/10.1038/nbt831.

Jahangir, T., Sultana, S., 2007. Perillyl alcohol protects against Fe-NTA-Induced nephrotoxicity and early tumor promotional events in rat experimental model. Evid.-Based compl. Altern. Med. ECAM 4, 439–445. https://doi.org/10.1093/ecam/nel104.

Jaishree, V., Badami, S., 2010. Antioxidant and hepatoprotective effect of swertiamarin from Enicostemma axillare against D-galactosamine induced acute liver damage in rats. J. Ethnopharmacol. 130, 103–106. https://doi.org/10.1016/j.jep.2010.04.019.

Jaishree, V., Badami, S., Rupesh Kumar, M., Tamizhmani, T., 2009. Antinociceptive activity of swertiamarin isolated from Enicostemma axillare. Phytomedicine Int. J. Phytother. Phytopharm. 16, 227–232. https://doi.org/10.1016/j.phymed.2008.09.010.

Janahmadi, Z., Nekooeian, A.A., Moaref, A.R., Emamghoreishi, M., 2015. Oleuropein offers cardioprotection in rats with acute myocardial infarction. Cardiovasc. Toxicol. 15, 61–68. https://doi.org/10.1007/s12012-014-9271-1.

Ji, W.-W., Wang, S.-Y., Ma, Z.-Q., Li, R.-P., Li, S.-S., Xue, J.-S., Li, W., Niu, X.-X., Yan, L., Zhang, X., Fu, Q., Qu, R., Ma, S.-P., 2014. Effects of perillaldehyde on alternations in serum cytokines and depressive-like behavior in mice after lipopolysaccharide administration. Pharmacol. Biochem. Behav. 116, 1–8. https://doi.org/10.1016/j.pbb.2013.10.026.

Jiang, B., Shen, R.F., Bi, J., Tian, X.S., Hinchliffe, T., Xia, Y., 2015. Catalpol: a potential therapeutic for neurodegenerative diseases. Curr. Med. Chem. 22, 1278–1291.

Jin, W., Dong, C., 2013. IL-17 cytokines in immunity and inflammation. Emerg. Microb.

Infect. 2, e60. https://doi.org/10.1038/emi.2013.58.

Juergens, U.R., 2014. Anti-inflammatory properties of the monoterpene 1.8-cineole: current evidence for co-medication in inflammatory airway diseases. Drug Res. 64, 638–646. https://doi.org/10.1055/s-0034-1372609.

Juhás, S., Cikos, S., Czikková, S., Veselá, J., Il'ková, G., Hájek, T., Domaracká, K., Domaracký, M., Bujnáková, D., Rehák, P., Koppel, J., 2008. Effects of borneol and thymoquinone on TNBS-induced colitis in mice. Folia Biol. (Praha) 54, 1–7.

Kameoka, H, Nakai K, n.d. Components of essential oil from the root of Glycyrrhiza glabra. Nippon. Nogeikagaku Kaishi 61, 1119–1121.

Kara, M., Uslu, S., Demirci, F., Temel, H.E., Baydemir, C., 2015. Supplemental carvacrol can reduce the severity of inflammation by influencing the production of mediators of inflammation. Inflammation 38, 1020–1027. https://doi.org/10.1007/s10753-014-0066-0.

Katsukawa, M., Nakata, R., Takizawa, Y., Hori, K., Takahashi, S., Inoue, H., 2010. Citral, a component of lemongrass oil, activates PPARα and γ and suppresses COX-2 expression. Biochim. Biophys. Acta 1801, 1214–1220. https://doi.org/10.1016/j.bbalip.2010.07.004.

Kaufmann, D., Dogra, A.K., Wink, M., 2011. Myrtenal inhibits acetylcholinesterase, a known Alzheimer target. J. Pharm. Pharmacol. 63, 1368–1371. https://doi.org/10.1111/j.2042-7158.2011.01344.x.

Khan, A.Q., Nafees, S., Sultana, S., 2011. Perillyl alcohol protects against ethanol induced acute liver injury in Wistar rats by inhibiting oxidative stress, NFκ-B activation and proinflammatory cytokine production. Toxicology 279, 108–114. https://doi.org/10.1016/j.tox.2010.09.017.

Khan, A.Q., Khan, R., Qamar, W., Lateef, A., Rehman, M.U., Tahir, M., Ali, F., Hamiza, O.O., Hasan, S.K., Sultana, S., 2013. Geraniol attenuates 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced oxidative stress and inflammation in mouse skin: possible role of p38 MAP Kinase and NF-κB. Exp. Mol. Pathol. 94, 419–429. https://doi.org/10.1016/j.yexmp.2013.01.006.

Kim, S.-J., Kim, J.-K., Lee, D.-U., Kwak, J.-H., Lee, S.-M., 2010. Genipin protects lipopolysaccharide-induced apoptotic liver damage in D-galactosamine-sensitized mice. Eur. J. Pharmacol. 635, 188–193. https://doi.org/10.1016/j.ejphar.2010.03.007.

Kim, T.-H., Yoon, S.-J., Lee, S.-M., 2012. Genipin attenuates sepsis by inhibiting Toll-like receptor signaling. Mol. Med. Camb. Mass 18, 455–465. https://doi.org/10.2119/molmed.2011.00308.

Kim, S.-J., Kim, K.-M., Park, J., Kwak, J.-H., Kim, Y.S., Lee, S.-M., 2013. Geniposidic acid protects against D-galactosamine and lipopolysaccharide-induced hepatic failure in mice. J. Ethnopharmacol. 146, 271–277. https://doi.org/10.1016/j.jep.2012.12.042.

Kim, D.-S., Lee, H.-J., Jeon, Y.-D., Han, Y.-H., Kee, J.-Y., Kim, H.-J., Shin, H.-J., Kang, J., Lee, B.S., Kim, S.-H., Kim, S.-J., Park, S.-H., Choi, B.-M., Park, S.-J., Um, J.-Y., Hong, S.-H., 2015a. Alpha-pinene exhibits anti-inflammatory activity through the suppression of MAPKs and the NF-κB pathway in mouse peritoneal macrophages. Am. J. Chin. Med. 43, 731–742. https://doi.org/10.1142/S0192415X15500457.

Kim, K.Y., Lee, H.S., Seol, G.H., 2015b. Eucalyptol suppresses matrix metalloproteinase-9 expression through an extracellular signal-regulated kinase-dependent nuclear factor-kappa B pathway to exert anti-inflammatory effects in an acute lung inflammation model. J. Pharm. Pharmacol. 67, 1066–1074. https://doi.org/10.1111/jphp.12407.

Kim, M.-J., Bae, G.-S., Jo, I.-J., Choi, S.-B., Kim, D.-G., Shin, J.-Y., Lee, S.-K., Kim, Min-Jun, Shin, S., Song, H.-J., Park, S.-J., 2015c. Loganin protects against pancreatitis by inhibiting NF-κB activation. Eur. J. Pharmacol. 765, 541–550. https://doi.org/10.1016/j.ejphar.2015.09.019.

Kobayashi, E.H., Suzuki, T., Funayama, R., Nagashima, T., Hayashi, M., Sekine, H., Tanaka, N., Moriguchi, T., Motohashi, H., Nakayama, K., Yamamoto, M., 2016. Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription. Nat. Commun. 7, 11624. https://doi.org/10.1038/ncomms11624.

Kondamudi, P.K., Kovelamudi, H., Mathew, G., Nayak, P.G., Rao, C.M., Shenoy, R.R., 2013. Modulatory effects of sesamol in dinitrochlorobenzene-induced inflammatory bowel disorder in albino rats. Pharmacol. Rep. PR 65, 658–665.

Kondo, Y., Takano, F., Hojo, H., 1994. Suppression of chemically and immunologically induced hepatic injuries by gentiopicroside in mice. Planta Med. 60, 414–416. https://doi.org/10.1055/s-2006-959521.

Kondo, A., Otsuka, T., Kato, K., Natsume, H., Kuroyanagi, G., Mizutani, J., Ito, Y., Matsushima-Nishiwaki, R., Kozawa, O., Tokuda, H., 2012. AMP-activated protein kinase inhibitor decreases prostaglandin F2α-stimulated interleukin-6 synthesis through p38 MAP kinase in osteoblasts. Int. J. Mol. Med. 30, 1487–1492. https://doi.org/10.3892/ijmm.2012.1159.

Kong, Q., Wu, Z., Chu, X., Liang, R., Xia, M., Li, L., 2014. Study on the anti-cerebral ischemia effect of borneol and its mechanism. Afr. J. Tradit. Complement. Altern. Med. AJTCAM 11, 161–164.

Könner, A.C., Brüning, J.C., 2011. Toll-like receptors: linking inflammation to metabolism. Trends Endocrinol. Metab. TEM 22, 16–23. https://doi.org/10.1016/j.tem.2010.08.007.

Koo, H.-J., Song, Y.S., Kim, H.-J., Lee, Y.-H., Hong, S.-M., Kim, S.-J., Kim, B.-C., Jin, C., Lim, C.-J., Park, E.-H., 2004. Antiinflammatory effects of genipin, an active principle of gardenia. Eur. J. Pharmacol. 495, 201–208. https://doi.org/10.1016/j.ejphar.2004.05.031.

Koo, H.-J., Lim, K.-H., Jung, H.-J., Park, E.-H., 2006. Anti-inflammatory evaluation of gardenia extract, geniposide and genipin. J. Ethnopharmacol. 103, 496–500. https://doi.org/10.1016/j.jep.2005.08.011.

Kozioł, A., Stryjewska, A., Librowski, T., Sałat, K., Gaweł, M., Moniczewski, A., Lochyński, S., 2014. An overview of the pharmacological properties and potential applications of natural monoterpenes. Mini Rev. Med. Chem. 14, 1156–1168.

Kronenberg, M., 2005. Toward an understanding of NKT cell biology: progress and paradoxes. Annu. Rev. Immunol. 23, 877–900. https://doi.org/10.1146/annurev.immunol.23.021704.115742.

Kshirsagar, P.R., Pai, S.R., Nimbalkar, M.S., Gaikwad, N.B., 2016. RP-HPLC analysis of

seco-iridoid glycoside swertiamarin from different Swertia species. Nat. Prod. Res. 30, 865–868. https://doi.org/10.1080/14786419.2015.1071366.

Ku, C.-M., Lin, J.-Y., 2013. Anti-inflammatory effects of 27 selected terpenoid compounds tested through modulating Th1/Th2 cytokine secretion profiles using murine primary splenocytes. Food Chem. 141, 1104–1113. https://doi.org/10.1016/j.foodchem.2013.04.044.

Kumarasamy, Y., Nahar, L., Cox, P.J., Jaspars, M., Sarker, S.D., 2003. Bioactivity of secoiridoid glycosides from Centaurium erythraea. Phytomedicine Int. J. Phytother. Phytopharm. 10, 344–347. https://doi.org/10.1078/094471103322004857.

Kyriakis, J.M., Avruch, J., 2012. Mammalian MAPK signal transduction pathways activated by stress and inflammation: a 10-year update. Physiol. Rev. 92, 689–737. https://doi.org/10.1152/physrev.00028.2011.

Lan, H.Y., 2012. Transforming growth factor-β/Smad signalling in diabetic nephropathy. Clin. Exp. Pharmacol. Physiol. 39, 731–738. https://doi.org/10.1111/j.1440-1681.2011.05663.x.

Landa, P., Kokoska, L., Pribylova, M., Vanek, T., Marsik, P., 2009. In vitro anti-inflammatory activity of carvacrol: inhibitory effect on COX-2 catalyzed prostaglandin E(2) biosynthesis. Arch Pharm. Res. 32, 75–78. https://doi.org/10.1007/s12272-009-1120-6.

Lawrence, T., 2009. The nuclear factor NF-kappaB pathway in inflammation. Cold Spring Harb. Perspect. Biol. 1, a001651. https://doi.org/10.1101/cshperspect.a001651.

Lee, S., Tsao, R., Peterson, C., Coats, J.R., 1997. Insecticidal activity of monoterpenoids to western corn rootworm (Coleoptera: chrysomelidae), twospotted spider mite (Acari: Tetranychidae), and house fly (Diptera: Muscidae). J. Econ. Entomol. 90, 883–892.

Lee, J.-H., Lee, B.-K., Kim, J.-H., Lee, S.H., Hong, S.-K., 2009. Comparison of chemical compositions and antimicrobial activities of essential oils from three conifer trees; Pinus densiflora, Cryptomeria japonica, and Chamaecyparis obtusa. J. Microbiol. Biotechnol. 19, 391–396.

Lee, H.-S., Park, D.-E., Song, W.-J., Park, H.-W., Kang, H.-R., Cho, S.-H., Sohn, S.-W., 2016. Effect of 1.8-cineole in Dermatophagoides pteronyssinus-stimulated bronchial epithelial cells and mouse model of asthma. Biol. Pharm. Bull. 39, 946–952. https://doi.org/10.1248/bpb.b15-00876.

Leung, L., Cahill, C.M., 2010. TNF-alpha and neuropathic pain–a review. J. Neuroinflammation 7, 27. https://doi.org/10.1186/1742-2094-7-27.

Li, J.W.-H., Vederas, J.C., 2009. Drug discovery and natural products: end of an era or an endless frontier? Science 325, 161–165. https://doi.org/10.1126/science.1168243.

Li, X., Shen, J., Zhong, Z., Wen, H., Luo, Q., Wei, W., 2009. Paeoniflorin: a monomer from traditional Chinese medical herb ameliorates Schistosoma japonicum egg-induced hepatic fibrosis in mice. J. Parasitol. 95, 1520–1524. https://doi.org/10.1645/GE-1994.1.

Li, X., Shen, J., Zhong, Z., Peng, J., Wen, H., Li, J., Luo, Q., Wei, W., 2010. Paeoniflorin ameliorates schistosomiasis liver fibrosis through regulating IL-13 and its signalling molecules in mice. Parasitology 137, 1213–1225. https://doi.org/10.1017/S003118201000003X.

Li, C.-C., Hsiang, C.-Y., Lo, H.-Y., Pai, F.-T., Wu, S.-L., Ho, T.-Y., 2012. Genipin inhibits lipopolysaccharide-induced acute systemic inflammation in mice as evidenced by nuclear factor-κB bioluminescent imaging-guided transcriptomic analysis. Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc. 50, 2978–2986. https://doi.org/10.1016/j.fct.2012.05.054.

Li, J., Zhang, X., Huang, H., 2014. Protective effect of linalool against lipopolysaccharide/D-galactosamine-induced liver injury in mice. Int. Immunopharm. 23, 523–529. https://doi.org/10.1016/j.intimp.2014.10.001.

Li, Y., Lai, Y., Wang, Y., Liu, N., Zhang, F., Xu, P., 2016a. 1, 8-cineol protect against influenza-virus-induced pneumonia in mice. Inflammation 39, 1582–1593. https://doi.org/10.1007/s10753-016-0394-3.

Li, Z., Hua, C., Pan, X., Fu, X., Wu, W., 2016b. Carvacrol exerts neuroprotective effects via suppression of the inflammatory response in middle cerebral artery occlusion rats. Inflammation 39, 1566–1572. https://doi.org/10.1007/s10753-016-0392-5.

Lian, L.-H., Wu, Y.-L., Wan, Y., Li, X., Xie, W.-X., Nan, J.-X., 2010. Anti-apoptotic activity of gentiopicroside in D-galactosamine/lipopolysaccharide-induced murine fulminant hepatic failure. Chem. Biol. Interact. 188, 127–133. https://doi.org/10.1016/j.cbi.2010.06.004.

Liao, P., Liu, L., Wang, B., Li, W., Fang, X., Guan, S., 2014. Baicalin and geniposide attenuate atherosclerosis involving lipids regulation and immunoregulation in ApoE-/- mice. Eur. J. Pharmacol. 740, 488–495. https://doi.org/10.1016/j.ejphar.2014.06.039.

Lima, M. da S., Quintans-Júnior, L.J., de Santana, W.A., Martins Kaneto, C., Pereira Soares, M.B., Villarreal, C.F., 2013. Anti-inflammatory effects of carvacrol: evidence for a key role of interleukin-10. Eur. J. Pharmacol. 699, 112–117. https://doi.org/10.1016/j.ejphar.2012.11.040.

Lima, P.R., de Melo, T.S., Carvalho, K.M.M.B., de Oliveira, Í.B., Arruda, B.R., de Castro Brito, G.A., Rao, V.S., Santos, F.A., 2013. 1,8-cineole (eucalyptol) ameliorates cerulein-induced acute pancreatitis via modulation of cytokines, oxidative stress and NF-κB activity in mice. Life Sci. 92, 1195–1201. https://doi.org/10.1016/j.lfs.2013.05.009.

Lin, E., Calvano, S.E., Lowry, S.F., 2000. Inflammatory cytokines and cell response in surgery. Surgery 127, 117–126. https://doi.org/10.1067/msy.2000.101584.

Lin, T., Tamaki, Y., Pajarinen, J., Waters, H.A., Woo, D.K., Yao, Z., Goodman, S.B., 2014. Chronic inflammation in biomaterial-induced periprosthetic osteolysis: NF-κB as a therapeutic target. Acta Biomater. 10, 1–10. https://doi.org/10.1016/j.actbio.2013.09.034.

Lingaiah, H.B., Natarajan, N., Thamaraiselvan, R., Srinivasan, P., Periyasamy, B.M., 2013. Myrtenal ameliorates diethylnitrosamine-induced hepatocarcinogenesis through the activation of tumor suppressor protein p53 and regulation of lysosomal and mitochondrial enzymes. Fundam. Clin. Pharmacol. 27, 443–454. https://doi.org/10.1111/j.1472-8206.2012.01039.x.

Liu, G., Oettel, K., Bailey, H., Ummersen, L.V., Tutsch, K., Staab, M.J., Horvath, D., Alberti, D., Arzoomanian, R., Rezazadeh, H., McGovern, J., Robinson, E., DeMets, D., Wilding, G., 2003. Phase II trial of perillyl alcohol (NSC 641066) administered daily in patients with metastatic androgen independent prostate cancer. Invest. N. Drugs 21, 367–372.

Liu, D.-F., Wei, W., Song, L.-H., 2006. Protective effect of paeoniflorin on immunological liver injury induced by bacillus Calmette-Guerin plus lipopolysaccharide: modulation of tumour necrosis factor-alpha and interleukin-6 MRNA. Clin. Exp. Pharmacol. Physiol. 33, 332–339. https://doi.org/10.1111/j.1440-1681.2006.04371.x.

Liu, Y.-R., Li, P.-W., Suo, J.-J., Sun, Y., Zhang, B.-A., Lu, H., Zhu, H.-C., Zhang, G.-B., 2014. Catalpol provides protective effects against cerebral ischaemia/reperfusion injury in gerbils. J. Pharm. Pharmacol. 66, 1265–1270. https://doi.org/10.1111/jphp.12261.

Liu, J.-Y., Zheng, C.-Z., Hao, X.-P., Zhang, D.-J., Mao, A.-W., Yuan, P., 2016. Catalpol ameliorates diabetic atherosclerosis in diabetic rabbits. Am. J. Transl. Res. 8, 4278–4288.

Lv, C., Wang, L., Liu, X., Yan, S., Yan, S.S., Wang, Y., Zhang, W., 2015. Multi-faced neuroprotective effects of geniposide depending on the RAGE-mediated signaling in an Alzheimer mouse model. Neuropharmacology 89, 175–184. https://doi.org/10.1016/j.neuropharm.2014.09.019.

Meadows, Sherry Morgan, Mulkerin, D., Berlin, J., Bailey, H., Kolesar, J., Warren, D., Thomas, J.P., 2002. Phase II trial of perillyl alcohol in patients with metastatic colorectal cancer. Int. J. Gastrointest. Cancer 32, 125–128. https://doi.org/10.1385/IJGC:32:2-3:125.

Ma, T., Huang, C., Zong, G., Zha, D., Meng, X., Li, J., Tang, W., 2011. Hepatoprotective effects of geniposide in a rat model of nonalcoholic steatohepatitis. J. Pharm. Pharmacol. 63, 587–593. https://doi.org/10.1111/j.2042-7158.2011.01256.x.

Mahtaj, L.G., Feizpour, A., Kianmehr, M., Soukhtanloo, M., Boskabady, M.H., 2015. The effect of carvacrol on systemic inflammation in Guinea pigs model of COPD induced by cigarette smoke exposure. Pharmacol. Rep. PR 67, 140–145. https://doi.org/10.1016/j.pharep.2014.08.017.

Marcuzzi, A., Crovella, S., Pontillo, A., 2011. Geraniol rescues inflammation in cellular and animal models of mevalonate kinase deficiency. Vivo Athens Greece 25, 87–92.

Martinez, F.O., Helming, L., Gordon, S., 2009. Alternative activation of macrophages: an immunologic functional perspective. Annu. Rev. Immunol. 27, 451–483. https://doi.org/10.1146/annurev.immunol.021908.132532Meadows.

Medicherla, K., Sahu, B.D., Kuncha, M., Kumar, J.M., Sudhakar, G., Sistla, R., 2015. Oral administration of geraniol ameliorates acute experimental murine colitis by inhibiting pro-inflammatory cytokines and NF-κB signaling. Food Funct. 6, 2984–2995. https://doi.org/10.1039/c5fo00405e.

Medzhitov, R., 2010. Inflammation 2010: new adventures of an old flame. Cell 140, 771–776. https://doi.org/10.1016/j.cell.2010.03.006.

Migeotte, I., Communi, D., Parmentier, M., 2006. Formyl peptide receptors: a promiscuous subfamily of G protein-coupled receptors controlling immune responses. Cytokine Growth. Factor. Rev. 17, 501–519. https://doi.org/10.1016/j.cytogfr.2006.09.009.

Miller, J.A., Thompson, P.A., Hakim, I.A., Chow, H.-H.S., Thomson, C.A., 2011. Limonene: a bioactive food component from citrus and evidence for a potential role in breast cancer prevention and treatment. Onco Rev. 5, 31–42. https://doi.org/10.1007/s12156-010-0066-8.

Mockute, D., Judzentiene, A., 2003. The Myrtenol Chemotype of Essential Oil of Tanacetum Vulgare L. Var. Vulgare (Tansy) Growing Wild in the Vilnius Region.

Mollica, A., Paglialunga Paradisi, M., Torino, D., Spisani, S., Lucente, G., 2006. Hybrid alpha/beta-peptides: for-Met-Leu-Phe-OMe analogues containing geminally disubstituted beta2,2- and beta 3,3-amino acids at the central position. Amino Acids 30, 453–459. https://doi.org/10.1007/s00726-006-0260-y.

Nagoor Meeran, M.F., Jagadeesh, G.S., Selvaraj, P., 2015. Thymol attenuates inflammation in isoproterenol induced myocardial infarcted rats by inhibiting the release of lysosomal enzymes and downregulating the expressions of proinflammatory cytokines. Eur. J. Pharmacol. 754, 153–161. https://doi.org/10.1016/j.ejphar.2015.02.028.

Nakamura, T., Fukui, M., Ebihara, I., Osada, S., Nagaoka, I., Tomino, Y., Koide, H., 1993. mRNA expression of growth factors in glomeruli from diabetic rats. Diabetes 42, 450–456.

Nam, S.-Y., Chung, C., Seo, J.-H., Rah, S.-Y., Kim, H.-M., Jeong, H.-J., 2014. The therapeutic efficacy of α-pinene in an experimental mouse model of allergic rhinitis. Int. Immunopharm. 23, 273–282. https://doi.org/10.1016/j.intimp.2014.09.010.

Nathan, C., 2002. Points of control in inflammation. Nature 420, 846–852. https://doi.org/10.1038/nature01320.

Nazaroff, W.W., Weschler, C.J., 2004. Cleaning products and air fresheners: exposure to primary and secondary air pollutants. Atmos. Environ. 38, 2841–2865. https://doi.org/10.1016/j.atmosenv.2004.02.040.

Ngan, L.T.M., Moon, J.-K., Kim, J.-H., Shibamoto, T., Ahn, Y.-J., 2012. Growth-inhibiting effects of Paeonia lactiflora root steam distillate constituents and structurally related compounds on human intestinal bacteria. World J. Microbiol. Biotechnol. 28, 1575–1583. https://doi.org/10.1007/s11274-011-0961-6.

Nonato, F.R., Santana, D.G., de Melo, F.M., dos Santos, G.G.L., Brustolim, D., Camargo, E.A., de Sousa, D.P., Soares, M.B.P., Villarreal, C.F., 2012. Anti-inflammatory properties of rose oxide. Int. Immunopharm. 14, 779–784. https://doi.org/10.1016/j.intimp.2012.10.015.

Oliveira, M.A., Guimarães, A.G., Araújo, A.A.S., Quintans-Júnior, L.J., Quintans, J.S.S., 2017. New drugs or alternative therapy to blurring the symptoms of fibromyalgia-a patent review. Expert Opin. Ther. Pat. 27, 1147–1157. https://doi.org/10.1080/13543776.2017.1349105.

O'Shea, J.J., Park, H., Pesu, M., Borie, D., Changelian, P., 2005. New strategies for immunosuppression: interfering with cytokines by targeting the Jak/Stat pathway. Curr Opin Rheumatol. 17 (3), 305–311 May.

Oliveira, M.G.B., Brito, R.G., Santos, P.L., Araújo-Filho, H.G., Quintans, J.S.S., Menezes, P.P., Serafini, M.R., Carvalho, Y.M.B.G., Silva, J.C., Almeida, J.R.G.S., Scotti, L., Scotti, M.T., Shanmugam, S., Thangaraj, P., Araújo, A.A.S., Quintans-Júnior, L.J., 2016. α-Terpineol, a monoterpene alcohol, complexed with β-cyclodextrin exerts antihyperalgesic effect in animal model for fibromyalgia aided with docking study. Chem. Biol. Interact. 254, 54–62. https://doi.org/10.1016/j.cbi.2016.05.029.

Ozer, E.K., Goktas, M.T., Toker, A., Pehlivan, S., Bariskaner, H., Ugurluoglu, C., Iskit, A.B., 2017. Thymoquinone protects against the sepsis induced mortality, mesenteric hypoperfusion, aortic dysfunction and multiple organ damage in rats. Pharmacol. Rep. PR 69, 683–690. https://doi.org/10.1016/j.pharep.2017.02.021.

Park, E.-H., Joo, M.-H., Kim, S.-H., Lim, C.-J., 2003. Antiangiogenic activity of Gardenia jasminoides fruit. Phytother. Res. PTR 17, 961–962. https://doi.org/10.1002/ptr.1259.

Paul, A.T., Gohil, V.M., Bhutani, K.K., 2006. Modulating TNF-alpha signaling with natural products. Drug Discov. Today 11, 725–732. https://doi.org/10.1016/j.drudis.2006.06.002.

Pina, L.T.S., Gouveia, D.N., Costa, J.S., Quintans, J.S.S., Quintans-Júnior, L.J., Barreto, R.S.S., Guimarγes, A.G., 2017. New perspectives for chronic pain treatment: a patent review (2010-2016). Expert Opin. Ther. Pat. 27, 787–796. https://doi.org/10.1080/13543776.2017.1297425.

Polosukhin, V.V., Polosukhin, I.V., Hoskins, A., Han, W., Abdolrasulnia, R., Blackwell, T.S., Dworski, R., 2014. Glutathione S-transferase M1 modulates allergen-induced NF-κB activation in asthmatic airway epithelium. Allergy 69, 1666–1672. https://doi.org/10.1111/all.12506.

Prasad, G.V.R., 2014. Metabolic syndrome and chronic kidney disease: current status and future directions. World J. Nephrol. 3, 210–219. https://doi.org/10.5527/wjn.v3.i4.210.

Prevete, N., Liotti, F., Marone, G., Melillo, R.M., de Paulis, A., 2015. Formyl peptide receptors at the interface of inflammation, angiogenesis and tumor growth. Pharmacol. Res. 102, 184–191.

Quintans, J. de S.S., Menezes, P.P., Santos, M.R.V., Bonjardim, L.R., Almeida, J.R.G.S., Gelain, D.P., Araújo, A.A. de S., Quintans-Júnior, L.J., 2013. Improvement of p-cymene antinociceptive and anti-inflammatory effects by inclusion in β-cyclodextrin. Phytomedicine Int. J. Phytother. Phytopharm. 20, 436–440. https://doi.org/10.1016/j.phymed.2012.12.009.

Quintans-Júnior, L.J., Souza, T.T., Leite, B.S., Lessa, N.M.N., Bonjardim, L.R., Santos, M.R.V., Alves, P.B., Blank, A.F., Antoniolli, A.R., 2008. Phythochemical screening and anticonvulsant activity of Cymbopogon winterianus Jowitt (Poaceae) leaf essential oil in rodents. Phytomedicine Int. J. Phytother. Phytopharm. 15, 619–624. https://doi.org/10.1016/j.phymed.2007.09.018.

Quintans-Júnior, L.J., Oliveira, M.G.B., Santana, M.F., Santana, M.T., Guimarães, A.G., Siqueira, J.S., De Sousa, D.P., Almeida, R.N., 2011. α-Terpineol reduces nociceptive behavior in mice. Pharm. Biol. 49, 583–586. https://doi.org/10.3109/13880209.2010.529616.

Quintans-Júnior, L.J., Barreto, R.S.S., Menezes, P.P., Almeida, J.R.G.S., Viana, A.F.S.C., Oliveira, R.C.M., Oliveira, A.P., Gelain, D.P., de Lucca Júnior, W., Araújo, A.A.S., 2013. β-Cyclodextrin-complexed (-)-linalool produces antinociceptive effect superior to that of (-)-linalool in experimental pain protocols. Basic Clin. Pharmacol. Toxicol. 113, 167–172. https://doi.org/10.1111/bcpt.12087.

Raeburn, C.D., Sheppard, F., Barsness, K.A., Arya, J., Harken, A.H., 2002. Cytokines for surgeons. Am. J. Surg. 183, 268–273.

Ramalho, T.R. de O., Oliveira, M.T.P. de, Lima, A.L. de A., Bezerra-Santos, C.R., Piuvezam, M.R., 2015. Gamma-terpinene modulates acute inflammatory response in mice. Planta Med. 81, 1248–1254. https://doi.org/10.1055/s-0035-1546169.

Ramalho, T.R., Filgueiras, L.R., Pacheco de Oliveira, M.T., Lima, A.L. de A., Bezerra-Santos, C.R., Jancar, S., Piuvezam, M.R., 2016. Gamma-terpinene modulation of LPS-stimulated macrophages is dependent on the PGE2/IL-10 Axis. Planta Med. 82, 1341–1345. https://doi.org/10.1055/s-0042-107799.

Ramesh, G., MacLean, A.G., Philipp, M.T., 2013. Cytokines and chemokines at the crossroads of neuroinflammation, neurodegeneration, and neuropathic pain. Mediat. Inflamm. 2013, 480739. https://doi.org/10.1155/2013/480739.

Reeves, W.B., Andreoli, T.E., 2000. Transforming growth factor beta contributes to progressive diabetic nephropathy. Proc. Natl. Acad. Sci. U. S. A 97, 7667–7669.

Rehman, M.U., Tahir, M., Khan, A.Q., Khan, R., Oday-O-Hamiza, Lateef, A., Hassan, S.K., Rashid, S., Ali, N., Zeeshan, M., Sultana, S., 2014. D-limonene suppresses doxorubicin-induced oxidative stress and inflammation via repression of COX-2, iNOS, and NFκB in kidneys of Wistar rats. Exp. Biol. Med. Maywood NJ 239, 465–476. https://doi.org/10.1177/1535370213520112.

Reinhart, K., Karzai, W., 2001. Anti-tumor necrosis factor therapy in sepsis: update on clinical trials and lessons learned. Crit. Care Med. 29, S121–S125.

Rider, P., Carmi, Y., Cohen, I., 2016. Biologics for targeting inflammatory cytokines, clinical uses, and limitations. Int. J. Cell Biol. 2016, 9259646 11 pages. https://doi.org/10.1155/2016/9259646.

Ripple, G.H., Gould, M.N., Stewart, J.A., Tutsch, K.D., Arzoomanian, R.Z., Alberti, D., Feierabend, C., Pomplun, M., Wilding, G., Bailey, H.H., 1998. Phase I clinical trial of perillyl alcohol administered daily. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 4, 1159–1164.

Rodriguez-Pintó, I., Agmon-Levin, N., Howard, A., Shoenfeld, Y., 2014. Fibromyalgia and cytokines. Immunol. Lett. 161, 200–203. https://doi.org/10.1016/j.imlet.2014.01.009.

Roy, N.B., Fortin, P.M., Bull, K.R., Doree, C., Trivella, M., Hopewell, S., Estcourt, L.J., 2016. Interventions for chronic kidney disease in people with sickle cell disease. Cochrane Database Syst. Rev. 2016. https://doi.org/10.1002/14651858.CD012380.

Rozza, A.L., Meira de Faria, F., Souza Brito, A.R., Pellizzon, C.H., 2014. The gastroprotective effect of menthol: involvement of anti-apoptotic, antioxidant and anti-

inflammatory activities. PloS One 9, e86686. https://doi.org/10.1371/journal.pone.0086686.

Russo, E.B., 2011. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br. J. Pharmacol. 163, 1344–1364. https://doi.org/10.1111/j.1476-5381.2011.01238.x.

Sabio, G., Davis, R.J., 2014. TNF and MAP kinase signalling pathways. Semin. Immunol. 26, 237–245. https://doi.org/10.1016/j.smim.2014.02.009.

Sabogal-Guáqueta, A.M., Osorio, E., Cardona-Gómez, G.P., 2016. Linalool reverses neuropathological and behavioral impairments in old triple transgenic Alzheimer's mice. Neuropharmacology 102, 111–120. https://doi.org/10.1016/j.neuropharm.2015.11.002.

Saccani, S., Pantano, S., Natoli, G., 2002. p38-Dependent marking of inflammatory genes for increased NF-kappa B recruitment. Nat. Immunol. 3, 69–75. https://doi.org/10.1038/ni748.

Santana, M.F., Quintans-Júnior, L.J., Cavalcanti, S.C.H., Oliveira, M.G.B., Guimarães, A.G., Cunha, E.S., Melo, M.S., Santos, M.R.V., Araújo, A.A.S., Bonjardim, L.R., 2011. p-Cymene reduces orofacial nociceptive response in mice. Rev. Bras. Farmacogn. 21, 1138–1143. https://doi.org/10.1590/S0102-695X2011005000156.

Santos, F.A., Silva, R.M., Tomé, A.R., Rao, V.S., Pompeu, M.M., Teixeira, M.J., De Freitas, L.A., De Souza, V.L., 2001. 1,8-cineole protects against liver failure in an in-vivo murine model of endotoxemic shock. J. Pharm. Pharmacol. 53, 505–511.

Santos, M.R.V., Moreira, F.V., Fraga, B.P., Souza, D.P. de, Bonjardim, L.R., Quintans-Junior, L.J., 2011. Cardiovascular effects of monoterpenes: a review. Rev. Bras. Farmacogn. 21, 764–771. https://doi.org/10.1590/S0102-695X2011005000119.

Santos, P.L., Araújo, A.A.S., Quintans, J.S.S., Oliveira, M.G.B., Brito, R.G., Serafini, M.R., Menezes, P.P., Santos, M.R.V., Alves, P.B., de Lucca Júnior, W., Blank, A.F., La Rocca, V., Almeida, R.N., Quintans-Júnior, L.J., 2015. Preparation, characterization, and pharmacological activity of cymbopogon winterianus jowitt ex bor (poaceae) leaf essential oil of β-cyclodextrin inclusion complexes. Evid.-Based Complement. Altern. Med. ECAM 502454. 2015. https://doi.org/10.1155/2015/502454.

Saravanan, S., Islam, V.I.H., Babu, N.P., Pandikumar, P., Thirugnanasambantham, K., Chellappandian, M., Raj, C.S.D., Paulraj, M.G., Ignacimuthu, S., 2014a. Swertiamarin attenuates inflammation mediators via modulating NF-κB/IκB and JAK2/STAT3 transcription factors in adjuvant induced arthritis. Eur. J. Pharm. Sci. Off. J. Eur. Fed. Pharm. Sci. 56, 70–86. https://doi.org/10.1016/j.ejps.2014.02.005.

Saravanan, S., Pandikumar, P., Prakash Babu, N., Hairul Islam, V.I., Thirugnanasambantham, K., Gabriel Paulraj, M., Balakrishna, K., Ignacimuthu, S., 2014b. In vivo and in vitro immunomodulatory potential of swertiamarin isolated from Enicostema axillare (Lam.) A. Raynal that acts as an anti-inflammatory agent. Inflammation 37, 1374–1388. https://doi.org/10.1007/s10753-014-9862-9.

Schepetkin, I.A., Kushnarenko, S.V., Ozek, G., Kirpotina, L.N., Utegenova, G.A., Kotukhov, Y.A., Danilova, A.N., Ozek, T., Baser, K.H., Quinn, M.T., 2015. Inhibition of human neutrophil responses by the essential oil of Artemisia kotuchovii and its constituents. J. Agric. Food Chem. 63, 4999–5007. https://doi.org/10.1021/acs.jafc.5b01307.

Schepetkin, I.A., Kushnarenko, S.V., Ozek, G., Kirpotina, L.N., Utegenova, G.A., Kotukhov, Y.A., Danilova, A.N., Ozek, T., Baser, K.H., Quinn, M.T., et al., 2016. Modulation of human neutrophil responses by the essential oils from Ferula akitschkensis and their constituents. J. Agric. Food Chem. 64, 7156–7170. https://doi.org/10.1021/acs.jafc.6b03205.

Schiffmann, E., Corcoran, B.A., Wahl, S.M., 1975. N-formylmethionyl peptides as chemoattractants for leucocytes. Proc. Natl. Acad. Sci. U.S.A. 72, 1059–1062.

Shao, G., Julian, M.W., Bao, S., McCullers, M.K., Lai, J.P., Knoell, D.L., et al., 2011. Formyl peptide receptor ligands promote wound closure in lung epithelial cells. Am. J. Respir. Cell Mol. Biol. 44, 264–269. https://doi.org/10.1165/rcmb.2010-0246RC.

Shapiro, S., Guggenheim, B., 1995. The action of thymol on oral bacteria. Oral Microbiol. Immunol. 10, 241–246.

Shen, Y., Sun, Z., Guo, X., 2015. Citral inhibits lipopolysaccharide-induced acute lung injury by activating PPAR-γ. Eur. J. Pharmacol. 747, 45–51. https://doi.org/10.1016/j.ejphar.2014.09.040.

Shi, D., Ma, A., Zheng, H., Huo, G., Yan, H., Fu, H., Qiu, Y., Liu, W., 2014. Paeoniflorin inhibits the maturation and immunostimulatory function of allergen-induced murine dendritic cells. Int. Immunopharm. 19, 221–232. https://doi.org/10.1016/j.intimp.2014.02.001.

Shih, M.-F., Chen, L.-Y., Tsai, P.-J., Cherng, J.-Y., 2012. In vitro and in vivo therapeutics of β-thujaplicin on LPS-induced inflammation in macrophages and septic shock in mice. Int. J. Immunopathol. Pharmacol. 25, 39–48. https://doi.org/10.1177/039463201202500106.

Siani, A.C., Ramos, M.F., Menezes-de-Lima, O., Ribeiro-dos-Santos, R., Fernadez-Ferreira, E., Soares, R.O., Rosas, E.C., Susunaga, G.S., Guimarães, A.C., Zoghbi, M.G., Henriques, M.G., 1999. Evaluation of anti-inflammatory-related activity of essential oils from the leaves and resin of species of Protium. J. Ethnopharmacol. 66, 57–69.

Siani, A.C., Souza, M.C., Henriques, M.G., Ramos, M.F., 2013. Anti-inflammatory activity of essential oils from Syzygium cumini and Psidium guajava. Pharm. Biol. 51, 881–887. https://doi.org/10.3109/13880209.2013.768675.

Sica, A., Mantovani, A., 2012. Macrophage plasticity and polarization: in vivo veritas. J. Clin. Invest. 122, 787–795. https://doi.org/10.1172/JCI59643.

Silva, R.O., Salvadori, M.S., Sousa, F.B.M., Santos, M.S., Carvalho, N.S., Sousa, D.P., Gomes, B.S., Oliveira, F.A., Barbosa, A.L.R., Freitas, R.M., Almeida, R.N. de, Medeiros, J.-V.R., 2014. Evaluation of the anti-inflammatory and antinociceptive effects of myrtenol, a plant-derived monoterpene alcohol, in mice. Flavour Fragrance J. 29, 184–192. https://doi.org/10.1002/ffj.3195.

Siqueira, H.D.S., Neto, B.S., Sousa, D.P., Gomes, B.S., da Silva, F.V., Cunha, F.V.M., Wanderley, C.W.S., Pinheiro, G., Cândido, A.G.F., Wong, D.V.T., Ribeiro, R.A., Lima-Júnior, R.C.P., Oliveira, F.A., 2016. α-Phellandrene, a cyclic monoterpene, attenuates inflammatory response through neutrophil migration inhibition and mast cell

degranulation. Life Sci. 160, 27–33. https://doi.org/10.1016/j.lfs.2016.07.008.

Siqueira-Lima, P.S., Araújo, A.A.S., Lucchese, A.M., Quintans, J.S.S., Menezes, P.P., Alves, P.B., de Lucca Júnior, W., Santos, M.R.V., Bonjardim, L.R., Quintans-Júnior, L.J., 2014. β-cyclodextrin complex containing Lippia grata leaf essential oil reduces orofacial nociception in mice - evidence of possible involvement of descending inhibitory pain modulation pathway. Basic Clin. Pharmacol. Toxicol. 114, 188–196. https://doi.org/10.1111/bcpt.12145.

Siveen, K.S., Kuttan, G., 2011. Thujone inhibits lung metastasis induced by B16F-10 melanoma cells in C57BL/6 mice. Can. J. Physiol. Pharmacol. 89, 691–703. https://doi.org/10.1139/y11-067.

Sommer, C., White, F., 2010. Cytokines, chemokines, and pain. In: Beaulieu, P., Lussier, D., Porreca, F. (Eds.), Pharmacology of Pain. IASP Press, Seattle, pp. 279–302.

Song, X., Zhang, W., Wang, T., Jiang, H., Zhang, Z., Fu, Y., Yang, Z., Cao, Y., Zhang, N., 2014. Geniposide plays an anti-inflammatory role via regulating TLR4 and downstream signaling pathways in lipopolysaccharide-induced mastitis in mice. Inflammation 37, 1588–1598. https://doi.org/10.1007/s10753-014-9885-2.

Song, H.-H., Shin, I.-S., Woo, S.Y., Lee, S.U., Sung, M.H., Ryu, H.W., Kim, D.-Y., Ahn, K.-S., Lee, H.-K., Lee, D., Oh, S.-R., 2015. Piscroside C, a novel iridoid glycoside isolated from Pseudolysimachion rotundum var. subinegrum suppresses airway inflammation induced by cigarette smoke. J. Ethnopharmacol. 170, 20–27. https://doi.org/10.1016/j.jep.2015.04.043.

Souza, M.T., Almeida, J.R., Araujo, A.A., Duarte, M.C., Gelain, D.P., Moreira, J.C., dos Santos, M.R., Quintans-Júnior, L.J., 2014. Structure–activity relationship of terpenes with anti-inflammatory profile – a systematic review. Basic Clin. Pharmacol. Toxicol. 115 (3), 244–256.

Soomin, C., Youngshim, C., Soyoung, P., Taesun, P., 2012. Carvacrol prevents diet-induced obesity by modulating gene expressions involved in adipogenesis and inflammation in mice fed with high-fat diet. The. J. Nutri. Biochem. 23, 192–201. https://doi.org/10.1016/j.jnutbio.2010.11.016.

Spelman, K., Burns, J., Nichols, D., Winters, N., Ottersberg, S., Tenborg, M., 2006. Modulation of cytokine expression by traditional medicines: a review of herbal immunomodulators. Altern. Med. Rev. J. Clin. Ther. 11, 128–150.

Srinivasan, S., Muruganathan, U., 2016. Antidiabetic efficacy of citronellol, a citrus monoterpene by ameliorating the hepatic key enzymes of carbohydrate metabolism in streptozotocin-induced diabetic rats. Chem. Biol. Interact. 250, 38–46. https://doi.org/10.1016/j.cbi.2016.02.020.

Su, Y.-W., Chao, S.-H., Lee, M.-H., Ou, T.-Y., Tsai, Y.-C., 2010. Inhibitory effects of citronellol and geraniol on nitric oxide and prostaglandin E$_2$ production in macrophages. Planta Med. 76, 1666–1671. https://doi.org/10.1055/s-0030-1249947.

Sun, J., 2007. D-Limonene: safety and clinical applications. Altern. Med. Rev. J. Clin. Ther. 12, 259–264.

Sun, L.-R., Cao, X., Hou, F.-Q., Zhu, X.-H., Gao, T.-M., 2008. Progressive studies of paeoniflorin. Zhongguo Zhong Yao Za Zhi Zhongguo Zhongyao Zazhi China J. Chin. Mater. Medica 33, 2028–2032.

Sun, J., Wu, J., Xu, C., Luo, Q., Li, B., Dong, J., 2015a. Paeoniflorin attenuates allergic inflammation in asthmatic mice. Int. Immunopharm. 24, 88–94. https://doi.org/10.1016/j.intimp.2014.11.016.

Sun, Y., Zhang, J., Huo, R., Zhai, T., Li, H., Wu, P., Zhu, X., Zhou, Z., Shen, B., Li, N., 2015b. Paeoniflorin inhibits skin lesions in imiquimod-induced psoriasis-like mice by downregulating inflammation. Int. Immunopharm. 24, 392–399. https://doi.org/10.1016/j.intimp.2014.12.032.

Suntres, Z.E., Coccimiglio, J., Alipour, M., 2015. The bioactivity and toxicological actions of carvacrol. Crit. Rev. Food Sci. Nutr. 55, 304–318. https://doi.org/10.1080/10408398.2011.653458.

Suroowan, S., Mahomoodally, F., 2018. Herbal products for common auto-inflammatory disorders - novel approaches. Comb. Chem. High Throughput Screen. 21, 161–174. https://doi.org/10.2174/1386207321666180213093449.

Suryawanshi, S., Mehrotra, N., Asthana, R.K., Gupta, R.C., 2006. Liquid chromatography/tandem mass spectrometric study and analysis of xanthone and secoiridoid glycoside composition of Swertia chirata, a potent antidiabetic. Rapid Commun. Mass Spectrom. RCM 20, 3761–3768. https://doi.org/10.1002/rcm.2795.

Tabassum, N., Vaibhav, K., Shrivastava, P., Khan, A., Ahmed, M.Es, Ashafaq, M., Khan, M.B., Islam, Farah, Safhi, M.M., Islam, Fakhrul, 2015. Perillyl alcohol improves functional and histological outcomes against ischemia-reperfusion injury by attenuation of oxidative stress and repression of COX-2, NOS-2 and NF-κB in middle cerebral artery occlusion rats. Eur. J. Pharmacol. 747, 190–199. https://doi.org/10.1016/j.ejphar.2014.09.015.

Tang, N.-Y., Liu, C.-H., Hsieh, C.-T., Hsieh, C.-L., 2010. The anti-inflammatory effect of paeoniflorin on cerebral infarction induced by ischemia-reperfusion injury in Sprague-Dawley rats. Am. J. Chin. Med. 38, 51–64. https://doi.org/10.1142/S0192415X10007786.

Tavares, E.S., Julião, L.S., Lopes, D., Bizzo, H.R., Lage, C.L.S., Leitão, S.G., 2005. Analysis of the essential oil from leaves of three Lippia alba (Mill.) N. E. Br. (Verbenaceae) chemotypes cultivated on the same conditions. Rev. Bras. Farmacogn. 15, 1–5. https://doi.org/10.1590/S0102-695X2005000100002.

Tekeoglu, I., Dogan, A., Demiralp, L., 2006. Effects of thymoquinone (volatile oil of black cumin) on rheumatoid arthritis in rat models. Phytother. Res. PTR 20, 869–871. https://doi.org/10.1002/ptr.1964.

Thapa, D., Losa, R., Zweifel, B., Wallace, R.J., 2012. Sensitivity of pathogenic and commensal bacteria from the human colon to essential oils. Microbiol. Read. Engl. 158, 2870–2877. https://doi.org/10.1099/mic.0.061127-0.

Torino, D., Mollica, A., Pinnen, F., Feliciani, F., Spisani, S., Lucente, G., 2009. Novel chemotactic For-Met-Leu-Phe-OMe (fMLF-OMe) analogues based on Met residue replacement by 4-amino-proline scaffold: synthesis and bioactivity. Bioorg. Med. Chem. 17, 251–259. https://doi.org/10.1016/j.bmc.2008.11.010.

Trinh, H.-T., Lee, I.-A., Hyun, Y.-J., Kim, D.-H., 2011. Artemisia princeps Pamp. Essential

oil and its constituents eucalyptol and α-terpineol ameliorate bacterial vaginosis and vulvovaginal candidiasis in mice by inhibiting bacterial growth and NF-κB activation. Planta Med. 77, 1996–2002. https://doi.org/10.1055/s-0031-1280094.

Uddin, R., Saha, M.R., Subhan, N., Hossain, H., Jahan, I.A., Akter, R., Alam, A., 2014. HPLC-analysis of polyphenolic compounds in gardenia jasminoides and determination of antioxidant activity by using free radical scavenging assays. Adv. Pharmaceut. Bull. 4, 273–281. https://doi.org/10.5681/apb.2014.040.

Ultee, A., Kets, E.P., Smid, E.J., 1999. Mechanisms of action of carvacrol on the food-borne pathogen Bacillus cereus. Appl. Environ. Microbiol. 65, 4606–4610.

Uçeyler, N., Häuser, W., Sommer, C., 2011. Systematic review with meta-analysis: cytokines in fibromyalgia syndrome. BMC Muscoskel. Disord. 12, 245. https://doi.org/10.1186/1471-2474-12-245.

Vaidya, H., Rajani, M., Sudarsanam, V., Padh, H., Goyal, R., 2009. Swertiamarin: a lead from Enicostemma littorale Blume. for anti-hyperlipidaemic effect. Eur. J. Pharmacol. 617, 108–112. https://doi.org/10.1016/j.ejphar.2009.06.053.

Vaijanathappa, J., Badami, S., 2009. Antiedematogenic and free radical scavenging activity of swertiamarin isolated from Enicostemma axillare. Planta Med. 75, 12–17. https://doi.org/10.1055/s-0028-1088333.

van Beilen, J.B., Holtackers, R., Lüscher, D., Bauer, U., Witholt, B., Duetz, W.A., 2005. Biocatalytic production of perillyl alcohol from limonene by using a novel Mycobacterium sp. cytochrome P450 alkane hydroxylase expressed in Pseudomonas putida. Appl. Environ. Microbiol. 71, 1737–1744. https://doi.org/10.1128/AEM.71.4.1737-1744.2005.

Verri, W.A., Cunha, T.M., Parada, C.A., Poole, S., Cunha, F.Q., Ferreira, S.H., 2006. Hypernociceptive role of cytokines and chemokines: targets for analgesic drug development? Pharmacol. Ther. 112, 116–138. https://doi.org/10.1016/j.pharmthera.2006.04.001.

Vervoordeldonk, M.J.B.M., Tak, P.P., 2002. Cytokines in rheumatoid arthritis. Curr. Rheumatol. Rep. 4, 208–217.

Viljoen, A., Mncwangi, N., Vermaak, I., 2012. Anti-inflammatory iridoids of botanical origin. Curr. Med. Chem. 19, 2104–2127.

Waage, A., Halstensen, A., Espevik, T., 1987. Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease. Lancet Lond. Engl. 1, 355–357.

Wang, C.-F., Li, D.-Q., Xue, H.-Y., Hu, B., 2010. Oral supplementation of catalpol ameliorates diabetic encephalopathy in rats. Brain Res. 1307, 158–165. https://doi.org/10.1016/j.brainres.2009.10.034.

Wang, J., Hou, J., Zhang, P., Li, D., Zhang, C., Liu, J., 2012. Geniposide reduces inflammatory responses of oxygen-glucose deprived rat microglial cells via inhibition of the TLR4 signaling pathway. Neurochem. Res. 37, 2235–2248. https://doi.org/10.1007/s11064-012-0852-8.

Wang, C., Yuan, J., Wu, H.-X., Chang, Y., Wang, Q.-T., Wu, Y.-J., Liu, L.-H., Wei, W., 2013. Paeoniflorin inhibits inflammatory responses in mice with allergic contact dermatitis by regulating the balance between inflammatory and anti-inflammatory cytokines. Inflamm. Res. Off. J. Eur. Histamine Res. Soc. Al 62, 1035–1044. https://doi.org/10.1007/s00011-013-0662-8.

Wang, F., Wu, L., Li, L., Chen, S., 2014a. Monotropein exerts protective effects against IL-1β-induced apoptosis and catabolic responses on osteoarthritis chondrocytes. Int. Immunopharm. 23, 575–580. https://doi.org/10.1016/j.intimp.2014.10.007.

Wang, Y., Zhang, R., Xie, J., Lu, J., Yue, Z., 2014b. Analgesic activity of catalpol in rodent models of neuropathic pain, and its spinal mechanism. Cell Biochem. Biophys. 70, 1565–1571. https://doi.org/10.1007/s12013-014-0096-0.

Wang, M.-L., Yu, G., Yi, S.-P., Zhang, F.-Y., Wang, Z.-T., Huang, B., Su, R.-B., Jia, Y.-X., Gong, Z.-H., 2015. Antinociceptive effects of incarvillateine, a monoterpene alkaloid from Incarvillea sinensis, and possible involvement of the adenosine system. Sci. Rep. 5, 16107. https://doi.org/10.1038/srep16107.

Wang, S., Zhang, D., Hu, J., Jia, Q., Xu, W., Su, D., Song, H., Xu, Z., Cui, J., Zhou, M., Yang, J., Xiao, J., 2017. A clinical and mechanistic study of topical borneol-induced analgesia. EMBO Mol. Med. 9, 802–815. https://doi.org/10.15252/emmm.201607300.

Ward, W.K., Li, A.G., Siddiqui, Y., Federiuk, I.F., Wang, X.-J., 2008. Increased expression of Interleukin-13 and connective tissue growth factor, and their potential roles during foreign body encapsulation of subcutaneous implants. J. Biomater. Sci. Polym. Ed. 19, 1065–1072. https://doi.org/10.1163/156856208784909408.

Williams, A.C., Barry, B.W., 1991. Terpenes and the lipid-protein-partitioning theory of skin penetration enhancement. Pharm. Res. 8, 17–24.

Wu, H., Wei, W., Song, L., Zhang, L., Chen, Y., Hu, X., 2007. Paeoniflorin induced immune tolerance of mesenteric lymph node lymphocytes via enhancing beta 2-adrenergic receptor desensitization in rats with adjuvant arthritis. Int. Immunopharm. 7, 662–673. https://doi.org/10.1016/j.intimp.2007.01.019.

Wu, Q., Yu, L., Qiu, J., Shen, B., Wang, D., Soromou, L.W., Feng, H., 2014. Linalool attenuates lung inflammation induced by Pasteurella multocida via activating Nrf-2 signaling pathway. Int. Immunopharm. 21, 456–463. https://doi.org/10.1016/j.intimp.2014.05.030.

Wu, K.-C., Huang, S.-S., Kuo, Y.-H., Ho, Y.-L., Yang, C.-S., Chang, Y.-S., Huang, G.-J., 2017. Ugonin M, a helminthostachys zeylanica constituent, prevents LPS-induced acute lung injury through TLR4-mediated MAPK and NF-κB signaling pathways. Mol. Basel Switz. 22. https://doi.org/10.3390/molecules22040573.

Wynn, T.A., Chawla, A., Pollard, J.W., 2013. Macrophage biology in development, homeostasis and disease. Nature 496, 445–455. https://doi.org/10.1038/nature12034.

Xiao, W.Q., Yin, G.J., Fan, Y.T., Qiu, L., Cang, X.F., Yu, G., Hu, Y.L., Xing, M., Wu, D.Q., Wang, X.P., Hu, G.Y., Wan, R., 2014. Catalpol ameliorates sodium taurocholate-induced acute pancreatitis in rats via inhibiting activation of nuclear factor kappa B. Int. J. Mol. Sci. 15, 11957–11972. https://doi.org/10.3390/ijms150711957.

Xiaofeng, Y., Qinren, C., Jingping, H., Xiao, C., Miaomiao, W., Xiangru, F., Xianxing, X.,

Meixia, H., Jing, L., Jingyuan, W., Xinxin, C., Hongyu, L., Yanhong, D., Lanxiang, J., Xuming, D., 2012. Geniposide, an iridoid glucoside derived from Gardenia jasminoides, protects against lipopolysaccharide-induced acute lung injury in mice. Planta Med. 78, 557–564. https://doi.org/10.1055/s-0031-1298212.

Xie, G., Chen, N., Soromou, L.W., Liu, F., Xiong, Y., Wu, Q., Li, H., Feng, H., Liu, G., 2012. p-Cymene protects mice against lipopolysaccharide-induced acute lung injury by inhibiting inflammatory cell activation. Mol. Basel Switz. 17, 8159–8173. https://doi.org/10.3390/molecules17078159.

Xu, L., Li, Y., Fu, Q., Ma, S., 2014. Perillaldehyde attenuates cerebral ischemia-reperfusion injury-triggered overexpression of inflammatory cytokines via modulating Akt/JNK pathway in the rat brain cortex. Biochem. Biophys. Res. Commun. 454, 65–70. https://doi.org/10.1016/j.bbrc.2014.10.025.

Xu, B., Li, Y.-L., Xu, M., Yu, C.-C., Lian, M.-Q., Tang, Z.-Y., Li, C.-X., Lin, Y., 2017. Geniposide ameliorates TNBS-induced experimental colitis in rats via reducing inflammatory cytokine release and restoring impaired intestinal barrier function. Acta Pharmacol. Sin. 38, 688–698. https://doi.org/10.1038/aps.2016.168.

Xue, J., Li, H., Deng, X., Ma, Z., Fu, Q., Ma, S., 2015. L-Menthone confers antidepressant-like effects in an unpredictable chronic mild stress mouse model via NLRP3 inflammasome-mediated inflammatory cytokines and central neurotransmitters. Pharmacol. Biochem. Behav. 134, 42–48. https://doi.org/10.1016/j.pbb.2015.04.014.

Ya, B., Li, C., Zhang, L., Wang, W., Li, L., 2010. Cornel iridoid glycoside inhibits inflammation and apoptosis in brains of rats with focal cerebral ischemia. Neurochem. Res. 35, 773–781. https://doi.org/10.1007/s11064-010-0134-2.

Yamamoto, M., Miura, N., Ohtake, N., Amagaya, S., Ishige, A., Sasaki, H., Komatsu, Y., Fukuda, K., Ito, T., Terasawa, K., 2000. Genipin, a metabolite derived from the herbal medicine Inchin-ko-to, and suppression of Fas-induced lethal liver apoptosis in mice. Gastroenterology 118, 380–389.

Yamazaki, M., Chiba, K., 2008. Genipin exhibits neurotrophic effects through a common signaling pathway in nitric oxide synthase-expressing cells. Eur. J. Pharmacol. 581, 255–261. https://doi.org/10.1016/j.ejphar.2007.12.001.

Yang, S.-M., Hua, K.-F., Lin, Y.-C., Chen, A., Chang, J.-M., Kuoping Chao, L., Ho, C.-L., Ka, S.-M., 2013. Citral is renoprotective for focal segmental glomerulosclerosis by inhibiting oxidative stress and apoptosis and activating Nrf2 pathway in mice. PloS One 8, e74871. https://doi.org/10.1371/journal.pone.0074871.

Yu, D., Shi, M., Bao, J., Yu, X., Li, Y., Liu, W., 2016. Genipin ameliorates hypertension-induced renal damage via the angiotensin II-TLR/MyD88/MAPK pathway. Fitoterapia 112, 244–253. https://doi.org/10.1016/j.fitote.2016.06.010.

Zanotti, S., Kumar, A., Kumar, A., 2002. Cytokine modulation in sepsis and septic shock. Expet Opin. Invest. Drugs 11, 1061–1075.

Zarai, Z., Kadri, A., Ben Chobba, I., Ben Mansour, R., Bekir, A., Mejdoub, H., Gharsallah, N., 2011. The in-vitro evaluation of antibacterial, antifungal and cytotoxic properties of Marrubium vulgare L. essential oil grown in Tunisia. Lipids Health Dis. 10, 161. https://doi.org/10.1186/1476-511X-10-161.

Zhang, X.L., Jiang, B., Li, Z.B., Hao, S., An, L.J., 2007. Catalpol ameliorates cognition deficits and attenuates oxidative damage in the brain of senescent mice induced by D-galactose. Pharmacol. Biochem. Behav. 88, 64–72. https://doi.org/10.1016/j.pbb.2007.07.004.

Zhang, P., Zhang, J.-J., Su, J., Qi, X.-M., Wu, Y.-G., Shen, J.-J., 2009. Effect of total glucosides of paeony on the expression of nephrin in the kidneys from diabetic rats. Am. J. Chin. Med. 37, 295–307. https://doi.org/10.1142/S0192415X09006850.

Zhang, X., Jin, C., Li, Y., Guan, S., Han, F., Zhang, S., 2013. Catalpol improves cholinergic function and reduces inflammatory cytokines in the senescent mice induced by D-galactose. Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc. 58, 50–55. https://doi.org/10.1016/j.fct.2013.04.006.

Zhang, J., Dou, W., Zhang, E., Sun, A., Ding, L., Wei, X., Chou, G., Mani, S., Wang, Z., 2014. Paeoniflorin abrogates DSS-induced colitis via a TLR4-dependent pathway. Am. J. Physiol. Gastrointest. Liver Physiol. 306, G27–G36. https://doi.org/10.1152/ajpgi.00465.2012.

Zhang, H.-R., Peng, J.-H., Cheng, X.-B., Shi, B.-Z., Zhang, M.-Y., Xu, R.-X., 2015a. Paeoniflorin attttenuates amyloidogenesis and the inflammatory responses in a transgenic mouse model of Alzheimer's disease. Neurochem. Res. 40, 1583–1592. https://doi.org/10.1007/s11064-015-1632-z.

Zhang, Y., Yin, F., Liu, J., Liu, Z., Guo, L., Xia, Z., Zidichouski, J., 2015b. Geniposide attenuates insulin-deficiency-induced acceleration of β-amyloidosis in an APP/PS1 transgenic model of Alzheimer's disease. Neurochem. Int. 89, 7–16. https://doi.org/10.1016/j.neuint.2015.04.002.

Zhang, A., Wang, S., Zhang, J., Wu, H., 2016a. Genipin alleviates LPS-induced acute lung injury by inhibiting NF-κB and NLRP3 signaling pathways. Int. Immunopharm. 38, 115–119. https://doi.org/10.1016/j.intimp.2016.05.011.

Zhang, Z., Zhang, Q., Yang, H., Liu, W., Zhang, Y., Liu, Q., Xin, H., 2016b. Monotropein isolated from the roots of Morinda officinalis increases osteoblastic bone formation and prevents bone loss in ovariectomized mice. Fitoterapia 110, 166–172. https://doi.org/10.1016/j.fitote.2016.03.013.

Zhang, Q.-L., Fu, B.M., Zhang, Z.-J., 2017. Borneol, a novel agent that improves central nervous system drug delivery by enhancing blood-brain barrier permeability. Drug Deliv. 24, 1037–1044. https://doi.org/10.1080/10717544.2017.1346002.

Zhao, L.M., He, X.J., Liu, Y.L., 2006. Effects of Borneol injection on learning and memory in mice after cerebral ischemia-reperfusion injury. West China J. Pharm. Sci. 21 (1), 600–621.

Zhao, C., Zeng, Y., Wan, M., Li, R., Liang, Y., Li, C., Zeng, Z., Chau, F.-T., 2009. Comparative analysis of essential oils from eight herbal medicines with pungent flavor and cool nature by GC-MS and chemometric resolution methods. J. Separ. Sci. 32, 660–670. https://doi.org/10.1002/jssc.200800484.

Zhao, C., Sun, J., Fang, C., Tang, F., 2014. 1,8-cineol attenuates LPS-induced acute pulmonary inflammation in mice. Inflammation 37, 566–572. https://doi.org/10.1007/

s10753-013-9770-4.

Zheng, Y.-Q., Wei, W., 2005. Total glucosides of paeony suppresses adjuvant arthritis in rats and intervenes cytokine-signaling between different types of synoviocytes. Int. Immunopharm. 5, 1560–1573. https://doi.org/10.1016/j.intimp.2005.03.010.

Zheng, X., Yang, D., Liu, X., Wang, N., Li, B., Cao, H., Lu, Y., Wei, G., Zhou, H., Zheng, J., 2010. Identification of a new anti-LPS agent, geniposide, from Gardenia jasminoides Ellis, and its ability of direct binding and neutralization of lipopolysaccharide in vitro and in vivo. Int. Immunopharm. 10, 1209–1219. https://doi.org/10.1016/j.intimp. 2010.07.001.

Zhong, W., Chi, G., Jiang, L., Soromou, L.W., Chen, N., Huo, M., Guo, W., Deng, X., Feng, H., 2013. p-Cymene modulates in vitro and in vivo cytokine production by inhibiting MAPK and NF-κB activation. Inflammation 36, 529–537. https://doi.org/10.1007/ s10753-012-9574-y.

Zhou, H., Bian, D., Jiao, X., Wei, Z., Zhang, H., Xia, Y., He, Y., Dai, Y., 2011. Paeoniflorin protects against lipopolysaccharide-induced acute lung injury in mice by alleviating inflammatory cell infiltration and microvascular permeability. Inflamm. Res. Off. J. Eur. Histamine Res. Soc. Al 60, 981–990. https://doi.org/10.1007/s00011-011-

0359-9.

Zhou, E., Fu, Y., Wei, Z., Yu, Y., Zhang, X., Yang, Z., 2014. Thymol attenuates allergic airway inflammation in ovalbumin (OVA)-induced mouse asthma. Fitoterapia 96, 131–137. https://doi.org/10.1016/j.fitote.2014.04.016.

Zhou, J., Xu, G., Ma, S., Li, F., Yuan, M., Xu, H., Huang, K., 2015. Catalpol ameliorates high-fat diet-induced insulin resistance and adipose tissue inflammation by suppressing the JNK and NF-κB pathways. Biochem. Biophys. Res. Commun. 467, 853–858. https://doi.org/10.1016/j.bbrc.2015.10.054.

Zhu, M.J., Du, M., Nathanielsz, P.W., Ford, S.P., 2010. Maternal obesity up-regulates inflammatory signaling pathways and enhances cytokine expression in the mid-ge-station sheep placenta. Placenta 31, 387–391. https://doi.org/10.1016/j.placenta. 2010.02.002.

Ziyadeh, F.N., Sharma, K., Ericksen, M., Wolf, G., 1994. Stimulation of collagen gene expression and protein synthesis in murine mesangial cells by high glucose is mediated by autocrine activation of transforming growth factor-beta. J. Clin. Invest. 93, 536–542. https://doi.org/10.1172/JCI117004.