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## Monoterpenes modulating cytokines - a review

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Abbreviations: AP-1, Activator protein 1; APP, Amyloid precursor protein; BCG, Bacillus Calmétte-Guérin;  $\beta$ CD,  $\beta$ -cyclodextrin, CFA, Complete Freund's Adjuvant; CT, Citronellol; CTGF, Connective tissue growth factor; DNCB, Dinitrochlorobenzene; DSS, Dextran sulfate sodium; EOs, Essential oils; ERK, Extracellular signal-regulated kinase; FSGS, Focal segmental glomerulosclerosis; GE, Geniposide; Ge-OH, Geraniol; LPS, Lipopolysaccharide; MCAO, Middle cerebral artery occlusion; MMPs, Matrix metalloproteinases; NKT, Natural killer T; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; NSAID, Non-steroidal anti-inflammatory drugs; OVA, Ovalbumin; PA, Perillyl alcohol; PAH, Perillaldehyde; PF, Paeoniflorin; PS1, Presenilin 1; RA, rheumatoid arthritis; STAT-1, Activator of transcription 1; Th1, T helper 1 cells; Th2, T helper 2 cells; TLR, Toll Like Receptor; TNBS, Trinitrobenzenesulfonic acid; TPN,  $\alpha$ -terpineol; TQ, Thymoquinone; VEGF, Vascular endothelial growth factor;

## **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- $\alpha$ , IL-1 $\beta$ , IL-2, IL-5, IL-4, IL-6, IL-8, IL-10, IL-12 IL-13, IL-17A, IFN $\gamma$ , TGF- $\beta$ 1 and IFN- $\gamma$ . Our review found evidence that NF- $\kappa$ B 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.

**Keywords:** Natural products, terpenes, inflammation, cytokines

## **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<sub>2</sub>, 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, C and White, F, n.d. 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, C and White, F, n.d.). 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-1 $\beta$  and TNF- $\alpha$  (Sommer, C and White, F, n.d.). Interestingly, cytokines contribute to the status quo of rheumatic but non-inflammatory syndromes such as fibromyalgia (Rodríguez-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- $\alpha$  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 IFN $\gamma$  and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) 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- $\beta$ s), 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- $\kappa$ B, 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- $\kappa$ B 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- $\kappa$ B is regulated by binding with inhibitory molecules such as I $\kappa$ B $\alpha$

NF- $\kappa$ B subunits p65 dissociate from their inhibitory protein I $\kappa$ B $\alpha$  and translocate from the cytoplasm to the nucleus where they influence the expression of proinflammatory cytokines (e.g., TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8) (Hayden and Ghosh, 2012; Lawrence, 2009; Prasad, 2014). Preventing NF- $\kappa$ B 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-1 $\beta$ . In addition Nrf2 is associated with NF- $\kappa$ B-mediated transcription of proinflammatory cytokine genes (Kobayashi et al., 2016). Saccani et al. (Saccani et al., 2002) proposed that p38 MAPK regulates the activation of NF- $\kappa$ B.

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 1/2 (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- $\kappa$ B can collaborate synergistically to induce proinflammatory cytokine gene products.(Craig et al., 2000) Therefore, treatments aimed at the inhibition of NF- $\kappa$ B 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<sub>5</sub>) joined in a head-to-tail fashion (Figure 1). The biochemically active isoprene units were identified as the diphosphate (pyrophosphate) esters dimethylallyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP) (Dewick P. M., n.d.).

<INSERT FIGURE 1>

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; Koziol 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 Figure 2.

<INSERT FIGURE 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. (Quintans-Júnior et al., 2013), Wu et al. (Wu et al., 2014), Li et al. (Li et al., 2014); Sabogal-Guaqueta et al. (Sabogal-Guáqueta et al., 2016) revealed that 10 to 40 mg/kg of linalool taken orally reduced the pro-inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , 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-1 $\beta$  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- $\kappa$ B 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).

Figure 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- $\kappa$ B signaling and IL-1 $\beta$  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-1 $\beta$ , TNF- $\alpha$  as well as NF- $\kappa$ B signalling (Babu et al., 2012; Polosukhin et al., 2014). Finally, linalool, complexed or non-complexed with  $\beta$ -CD, decreases TNF- $\alpha$  levels in animals with carrageenan-induced paw edema (Quintans-Júnior et al., 2013). Therefore, the findings described in Figure 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.

<INSERT FIGURE 3>

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-1 $\beta$ , IL-17, IFN- $\gamma$ , and TNF- $\alpha$  (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- $\alpha$ , IL-1 $\beta$  and IL-6 and NF- $\kappa$ B 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, B 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- $\kappa$ B activation on lipopolysaccharide (LPS)-induced inflammation in the mouse macrophage cell line RAW 264.7 (Su et al., 2010). Brito et al. (Brito et al., 2012) reported that CT (25-100 mg/kg, ip) significantly suppressed the increase of TNF- $\alpha$  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- $\alpha$ , and IL-1 $\beta$  by the administration of citral in renal inflammation. Similarly, citral inhibits LPS-induced acute lung injury by activating peroxisome proliferator activated receptor- $\gamma$  (PPAR- $\gamma$ ) and when compared to control group, LPS instillation dramatically increased TNF- $\alpha$ , IL-6 and IL-1 $\beta$  expression. However, TNF- $\alpha$ , IL-6 and IL-1 $\beta$  production induced by LPS were down-regulated 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<sub>2</sub>, IL-1 $\beta$  and TNF- $\alpha$  (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-1 $\beta$  and PGE<sub>2</sub>. 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- $\alpha$  and PPAR- $\gamma$  (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 (Feng and Jia, 2014), and Kara et al (Kara et al., 2015) experimentally proved that carvacrol at doses of 20, 40, and 80 mg/kg also significantly reduced TNF- $\alpha$ , IL-1 $\beta$  and IL-6 in LPS induced inflammation, and in acute lung injury induced by lipopolysaccharide in mice. Arigesavan and Sudhandiran (Arigesavan and Sudhandiran, 2015) reported that 50 mg/kg of carvacrol controls the IL-1 $\beta$  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., 2016) investigated the levels of TNF- $\alpha$  and IL-1 $\beta$  and showed that carvacrol treatment prevented middle cerebral artery occlusion (MCAO), and reduced TNF- $\alpha$  and IL-1 $\beta$  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- $\kappa$ B signaling pathway (Z. Li et al., 2016) , the MAPK cascade (ERK, SAP/JNK and p38<sup>MAPK</sup>) (Cui et al., 2015) and TLR2 and TLR4 production (Cho et al., 2012) (Figure 3).

Carvacrol inhibits NF- $\kappa$ B activation (Z. Li et al., 2016), with this effect possibly being related to downregulated phosphorylated/activated NF- $\kappa$ B 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 pathway. This would cause decreased MAPK phosphorylation and consequently inhibit the NF- $\kappa$ B 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 (Figure 4).

<INSERT FIGURE 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.<sup>108</sup> 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- $\alpha$ , IL-1 $\beta$  and IL-6 in the model of 12-*O*-

Tetradecanoylphorbol-13-Acetate (TPA)-induced dermatitis. Furthermore, Hansen et al., (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 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, (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.,(Rehman et al., 2014), showed that limonene knocks out TNF- $\alpha$  expression in a doxorubicin-induced inflammation model and that this effect is related to NF- $\kappa$ B downregulation. Additionally, the anti-inflammatory effect produced by limonene was associated with repression of COX-2 and iNOS enzymes, as well as decreased PGE<sub>2</sub> 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- $\alpha$  serum levels after 2,5,6-trinitrobenzene sulfonic acid-induced colitis by decreasing NF- $\kappa$ B 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-inflammatory or anti-inflammatory production of cytokines and decreases some key inflammatory mediators (e.g. PGE<sub>2</sub>). Furthermore, it is indeed possible that decreased activation of NF- $\kappa$ B 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. (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- $\alpha$ , IL-1 $\beta$ , 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. (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- $\alpha$ , IL-1 $\beta$ , 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., (Quintans et al., 2013), developed an inclusion complex containing *p*-cymene and  $\beta$ -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- $\alpha$  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 biocatalytically 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. (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- $\gamma$  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., (Tabassum et

al., 2015), showed in an ischemia/reperfusion injury model that PA acts on the inflammation by inhibiting the expression of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , NOS-2 COX-2 and NF- $\kappa$  $\beta$  (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-1 $\beta$ , TNF- $\alpha$  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  $\gamma$ -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  $\gamma$ -terpinene in LPS-induced production of cytokines by murine peritoneal macrophages induced a significant inhibition of pro-inflammatory cytokines, such as IL-1 $\beta$  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<sub>2</sub>. Interestingly, COX-2 inhibition by nimesulide abolished the potentiating effect of  $\gamma$ -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 XJ et al., 2006; Zhao LM et al., 2006). Recently, Zhang et al., (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., (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- $\alpha$  positive cells, and leukocyte infiltration in the brains of rats. In addition, no statistically significant difference was observed in IL-1 $\beta$  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-1 $\beta$  mRNA levels in TNBS (2,4,6-trinitrobenzene sulfonic acid)-induced colitis in mice, however, no changes were observed in TNF- $\alpha$  (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 TNF $\alpha$ , IL-6 and IL-1 $\beta$  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- $\alpha$ , IL-1 $\beta$  and IL-6 triggered by sepsis., (Ozer et al., 2017). These findings are corroborated by Tekeoglu et al., (Tekeoglu et al., 2006), who described the anti-inflammatory effects of TQ on experimentally-induced arthritis in rats, which equally reduced levels of TNF- $\alpha$  and IL-1 $\beta$  plasma in the rodents.

Trinh (Trinh et al., 2011) evaluated the effect of  $\alpha$ -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 AA 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- $\kappa$ B. 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- $\kappa$ B 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- $\alpha$ ) 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., (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- $\alpha$ , IL-1 $\beta$ , and IL-6). Interestingly, pre-treatment 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- $\kappa$ B p65 translocation via I $\kappa$ B $\alpha$ , resulting in decreased levels of proinflammatory NF- $\kappa$ B 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- $\alpha$ , IL-1 $\beta$ , and IL-6 through inhibition of the NF- $\kappa$ B 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, H and Nakai K, 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- $\alpha$  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-1 $\beta$ .

$\alpha$ -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  $\alpha$ -pinene. Kim et al. (D.-S. Kim et al., 2015) suggested that  $\alpha$ -pinene suppresses IL-6 and TNF- $\alpha$  release in a dose dependent manner in a protocol using LPS-stimulated macrophages, with the monoterpene significantly inhibiting PGE<sub>2</sub> 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- $\alpha$ , IL-1 $\beta$ , 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- $\alpha$  and IL-6 were induced by  $\alpha$ -pinene in an ovalbumin-sensitized allergic rhinitis animal model, however, no change was observed in IL-1 $\beta$  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., 2015) and inhibited NF- $\kappa$ B activity (D.-S. Kim et al., 2015; Nam et al., 2014). Our review corroborates the evidence that  $\alpha$ -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 P. M., 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 2,000 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- $\alpha$ , IFN- $\gamma$  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- $\alpha$ , IFN- $\gamma$  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., (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- $\gamma$ , TNF- $\alpha$ , 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- $\beta$  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.(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-13R $\alpha$ 2 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., (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., 2015).

Recently, Zhang et al.(H.-R. Zhang et al., 2015) 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-3 $\beta$  and NF- $\kappa$ B signaling pathways and the nucleotide-binding domain-like receptor protein 3 inflammasome. The pretreatment of mice with PF produced a significant inhibition of TNF- $\alpha$  and IL-1 $\beta$  levels, and significantly upregulated 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- $\beta$  are the most commonly studied immunosuppressive cytokines; they induce the proliferation of Treg cells, e.g., IL-10-producing T-cells and CD4<sup>+</sup> CD25<sup>+</sup> Foxp3<sup>+</sup> T-cells. IL-10 is produced by activated B- and T-cells, monocytes and macrophages ,(Cicutini 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 Calm ette-Gu erin (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- $\alpha$ , IL-1 $\beta$ , IL-6, IL-12, IL-5, IL-13, IL-17 and INF- $\gamma$  as reported in recent studies ,(C. Chen et al., 2015; J. Sun et al., 2015; Y. Sun et al., 2015; Tang et al., 2010; Zhang et al., 2014; Zhou et al., 2011). The cytokines TNF- $\alpha$ , IL-1 $\beta$ , 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- $\alpha$  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, (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., (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- $\alpha$ , IL-6, IL-4 and IL-1 $\beta$  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- $\alpha$ , IL-6, IL-4 and IL-1 $\beta$  production and up-regulated IL-10 expression in LPS-stimulated alveolar macrophages. In addition, it is known that the activation of the NF- $\kappa$ B pathway has been considered as a dominant transcription factor responsible for inflammation. Because NF- $\kappa$ B 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- $\kappa$ B 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., 2015a).

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., 2015; 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., (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- $\alpha$ , 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., 2013).

GE was also assessed by Lv et al., (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- $\alpha$ , IL-1 $\beta$  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<sup>+</sup> T-cells and Th17 regulatory T-cells (Tregs) are related to the development of RA (Wang et al., 2012). According to Dai et al., (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- $\beta$ 1. 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., 2015), reported that GE-treated rodents increased the production of IL-10 and reduced IL-1, IL-6 and TNF- $\alpha$ , 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- $\alpha$ , IL-1 $\beta$ , IL-6, IFN- $\gamma$ , 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., 2015; Kim et al., 2012; Li et al., 2012; Yu et al., 2016).

Zhang et al., (A. Zhang et al., 2016), demonstrated that the NF- $\kappa$ B 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- $\alpha$ , IL-1 $\beta$  and IL-6 which have been significantly increased in BALF 7 h after LPS stimulation. Li et al., (Li et al., 2012), corroborated this finding, demonstrating that genipin can reduce the levels of IL-1 $\beta$  and TNF- $\alpha$  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., (Impellizzeri et al., 2011a), showed that oleuropein significantly attenuated the release of TNF- $\alpha$  and IL-1 $\beta$  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- $\gamma$ , TNF- $\alpha$  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 (Saravanan et al., 2014b, 2014a) 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- $\alpha$  and IL-1 $\beta$  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- $\gamma$ . In general, Th1 cells which produce mainly IL-2 and IFN- $\gamma$  effect immunity against intracellular pathogens, while Th2 cells producing mainly IL-4, IL-5, IL-10, IL-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; Filep 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., 2003; 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; Schepetkin et al., 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,  $\alpha$ -pinene,  $\beta$ -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  $\beta$ -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 (Dumont, 2002; Hur et al., 2012). Moreover, T helper Th1 and Th2 cytokines have been shown to play an 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; Ogawa et al., 2014; 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- $\alpha$  inhibitor etanercept (Enbrel<sup>®</sup>) which was the first biopharmaceutical on the market approved by U.S. F.D.A to treat 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<sup>®</sup>), a fully human monoclonal antibody against TNF- $\alpha$ , that can relieve

symptoms of autoimmune diseases, reduce inflammation and inhibit chronic pain (Aitken et al., 2018). The TNF- $\alpha$  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- $\alpha$ , prototypic pro-inflammatory 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, 2012). These reviews, which demonstrated the results of clinical trials with TNF- $\alpha$  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<sup>®</sup>), 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- $\alpha$ , IL-1 $\beta$  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- $\alpha$  and IL-1 $\beta$  (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- $\beta$ , TGF- $\beta$ ) 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 generate 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- $\alpha$  and IL-1 $\beta$  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- $\alpha$ , IL-1 $\beta$ , IL-2, IL-5, IL-4, IL-6, IL-8, IL-10, IL-12 IL-13, IL-17A, IFN $\gamma$ , TGF- $\beta$ 1 and IFN- $\gamma$ . 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- $\alpha$ , IL-1 $\beta$ , 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  $\alpha$ -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- $\alpha$  have already entered clinical trials as a potential treatments for inflammatory disorders (Reinhart and Karzai, 2001).

Furthermore, our survey provides evidence that NF- $\kappa$ B signaling is one of the most important pathways for the anti-inflammatory action of monoterpenes. The transcription factor NF- $\kappa$ B plays an important role in inflammation progression. Upon activation of the inflammation processes, NF- $\kappa$ B induces the expression of many inflammatory genes, including COX-2 and iNOS which influences the expression of proinflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , 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- $\kappa$ B 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.

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## LEGENDS

**Figure 1.** Schematic of biosynthesis of monoterpenes.(Dewick P. M., n.d.)

**Figure 2.** Chemical structures of representative monoterpenes.

**Figure 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/  $\beta$ CD or aspirin on leucocyte migration into the peritoneal cavity induced by carrageenan (CG) in mice and determination of TNF- $\alpha$  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).

**Figure 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- $\kappa$ B nuclear translocation (Adapted from Cui et al., 2015) **D)** Effect of carvacrol or indomethacin on TNF $\alpha$  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)



**Table 1-** Characteristics of studies of anti-inflammatory cytokines

<b>ACYCLIC MONOTERPENES</b>									
<b>Authors, year, Country</b>	<b>Substance/ Chemical group</b>	<b>Animals (Strain/Sex)</b>	<b>Dose (route)</b>	<b>Model</b>	<b>Sample</b>	<b>Evaluation</b>	<b>Cytokines</b>	<b>R</b>	<b>B</b>
De Fazio et al., 2016, Italy <sup>73</sup>	Geraniol Compound (2) Figure 2	Male C57BL/6 mice	30 and 120 mg/kg (p.o.)	(DSS)-induced colitis mouse model.	Plasma	IA	↓ (IL-10)	Y	N
<b>MONOCYCLIC MONOTERPENES</b>									
Trinh et al., 2011, Korea <sup>151</sup>	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 <sup>286</sup>	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)	Mice	50-100 mg/kg (i.p.)	CFA-induced inflammation	Skin tissue	ELISA	↑ (IL-10)	N	N

	Figure 2	(Swiss/M)				RT-PCR			
Zhong et al., 2013, China <sup>121</sup>	<i>p</i> -Cymene Compound (8) Figure 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 <sup>148</sup>	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 <sup>148</sup>	Borneol Compound (12) Figure 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, 2010 <sup>280</sup>	1,8-Cineole	Pigs (guinea/M)	1 mg/mL (Inhalation)	Ovalbumin - Challenged	BALF	ELISA	↑ (IL-10)	N	N
Trinh et al., 2011, Korea <sup>151</sup>	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 <sup>164</sup>	1,8-Cineole	Mice	100-400 mg/kg (p.o.)	Cerulein-induced acute	Serum sample	ELISA	↑ (IL-10)	N	N

		(Swiss/M)		pancreatitis					
Zhao et al., 2014 China <sup>162</sup>	1,8-Cineole	Mice (ICR/M)	10-100 mg/kg (p.o.)	(LPS)-induced ALI	Lung tissues	ELISA	↑ (IL-10)	Y	N
Siveen, Kuttan, 2011, India <sup>308</sup>	Thujone	Mice (Balb/c/-)	1 (i.p)	EAC cells-induced tumor	Serum sample	ELISA	↑ (IL-2 and IFN-γ)	N	N
<b>IRIDOID GLYCOSIDES</b>									
<b>Authors, year, Country</b>	<b>Substance/ Chemical group</b>	<b>Animals (Strain/Sex)</b>	<b>Dose (route)</b>	<b>Model</b>	<b>Sample</b>	<b>Evaluation</b>	<b>Cytokines</b>	<b>R</b>	<b>B</b>
Xiaofeng et al., 2012. China <sup>230</sup>	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 <sup>307</sup>	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 <sup>234</sup>	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,	Catalpol	Mice (BALBc/M)	2.5-10 mg/kg (i.p.)	LPS – induced ALI	BALF	ELISA	↑ (IL-10)	Y	N

China <sup>211</sup>									
Zhou et al., 2015, China <sup>295</sup>	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 <sup>301</sup>	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 <sup>252</sup>	Oleuropein	Rat (Wistar/M)	20 mg/kg (p.o.)	BPDO-induced pancreatitis	Serum sample	ELISA	☒ (IL-10)	Y	N
Wang et al., 2013, China <sup>190</sup>	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., 2015, China <sup>199</sup>	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., 2014, India <sup>263</sup>	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), amyloid precursor 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

<b>ACYCLIC MONOTERPENES</b>									
<b>Authors, year, Country</b>	<b>Substance/ Chemical group</b>	<b>Animals (Strain/Sex)</b>	<b>Dose (mg/kg) (route)</b>	<b>Model</b>	<b>Sample</b>	<b>Evaluation</b>	<b>Cytokines</b>	<b>R</b>	<b>B</b>
Deepa and Anuradha, 2011, India <sup>62</sup>	Linalool Compound (1) Figure 2	Rat (Wistar/M)	25 (p.o.)	Diabetes-induced Nephropathic changes	Plasm/ kidney tissue	ELISA/ PCR	↓ (TNF- $\alpha$ , IL-6)	N	N
Quintans-Júnior et al., 2013, Brazil <sup>63</sup>	Linalool	Mice (Swiss/M)	20 or 40 (p.o.)	Antinociceptive effect	Peritoneal fluid	ELISA	↓ (TNF- $\alpha$ )	Y	N
Wu et al., 2014, China <sup>64</sup>	Linalool	Mice (C57BL6/M)	25 (p.o.)	Lung inflammation induced by Pasteurella multocida	Lung	ELISA	↓ (TNF- $\alpha$ , IL-6)	N	N
Li et al., 2014, China <sup>65</sup>	Linalool	Mice (BALBc/M)	10, 20, 40 (i.p.)	LPS/GalN-induced acute liver injury	Serum Liver tissue	ELISA	↓ (TNF- $\alpha$ , IL-6)	Y	N
Sabogal-Guaqueta et al., 2016, Colombia <sup>66</sup>	Linalool	Mice (3xTg-AD,	25 (p.o.)	Triple transgenic Alzheimer's mice	Brain tissue	ELISA	↓ (IL-1 $\beta$ )	Y	N

		Non-Tg/ -)							
Marcuzzi et al., 2011, Italy <sup>266</sup>	Geraniol Compound (2) Figure 2	Mice (BALBc/M)	100 (i.p.)	Mevalonate kinase deficiency	Serum	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Medicherla et al., 2015, India <sup>74</sup>	Geraniol	Mice (BALBc/M)	50, 100 (p.o.)	Acute experimental colitis	Colon tissue	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
De Fazio et al., 2016 Italy <sup>73</sup>	Geraniol	Mice (C57BL6/M)	30, 120 (p.o.)	(DSS)-induced colitis mouse model.	Plasma	Immune assay	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-17, IFN- $\gamma$ )	Y	N
Brito et al., 2012, Brazil <sup>81</sup>	Citronellol Compound (3) Figure 2	Mice (Swiss/M)	25-100 (i.p.)	Carrageenan-induced pleurisy	Pleural lavage	ELISA	↓ (TNF- $\alpha$ )	Y	Y
Yang et al., 2013, Taiwan <sup>86</sup>	Citral Compound (4) Figure 2	Mice(BALB/c M)	200 (p.o)	Renal inflammation	Renal tissues	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	N	N
Shen et al., 2015, China <sup>87</sup>	Citral	Mice (BALBc/M)	40 (i.p.)	(LPS)-induced acute lung injury	BALF	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , 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 <sup>151</sup>	$\alpha$ -Terpineol	Mice (IRC/F)	10% v/v (topic)	Vaginosis and vulvovaginal candidiasis	Vaginal tissue	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	N	N
Ramalho et al 2015 Brazil <sup>138</sup>	$\gamma$ -Terpinene Compound (11) Figure 2	Mice (Swiss/F)	25 (p.o.)	Carrageenan-induced peritonitis	Peritoneal lavage	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ ) ☒ IL-6	N	N
Xue et al., 2015 China <sup>267</sup>	L-Menthone	Mice (ICR/M)	15, 30 (p.o.)	UCMS	Hippocampus samples	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	Y
Rozza et al., 2014 Brazil <sup>268</sup>	Menthol	Rats (Wistar/M)	50 (p.o.)	Ethanol-induced gastric ulcers	Gastric mucosal	ELISA	↓ (TNF- $\alpha$ , IL-6)	N	N
Cho et al., 2012 Korea <sup>101</sup>	Carvacrol Compound (5) Figure 2	Mice (C57BL/M)	0.1% (suppl diet)	HFD-induced obesity	Visceral adipose tissue	RT-PCR	↓ (TNF- $\alpha$ , INF- $\alpha$ )	N	N
Guimarães et al., 2012, Brazil <sup>92</sup>	Carvacrol	Mice (Swiss/M)	25, 50, 100 (i.p.)	Carrageenan-induced pleurisy	Pleural lavage	ELISA	↓ TNF- $\alpha$	Y	N
Lima et al., 2013, Brazil <sup>58</sup>	Carvacrol	Mice (Swiss/M)	50,100 (i.p.)	CFA-induced inflammation	Skin paw tissue	ELISA RT-PCR	☒ TNF- $\alpha$ ↓ IL-1 $\beta$	N	N

Aristatile et al., 2013, India <sup>269</sup>	Carvacrol	Rats (Wistar/M)	20 (p.o.)	D-GalN-induced hepatotoxic	Liver tissue	RT-PCR W.Blot	↓ (TNF- $\alpha$ , IL-6)	N	N
Deng et al., 2013, China <sup>270</sup>	Carvacrol	Rats (Wistar/M)	25, 50, 100 (i.p)	Streptozotocin-induced diabetic	Cerebral cortex Hippocampus	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	N
Celik et al., 2013, Turkey <sup>271</sup>	Carvacrol	Rats (Wistar/M)	73 (i.p)	Methotrexate induced toxicity	Sciatic nerve	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	N
Mahtaj et al., 2014, Iran <sup>272</sup>	Carvacrol	Pig (Guinea/ M,F)	60-240 $\mu$ g/mL (drinking water)	<a href="#">Cigarette Smoke-Induced</a> COPD	Serum samples	ELISA	↓ IL-8	Y	N
Feng and Jia, 2014, China <sup>96</sup>	Carvacrol	Mice (BALBc/M)	20, 40, 80 (i.p)	LPS-induced ALI	BALF	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Kara et al., 2015, Turkey <sup>97</sup>	Carvacrol	Rats (SD/F)	20, 40, 80 (p.o.)	LPS-induced Sepses	Serum samples	ELISA	↓ (TNF- $\alpha$ , IL-6)	N	N
Arigesavan, Sudhandiran, 2015, India <sup>98</sup>	Carvacrol	Rat (Fischer 344/M)	50 (p.o.)	DMH/DSS-induced colitis associated Colon cancer	Colonic tissue	IHC	↓ IL-1 $\beta$	N	N
Li et al., 2016, China <sup>99</sup>	Carvacrol	Rats (SD/M)	10, 20, 40 (i.p.)	MCAO	Cortical tissues	ELISA	↓(TNF- $\alpha$ , IL-1 $\beta$ )	Y	N

Zhou et al., 2014, China <sup>116</sup>	Thymol	Mice (BALBc/F)	4, 8, 16 (p.o.)	OVA-induced asthma	BALF	ELISA	↓(IL-4, IL-5, IL-13)	N	N
Deng et al., 2015, China <sup>273</sup>	Thymol Compound (7) Figure 2	Mice (ICR/M)	15, 30 (p.o.)	CUMS	Hippocampus	RT-PCR	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Meeran et al., 2015, India <sup>117</sup>	Thymol	Rats (Wistar/M)	7.5 (p.o.)	ISO induced MI	Heart tissue	RT-PCR	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	N	N
Xie et al., 2012, China <sup>274</sup>	<i>p</i> -Cymene Compound (8) Figure 2	Mice (BALB/c/M)	25, 50, 100 (i.p.)	LPS-Induced ALI	BALF	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Zhong et al., 2013, China <sup>121</sup>	<i>p</i> -Cymene	Mice (C57BL/6/F)	53, 107, 214 (i.p.)	LPS-induced inflammation	Serum sample	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	N
Chen et al., 2014. China <sup>275</sup>	<i>p</i> -Cymene	Mice (BALB/c/F)	5, 10 (i.p.)	LPS-Induced ALI	BALF	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
de Santana et al., 2015, Brazil <sup>122</sup>	<i>p</i> -Cymene	Mice (Swiss/M)	25, 50, 100 (i.p.)	Carrageenan-induced pleurisy	Pleural lavage	ELISA	↓ TNF- $\alpha$	N	N
Nonato et al., 2012, Brazil <sup>276</sup>	Rose oxide	Mice (Swiss/M)	100 (i.p.)	CFA-induced paw inflammation	Skin tissues	ELISA	☒TNF- $\alpha$ , ↓IL-1 $\beta$	N	N

Juhás et al., 2008, Slovak Republic <sup>148</sup>	Thymoquinone	Mice (ICR/M)	75 (suppl diet)	TNBS-induced colitis	Colon tissue	RT-PCR	☒ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Juhás et al., 2008, Slovak Republic <sup>148</sup>	Borneol Compound (12) Figure 2	Mice (ICR/M)	135, 270 (suppl diet)	TNBS-induced colitis	Colon tissue	RT-PCR	☒TNF- $\alpha$ , ↓ (IL-1 $\beta$ , IL-6)	Y	N
Kong et al., 2014, China <sup>147</sup>	Borneol	Rat (Wistar/M)	1, 2, 3 (i.v.)	Focal ischemia reperfusion	Brain tissue	IHC	↓TNF- $\alpha$ , ☒ IL-1 $\beta$	Y	N
Siqueira et al., 2016 Brazil <sup>277</sup>	$\alpha$ -Phellandrene	Mice (Swiss/M)	50 (p.o.)	Carrageenan-induced peritonitis	Peritoneal lavage	ELISA	↓ (TNF- $\alpha$ , IL-6)	N	N
d'Alessio et al., 2014, France <sup>110</sup>	<i>D</i> -Limonene	Mice (HS1/F)	10 (s.c.)	TPA-induced dermatitis	Serum sample	Bio-Plex	↓ (TNF- $\alpha$ , IL-6) ☒ IL-1 $\beta$	N	Y
Rehman, et al., 2014, India <sup>113</sup>	D-limonene	Rat (Wistar/M)	5%, 10% (suppl diet)	Doxorubicin induced inflammation	Serum sample	ELISA	↓TNF- $\alpha$	N	N
Hansen et al., 2016, Denmark <sup>111</sup>	Limonene Compound (6) Figure 2	Mice (BALBcJ/F)	40 ppm (via inhalation)	OVA-induced allergic airway inflammation	Lung tissues	Flow cytometer	☒ (TNF- $\alpha$ , IFN- $\gamma$ , IL-10) ↓ IL-5	Y	N
Khan et al., 2011, India <sup>126</sup>	Perillyl alcohol Compound (9) Figure 2	Rats (Wistar/M)	50, 100 (p.o.)	Ethanol induced acute hepatotoxicity	Liver Tissue	ELISA	↓ TNF- $\alpha$	Y	N

d'Alessio et al., 2014, France <sup>110</sup>	Perillyl alcohol	Mice (HS1/F)	10 (s.c.)	TPA-induced dermatitis	Serum sample	Bio-Plex	↓ (TNF- $\alpha$ , IL-6) ☒ IL-1 $\beta$	N	Y
Imamura et al., 2014, Japan <sup>132</sup>	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 <sup>133</sup>	Perillyl alcohol	Rats (Wistar/M)	100 (p.o.)	MCAO	Frontal cortex hippocampus	-	↓ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	Y
Xu et al., 2014, China <sup>136</sup>	Perillaldehyde Compound (10) Figure 2	Rats (SD/M)	18, 36 (i.g.)	MCAO	Serum	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Ji et al., 2014, China <sup>137</sup>	Perillaldehyde	Mice (ICR/M)	60, 120 (p.o.)	LPS-induced depressive-like behaviour and inflammation	Serum prefrontal cortex	ELISA RT-PCR	↓ (TNF- $\alpha$ , IL-6)	Y	Y
Shih et al., 2012. Taiwan <sup>278</sup>	$\beta$ -Thujaplicin	Mice (ICR/M)	7, 14, 21 (p.o.)	LPS-induced inflammation	Serum	ELISA	↓ TNF- $\alpha$	N	N
<b>BICYCLIC MONOTERPENES</b>									
<b>Authors, year, Country</b>	<b>Substance/ Chemical group</b>	<b>Animals (Strain/Sex)</b>	<b>Dose (route)</b>	<b>Model</b>	<b>Sample</b>	<b>Evaluation</b>	<b>Cytokines</b>	<b>R</b>	<b>B</b>

Bae et al., 2012, South Korea <sup>180</sup>	$\alpha$ -Pinene	Mice (C57BL/6/F)	5, 25, 50 (p.o.)	Cerulein-induced acute pancreatitis	Pancreas tissue	RT-PCR	↓( TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Nam et al., 2014. Republic Korea <sup>181</sup>	$\alpha$ -Pinene	Mice (BALBc/F)	0.1, 1,10 (p.o.)	OVA-induced allergic rhinitis	Nasal mucosa	ELISA	↓ (TNF- $\alpha$ , IL-6) ☒IL-1 $\beta$	N	N
Santos et al., 2001 Brazil <sup>279</sup>	1,8-Cineole	Mice (Swiss/M)	400 (p.o.)	GalN/LPS-induced shock	Serum sample	ELISA	↓ (TNF- $\alpha$ )	N	N
Bastos et al, 2010 Brazil <sup>280</sup>	1,8-Cineole	Pigs (guinea/M)	1mg/mL (Inhalation)	Ovalbumin-Challenged	BALF	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	N	N
Lima et al., 2013b Brazil <sup>164</sup>	1,8-Cineole	Mice (Swiss/M)	100-400 (p.o.)	Cerulein-induced acute pancreatitis	Serum sample	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	N	N
Zhao et al., 2014 China <sup>162</sup>	1,8-Cineole	Mice (ICR/M)	10 -100 (p.o.)	LPS-induced ALI	Lung tissues	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	N
Li et al., 2016 China <sup>281</sup>	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- $\alpha$ ,IL-1 $\beta$ , IL-6, IFN- $\gamma$ )	Y	N
Lee et al., 2016 South Korea <sup>282</sup>	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., 2015 Republic of Korea 283	1,8-Cineole	Mice (BALBc/M)	200, 400  (i.p.)	LPS-induced ALI	BALF	ELISA	↓ (TNF- $\alpha$ , IL-6)	Y	N
Chen et al., 2014 China 284	Bornyl acetate	Mice (BALBc/M)	25, 50, 100  (i.p.)	LPS-induced ALI	BALF	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ , 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- $\alpha$	N	N
Silva et al., 2014 Brazil 175	Myrtenol	Mice (Swiss/M)	75  (i.p.)	carrageenan-induced peritonitis	Peritoneal exudates	ELISA	☒ TNF- $\alpha$ , ↓ IL-1 $\beta$	Y	N

**IRIDOID GLYCOSIDES**

<b>Authors, year, Country</b>	<b>Substance/ Chemical group</b>	<b>Animals (Strain/Sex)</b>	<b>Dose (route)</b>	<b>Model</b>	<b>Sample</b>	<b>Evaluation</b>	<b>Cytokines</b>	<b>R</b>	<b>B</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- $\alpha$ )	Y	N
Kim et al., 2012	Genipin	Mice	2.5	Cecal ligation and puncture	Serum sample	ELISA	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N

Republic of Korea <sup>242</sup>		(ICR/M)	(i.v.)						
Li et al., 2012, Taiwan <sup>243</sup>	Genipin	Mice (Transgenic/F)	100  (i.p.)	LPS-induced inflammation	Serum sample	ELISA	↓(TNF- $\alpha$ , IL-1 $\beta$ )	Y	N
Cho et al., 2016, Republic of Korea <sup>246</sup>	Genipin	Mice (ICR/M)	2.5  (i.v.)	Cecal ligation and puncture	Serum Sample	ELISA	↓ (TNF- $\alpha$ , IL-6)	Y	N
Zhang et al., 2016, China <sup>247</sup>	Genipin	Mice (Balb/c/M)	1, 2.5, 5  (i.v.)	LPS-induced acute lung injury	BALF	ELISA	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Zheng et al., 2010. China <sup>224</sup>	Geniposide	Mice (KM/M,F)	40  (i.v.)	LPS-induced sepsis	Serum sample	ELISA	↓ (TNF- $\alpha$ , IL-6)	Y	N
Ma et al., 2011, China <sup>286</sup>	Geniposide	Rats (SD/M)	25-100  (diet)	Nonalcoholic steatohepatitis	Liver	RT-PCR	↓ TNF- $\alpha$	Y	N
Xiaofeng et al., 2012. China <sup>230</sup>	Geniposide	Mice (Balb/c/M)	20-80  (i.p.)	LPS-induced ALI	BALF	ELISA	↓ (TNF- $\alpha$ , IL-6)	Y	N
Deng et al., 2013. China <sup>232</sup>	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 <sup>287</sup>	Geniposide	Mice (BALBc/M,F)	5,10 (3x/d)	LPS mastitis	mammary gland tissues	ELISA	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	N	N



			(i.p.)						
Dai et al., 2014. China <sup>234</sup>	Geniposide	Rats (SD/M)	30-120 (p.o.)	FCA- induced arthritis	PBL	ELISA	↓ (IL-6, IL-17)	Y	Y
Lv et al., 2015. China <sup>233</sup>	Geniposide	Mice (APP/PS1/M)	25 (p.o.)	APP/PS1 model Alzheimer disease	Brain tissue	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	N
Xu et al., 2017, China <sup>288</sup>	Geniposide	Rats (SD/M)	25, 50 (p.o.)	TNBS-induced experimental colitis	Colon tissue	ELISA	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Kondo et al., 1994. Japan <sup>289</sup>	Gentiopicroside	mice (ICR/ M)	30, 60 (p.o.)	BCG/LPS-induced Hepatitis	Serum sample	IA	↓ TNF- $\alpha$	N	N
Lian et al., 2010, China <sup>290</sup>	Gentiopicroside	Mice (C57BL/6/M)	40, 80 (p.o.)	GalN/LPS - induced hepatic failure	Serum sample	IA	↓ TNF- $\alpha$	N	N
Lv et al., 2015 China <sup>233</sup>	Gentiopicroside	Rats (SD/M)	100, 400 (p.o.)	Acute pancreatitis	Pancreas tissue	RIA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	N	N
Kim et al., 2013. Republic Korea <sup>291</sup>	Geniposidic acid	Mice (ICR/M)	50 (i.p.)	GalN/LPS - induced hepatic failure	Serum sample	ELISA	↓ (TNF- $\alpha$ , IL-6)	N	N
Zhang et al., 2013. China <sup>208</sup>	Catalpol	Mice (KM/M,F)	2.5-10 (s.c.)	D-galactose induced brain aging	Brain tissue	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	N

Xiao et al., 2014, China <sup>292</sup>	Catalpol	Rat (SD/M)	50 (p.o)	STC-induced pancreatitis	Serum sample	ELISA RT-PCR	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Wang et al., 2014, China <sup>293</sup>	Catalpol	Rat (S-D/M)	25, 125 (i.p.)	CCI	Spinal cord	Western blot	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	N	Y
Fu et al., 2014, China <sup>211</sup>	Catalpol	Mice (BALBc/M)	2.5-10 (i.p.)	LPS – induced ALI	BALF	ELISA	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-4)	Y	N
Liu, Zhang, 2015, China <sup>294</sup>	Catalpol	Rabbit (NZW/M)	5 (p.o.)	Hypercholesterolemia-induced atherosclerosis	Serum sample	ELISA	↓ (TNF- $\alpha$ , IL-6)	Y	N
Zhou et al., 2015, China <sup>295</sup>	Catalpol	Mice (C57BL6J/M)	100 (p.o.)	HFD-induced insulin resistance	Epididymal adipose tissue	RT-PCR	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Chen et al., 2017, China <sup>296</sup>	Catalpol	Mice (BALBc/M)	5, 10 (i.p.)	OVA-induced asthma	Peripheral blood BALF	ELISA	↓ (IL-4, IL-5)	Y	N
Liu et al., 2016, China <sup>297</sup>	Catalpol	Rabbit (NZW/M)	5 (p.o.)	Diabetic atherosclerosis	Plasma	ELISA	↓ TNF- $\alpha$	Y	N
Wang et al., 2014, China <sup>298</sup>	Monotropein	Rats (KM/-)	25-100 (p.o.)	Osteoarthritis	Synovial fluid	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	N	N
Zhang et al., 2016.	Monotropein	Mice	40, 80	Ovariectomy induced	Serum sample	ELISA	↓ (IL-1 $\beta$ , IL-6)	Y	N

China <sup>299</sup>		(C57/BL6/F)	(p.o.)	osteoporosis					
Impellizzeri et al., 2011, Italy <sup>253</sup>	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 <sup>249</sup>	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., 2011, Italy <sup>248</sup>	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 <sup>301</sup>	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 <sup>250</sup>	Oleuropein	Rat (Wistar/M)	166, 333 (i.p.)	Doxorubicin-induced cardiomyopathy	Myocardial tissue	ELISA	↓(IL-6)	Y	N
Janahmadi et al., 2014, Iran <sup>251</sup>	Oleuropein	Rat (SD/M)	20, 30 (p.o.)	Myocardial Infarction	Serum sample	ELISA	↓(TNF-α, IL-1β)	Y	N
Caglayan et al., 2015, Turkey <sup>252</sup>	Oleuropein	Rat (Wistar/M)	20 (p.o.)	BPDO-induced pancreatitis	Serum sample	ELISA	⊠ (TNF-α, IL-6)	Y	N
Giner et al., 2016, Spain <sup>254</sup>	Oleuropein	Mice (C57BL/6/F)	50, 100 (drinking water)	AOM/DSS-induced	Colon tissue	ELISA	↓(TNF-α, IL-6, IFN-γ, IL-17)	Y	N

				colorectal cancer					
Liu et al., 2006, China <sup>302</sup>	Paeoniflorin	Mice (BALBc/M)	25, 50 (i.v.)	BCG/LPS induced liver injury	Liver tissue	RT-PCR	↓ (TNF- $\alpha$ , IL-6)	Y	N
Li et al., 2010, China <sup>196</sup>	Paeoniflorin	Mice (BALBc/F)	30 (p.o.)	<i>S. japonicum</i> cercariae infection	Liver tissue	ELISA	↓ (IL-13)	Y	N
Tang et al., 2010, Taiwan <sup>200</sup>	Paeoniflorin	Rat (S-D/M)	20 (i.v.)	Cerebral Infarct Induced by Ischemia-Reperfusion Injured	Brain sections	Immunostain	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	Y
Zhou et al., 2011, China <sup>201</sup>	Paeoniflorin	Mice (ICR/M)	100 (i.p.)	LPS-Induced ALI	BALF Lung tissue	ELISA RT-PCR	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	N
Guo et al., 2012. China <sup>300</sup>	Paeoniflorin	Rat (SD/M)	10 (i.p.)	MCAO	Serum sample Brain	ELISA RT-PCR	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	Y
Chen et al., 2012, China <sup>303</sup>	Paeoniflorin	Rat (Wistar/M)	20 (p.o.)	DMN-induced liver fibrosis	Serum sample	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	N
Wang et al., 2013, China <sup>190</sup>	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 <sup>202</sup>	Paeoniflorin	Mice (C57BL/6/F)	50 (p.o.)	DSS-induced colitis	Colon segments	ELISA RT-PCR	↓ (TNF- $\alpha$ , INF- $\gamma$ , IL-6)	Y	N

Chen et al., 2015, China <sup>203</sup>	Paeoniflorin	Rat (SD/-)	5-20 (i.v.)	Acute myocardial infarction	Serum sample	ELISA	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	Y	N
Chen et al., 2015, China <sup>203</sup>	Paeoniflorin	Mice (C57BL/6/)	50 (i.v.)	Concanavalin A-induced hepatitis	Serum sample Liver tissue	ELISA RT-PCR	↓(TNF- $\alpha$ , INF- $\gamma$ , IL-6)	Y	N
Zhang et al., 2015, China <sup>199</sup>	Paeoniflorin	Mice (APP/PS1 and WT/M)	5 (i.p.)	APP/PS1 model Alzheimer disease	Brain tissue	ELISA	↓(TNF- $\alpha$ , IL-1 $\beta$ )	Y	N
Sun et al., 2015, China <sup>198</sup>	Paeoniflorin	Mice (BALBc/M)	10- 50 (p.o.)	OVA-induced asthma	BALF	ELISA	↓(IL-5, IL-13, IL-17)	Y	N
Sun et al., 2015a, China <sup>204</sup>	Paeoniflorin	Mice (BALBc/F)	150-300 (i.p.)	Imiquimod-induced psoriasis	Skin tissue	RT-PCR	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	N	N
Ya et al., 2010, China <sup>304</sup>	Cornel	Rat (SD/M)	60,180 (p.o.)	MCAO	Brain tissue	ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	N
Kim et al., 2015, South Korea <sup>244</sup>	Loganin	Mice (C57BL/6/F)	10-100 (p.o.)	Cerulein-induced pancreatitis	Pancreas tissue Serum sample	RT-PCR ELISA	↓ (TNF- $\alpha$ , IL-1 $\beta$ )	Y	N
Song et al., 2015, Republic of Korea <sup>305</sup>	Piscroside C	Mice (C57BL/6N/M)	15, 30 (p.o.)	cigarette smoke/LPS induced COPD	BALF	ELISA	↓ (TNF- $\alpha$ , IL-6)	N	N

Saravanan et al., 2014, India <sup>263</sup>	Swertiamarin	Rat (SD/F)	2-10 (p.o.)	Adjuvant induced arthritis	Serum	ELISA	↓(TNF- $\alpha$ , IL-1 $\beta$ , IL-6)	N	Y
Wang et al., 2015, China <sup>306</sup>	Incarvillateine monoterpene alkaloid	Mice (C57/BL6/M)	20 (i.p.)	CFA-induced inflammation and pain	Hindpaw tissue	ELISA	↓ IL-1 $\beta$	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)

