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The mechanistic aspects of the anti-inflammatory activity of *Lavandula stoechas*

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DEDICATION

I'd like to wholeheartedly dedicate with genuine gratitude this work to my passionately supportive mother who has been my constant source of strength.

To the biggest love, Tannies for the endless and unconditional emotional support.

To my family, friends, and loved ones.

To my sisters and brother, to my nieces and nephews.

To my favorite person on the planet Joo, and to my lovely friend Chahra.

To my very precious friends Nicole and Melina.

And the last word goes to the light of my life, my very dear father who took the lead to heaven before the completion of this work. This thesis is especially dedicated to him.

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CHAPTER II: *LAVANDULA STOCHEAS* AS A MEDICINAL PLANT

AA: Arachidonic acid

AP-1: Activator protein-1

APC: Antigen-presenting cells

COPD: Obstructive pulmonary disease

COX: Cyclooxygenases

CRP: C reactive protein

CYP: Cytochrome P450

DAMPs: Danger associated molecular patterns

Egr-1: Early growth response protein 1

ERK1/2: Extracellular signal-regulated protein kinases 1 and 2

IBD: Inflammatory bowel disease

ICAM: Intracellular adhesion molecules

IFNs: Interferons

IKK: IκB kinase

IL-1R: IL-1 receptor

IL-6R: IL-6 receptor

ILs: Interleukins

iNOS: Inducible nitric oxygen synthase

IRF-1: Interferon regulatory factor 1

IκBα: Inhibitor of kappa Bα

JAK: Janus kinase

L7G: Luteolin-7-glucoside

LOX: Lipoxygenases

LPS: Lipopolysaccharide

LSEO: *Lavandula stoechas* essential oil

LTB 4: Leukotriene B4

LTC4: Leukotriene C4

MAPK: Mitogen-activated protein kinase

MCP-1: Monocyte chemoattractant protein-1

MHC: Major histocompatibility complex

MPO: Myeloperoxidase

MyD88: Myeloid differentiation primary response 88

NF-κB: Nuclear factor kappa-B

NO: Nitric oxide

NSAIDs: Nonsteroidal anti-inflammatory drugs

PAF: Platelet-activating factor

PAMPs: Pathogen associated molecular patterns

PG: Prostaglandins

PGE2: Prostaglandin E2

PGI2: Prostacyclin

PKC: Protein kinase C

PLA2: Phosphlipase A2

PRRs: Pattern-recognition receptors

PUFAs: Polyunsaturated fatty acids

ROS: Reactive oxygen species

SOCS−3: Suppressor of cytokine signaling 3

STAT3: Signal transducer and activator of transcription 3

TLR4: Toll-like receptor 4

TLRs: Toll-like receptors

TNF: Tumor necrosis factor

Tregs: Regulatory T cells

TxB2: Thromboxane B2

TxbA2: Thromboxane A2

Tyk2: Tyrosine Kinase 2

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INTRODUCTION

Inflammation has always accompanied humans, as evidenced by its presence on the first humanoids and Homo sapiens bones. The first precise diagnoses of inflammatory diseases were provided by Sir Marc Armand Ruffer (1859–1917) on Egyptian mummies (Frangogiannis *et al*., 2018).

Nowadays, it is well established that inflammation is a physiologic response and a critical survival mechanism aimed at combating and repairing different types of injurious events. However, a persistent inflammatory state is mainly correlated with various disorders and chronic diseases (Kim *et al*., 2018). This has led even ancient civilizations to propose various therapeutic approaches to manage or treat different types of inflammatory disorders such as the use of medicinal plants including Lavender which is mainly characterized by the production of curative secondary metabolites (Nunes *et al*., 2020). Moreover, the first documented reports on lavenders can be found in the writings of the early Greek scholars such as Theophrastus (Frangogiannis *et al*., 2018).

The classical steroidal and non-steroidal anti inflammatory drugs carry the risk of various side effects including osteoporosis and peptic ulcers (Abdulkhaleq *et al*., 2018; Craig and Stitzel, 2004). In this context, the potent medicinal plant, *Lavandula stoechas* could serve as a novel therapeutic agent that challenges the unmet or undesirable effects of synthetic anti-inflammatory drugs (Akbar, 2020).

This review reflects on inflammation and provides a comprehensive, yet non-exhaustive overview of the anti-inflammatory molecular mechanisms of action of some bioactive molecules found in *Lavandula stoechas* essential oils and extracts.
The first chapter introduces the basic concepts of the inflammatory response while the second chapter highlights generalities on *Lavandula stoechas*. Finally, chapter three emphasizes the possible anti-inflammatory mechanistic aspects of some of the compounds found in *Lavandula stoechas*.

CHAPTER I :
GENERALITIES ON INFLAMMATION

Inflammatory reactions serve as the major defense mechanism against numerous injurious events and are engaged in the healing and repair processes. Paradoxically, the inflammatory response itself may act as a central executor in the pathogenesis of many diseases ranging from rheumatoid arthritis, arteriosclerosis, inflammatory bowel disease (IBD), myocarditis, infections, metabolic disorders, to cancer (Chen *et al*., 2018).

1. Definition

Inflammation is a biological reaction to disrupted tissue homeostasis (Medzhitov, 2008). Inflammation is, therefore, a fundamental and complex physiologic immune response to tissue damage induced by potentially harmful stimuli (Riccardi *et al*., 2018). It is viewed as a purposeful reaction aimed to repair, salvage, and restore the structure, function, and integrity of the injured tissue, organ, and organism well-being. Inflammation involves a highly dynamic process employed by both innate and adaptive immune systems that comprise diverse cellular, neural, hormonal, and humoral systems (Fink, 2010).

2. Etiology

Inflammation can be the result of infectious or non-infectious agents (Chen *et al*., 2018), endogenous or exogenous injurious events (table 1) (Fialho *et al*., 2018; Jang *et al*., 2016).

Table 1. Etiology of inflammation (Fialho *et al*., 2018; Jang *et al*., 2016).

Stimuli	**Description**
Infectious agents or substances from their metabolism	Microorganisms and toxins
Physical agents	Radiation, burn, and trauma
Chemicals	Caustic substances
Biological	Damaged cells

3. Characteristics of inflammation

The symptoms of inflammation are usually characterized by five cardinal signs (Virshette *et al*., 2019), namely local redness, swelling, pain, heat, and loss of function (figure 1) (Burmester *et al*., 2003).

The physiological basis of the five cardinal signs of inflammation includes:

- Vasodilation of the blood vessel and increase in blood flow due to the release of vasodilators.
- Increase in permeability of capillaries leading to leakage of fluid into the interstitial spaces.
- Fluid clotting in the interstitial space due to the leakage of excess fibrinogen and other proteins from the capillaries.
- Infiltration of granulocyte monocyte to the injured tissue.
- Swelling of the tissue cells (Guyton and Hall, 2006).

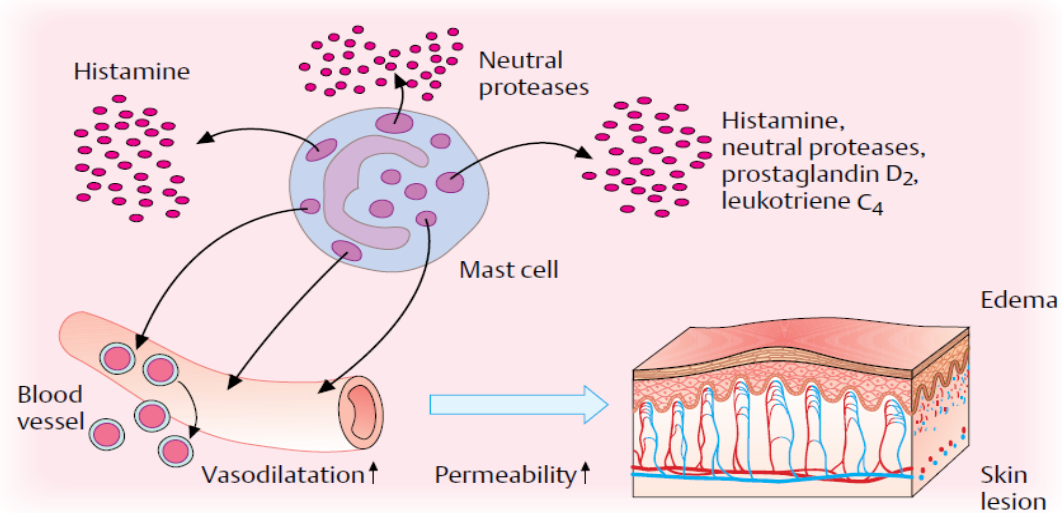

Figure 1. Characteristics of inflammation (Burmester *et al*., 2003). After precipitating stimulus, mast cells release inflammatory mediators such as cytokines, serotonin, histamine, prostaglandin and leukotrienes that induce vasodilation, increase vascular permeability, and cause edema.

4. Types of inflammation

The inflammatory response is triggered through two major phases; it regularly progresses to acute (Serhan et al., 2015b) or chronic (Isailovic *et al*., 2015).

4.1. Acute inflammation

The Acute inflammation consists of the initial response of the body to harmful stimuli (Arome *et al*., 2014). This response is usually short-term and limited to the area where the tissue damage occurs (Opriessnig *et al*., 2011). Therefore, it serves as a mechanism to restore normal homeostasis (Ceron *et al*., 2005). Acute inflammation manifests histologically by the exudation of fluids and plasma proteins in addition to the recruitment of leukocytes, most notably neutrophils into the injured area. This acute phase is usually sufficient to resolve the injury. However, persistent or uncontrolled inflammation can lead to the development of chronic inflammation (Germolec *et al*., 2018).

4.2. Chronic inflammation

Chronic inflammation occurs as a result of inflammation being prolonged for a while (weeks to months to years) (Arome *et al*., 2014). It is histologically characterized by infiltration of mononuclear cells including macrophages, lymphocytes, and plasma cells, resulting in fibrosis and tissue necrosis (Iwalewa *et al*., 2007).

Among other less common types, subacute inflammation is considered as an intermediate stage between the two major types of inflammation (Arome *et al*., 2014).

5. Inflammatory phases

The inflammatory reaction is characterized by three successive phases:

- **The silent phase** which is characterized by the release of the first inflammatory mediators by cells resident in the damaged tissue.
- **The vascular phase** which is characterized by a vasodilation and increased vascular permeability.
- **The cellular phase** which is characterized by the infiltration of leukocytes into the injured area (Vergnolle, 2003).

6. Inflammatory cells

The inflammatory response involves a highly coordinated network of many cell types (Chen *et al*., 2018), including basophils, monocytes, neutrophils, eosinophils, mast cells, macrophages, lymphocytes (T cells, B cells, natural killer cells), and platelets (Iwalewa *et al*., 2007).

6.1. Neutrophils

Neutrophils are the primary participant of the inflammatory response (Jabbour *et al*., 2009). They have a key role in inflammatory reactions and take a predominant role in acute inflammation (Baum and Arpey, 2005; Lawrence, 1998). They are recruited to the site of injury by many chemoattractants (Kukulski *et al*., 2009) and then activated to perform several functions including local killing and degradation of bacterial macromolecules via phagocytosis, release of superoxide radicals and other toxic molecules, and the formation of neutrophil extracellular traps. Moreover, neutrophils produce several pro-inflammatory cytokines that stimulate further inflammation (Baum and Arpey, 2005).

6.2. Eosinophils

Eosinophils are multifunctional leukocytes that have a role in the pathophysiology of a variety of inflammatory conditions, especially allergies (Weller, 1991). They can release a range of cytokines, chemokines, and neuromediators, as well as huge amounts of leukotriene C4 (LTC4), in addition to their preformed cationic proteins. Finally, eosinophils can express MHC class II antigens for T lymphocytes to recognize (Figure 2) (Davis and Rothenberg, 2015).

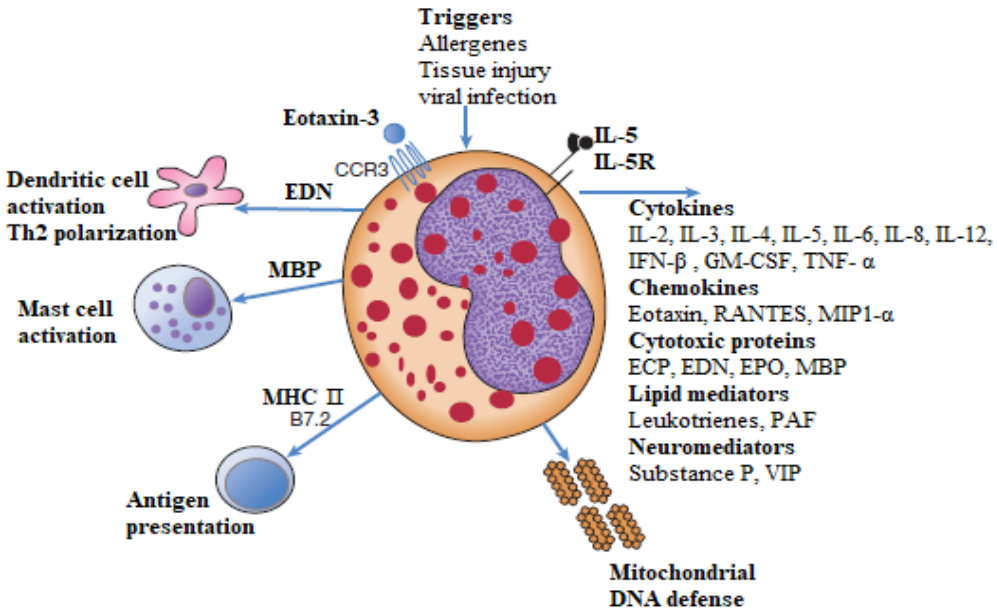

Figure 2. Schematic diagram of an eosinophil and its diverse properties (Davis and Rothenberg, 2015).

6.3. Monocytes/macrophages

Macrophages are important components of the mononuclear phagocyte system and are integral to the inflammatory response (Fujiwara and Kobayashi, 2005). There are two types: the tissue-resident macrophages and the circulating equivalent monocytes (Baum and Arpey, 2005) these latters once in the tissue, can differentiate into macrophages (Gonzalez-Mejia and Doseff, 2009).

In an inflammatory environment, macrophages are responsible for the early recognition of inflammatory stimuli and are a major, early source of pro-inflammatory cytokines (Chen *et al*., 2009; Lomas-Neira *et al*., 2006), and growth factors (Chen *et al*., 2018).

In addition to their role in debridement and tissue remodeling, macrophages also interact with lymphocytes as antigen-presenting cells and therefore influencing the adaptive immune system (Figure 3) (Burmester *et al*., 2003; Johnston and Tobias, 2017).

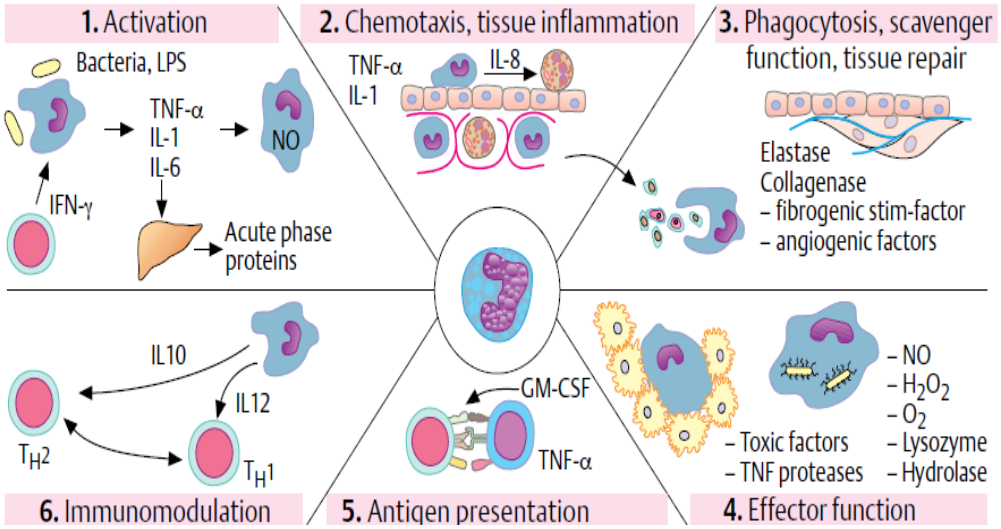

Figure 3. Role of monocytes/macrophages (Burmester *et al*., 2003). 1. Activation of monocytes. **2.** Active recruitment of the cells to the site of injury. **3.** Phagocytosis. **4.** Production of pro-inflammatory mediators and toxic factors. **5.** Antigen-presenting and displaying for recognition by lymphocytes. **6.** Immunomodulation by the release of various cytokines that participate in the regulation of the inflammatory response.

6.4. Dendritic cells

Dendritic cells (DCs), together with monocytes and macrophages, comprise the mononuclear phagocyte system. DCs are central regulators of the adaptive inflammatory response and well-known antigen-presenting cells (APC). There are several subtypes of DCs; the human plasmacytoid DCs (pDCs) subtype is rapidly recruited to tissue sites during inflammation. This subtype has both pro-inflammatory and tolergenic functions (Roll *et al*., 2008). pDCs can induce T cells to differentiate into suppressor or regulatory T

cells (Tregs) that can contribute to down-regulation of inflammation (Koble and Kyewski, 2009; Steinman *et al*., 2003).

6.5. Mast cells

Mast cells contain many granules and reside in connective tissue matrices and on epithelial surfaces. They are effector cells that initiate inflammatory responses. Activated mast cells release a variety of inflammatory mediators, including cytokines, chemokines, histamine, proteases, prostaglandins, leukotrienes, and others (Huang *et al*., 1998).

Overall, mast cell degranulation in response to several stimuli promotes the local inflammatory response (Johnston and Tobias, 2017).

6.6. Platelets (thrombocytes)

In addition to their role in hemostasis and thrombosis, platelets are inflammatory cellular elements (Metzger and Page, 1998; Weksler, 1983) that may mediate pro-inflammatory effects through several interactions with inflammatory cells and eventually induce the acute phase response (Aggrey *et al*., 2013). Several pro-inflammatory mediators are derived from platelets, including thromboxane A2, serotonin, and others (Metzger and Page, 1998).

6.7. Endothelial Cells

Endothelial cells are a dynamic cell population that composes the inner lining of the vasculature and lymphatic systems. During inflammation, they can increase vascular permeability, regulate the migration of inflammatory cells into tissue (Alexander *et al*., 2017), and alter coagulation. They are activated by cytokines and bacterial products such as endotoxin (Mai *et al*., 2013; Xiao *et al*., 2014).

In certain circumstances, endothelial cells effectively connect both the innate and adaptive inflammatory responses by acting as APC (Leeuwenberg *et al*., 1988).

6.8. Lymphocytes

Lymphocytes are essential for the development of a complete innate and adaptive immune response. In epithelial-associated tissues, innate lymphocytes act as sentinels, releasing cytokines that aid in development of the adaptive response. Lymphocytes play a role in pathogen defense and facilitate allergic diseases. In addition to Th2 cells, many lymphocytes, including Th1 cells, Th17 cells, CD8+ T cells, B cells, natural killer cells (NK), and natural killer T (NKT) cells, can participate in allergic inflammation (Davis and Rothenberg, 2015).

7. Mediators of inflammation

The vascular and cellular events of the inflammatory response are mediated by different factors derived from inflammatory cells or plasma proteins. These factors are implied in the contribution and the adjustment of the inflammatory response (Beutler *et al*., 1985).

7.1. Cell-driven mediators

7.1.1. Vasoactive amines

Vasoactive amines, namely histamine, and serotonin, have an important role in the inflammatory response. They are the primary mediators of the acute inflammatory response (Johnston and Tobias, 2017).

7.1.1.1. Histamine

Histamine is a major vasoactive amine in the acute inflammatory response that is preformed then stored within cellular granules. Histamine is primarily produced and released by mast cells besides other cell types like basophils and platelets (Jutel *et al*., 2002). Histamine plays an important role in inflammatory responses, mainly in hypersensitive responses (Riccardi *et al*., 2018). During an inflammatory response, histamine interacts mainly with a specific receptor (H1) on endothelial cells resulting in arteriolar vasodilation, increased venule permeability, and constriction of large arteries (Thurmond *et al*., 2008). Histamine can also induce vasodilation indirectly through prostaglandin synthesis. (Hebda *et al*., 1993)

7.1.1.2. Serotonin

Serotonin is a vasoactive amine that has actions similar to histamine (Majno *et al*., 1969). It is mostly produced by enterochromaffin cells in addition to neuronal cells, B and T lymphocytes, monocytes, and mast cells (Kushnir-Sukhov *et al*., 2007; O'connell *et al*., 2006). It can also be present in other cells, like blood platelets, and dendritic cells (Leon-Ponte *et al*., 2007). Serotonin contributes to the regulation of many physiological functions, like vasoconstriction, inflammatory responses, intestinal motility, and wound healing (Gershon and Tack, 2007; Mann and Oakley, 2013; Shajib and Khan, 2015).

7.1.2. Arachidonic acid metabolites: Eicosanoids

Eicosanoids comprise a family of locally acting bioactive lipid mediators of the inflammation (Mak *et al*., 2013). They are biosynthesized by the oxidation of arachidonic acid (AA)

or related polyunsaturated fatty acids (PUFAs) that produces prostaglandins, thromboxane, leukotrienes, endocannabinoids, and isoeicosanoids (Subhash *et al*., 2007), by the initial activities of cyclooxygenases (COX), lipoxygenases (LOX), cytochrome P450 (CYP) and by a non-enzymatic pathway (Nakaya *et al*., 2017).

Eicosanoid signaling is critical for generating, maintaining, and mediating inflammatory responses (Janeway and Medzhitov, 2002; Nakaya *et al*., 2017). Although eicosanids are mainly associated with their pro-inflammatory activities such as prostaglandins (PG), prostacyclin (PGI2), thromboxanes (TX), and leukotrienes (Kotsovolis and Kallaras, 2010; Sun *et al*., 2013), there are unique eicosanoids and related docosanoids with anti-inflammatory and pro-resolution activities as well (Achek *et al*., 2016). During inflammatory responses, the predominant is PGE2 and thromboxane A2 (Dennis and Norris, 2015).

7.1.2.1. Prostaglandins

Prostaglandins are chemotactic agents that cause leukocyte recruitment and vasodilation (Clarke *et al*., 1998; Williams and Peck, 1977). They mediate many inflammatory responses (Moriyama *et al*., 2005) and also play a major role in the pathogenesis of many diseases such as rheumatoid arthritis and osteoarthritis (Kosaka *et al*., 2013). This group of molecules is targeted for many anti-inflammatory drugs, since they are related to fever and pain caused by inflammation (Rodríguez-Hernández *et al*., 2013; Serhan *et al*., 2015a).

7.1.3. Platelet-activating factor (PAF)

Similar to eicosanoids, platelet-activating factor (PAF) is metabolized from cell membrane phospholipids by phospholipase A2. It is mainly produced by endothelial cells, platelets, neutrophils, macrophages, monocytes, and eosinophils (Chao and Olson, 1993; Franchi *et al*., 2009).

PAF is released in the early inflammatory response and it works as an intercellular mediator (Pahwa *et al*., 2016). It contributes to the inflammatory response through increasing vascular permeability, bronchoconstriction, and pulmonary vasoconstriction (Chao and Olson, 1993; Harris *et al*., 1999). PAF exerts pro-inflammatory effects by neutrophils degranulation (Prescott *et al*., 2000). It causes platelet aggregation and degranulation, as well as eosinophil degranulation and production of reactive oxygen species (Tachibana *et al*., 2002), stimulation of AA release and increase eicosanoid production (Johnston and Tobias, 2017).

7.1.4. Cytokines

Cytokines are major signaling proteins in the host response against different stimulus, predominantly released by immune cells, including monocytes, macrophages, and lymphocytes (Chen *et al*., 2018). They act as intercellular messengers during many physiologic processes (Johnston and Tobias, 2017) and as mediators of inflammation and immune response (Riccardi *et al*., 2018). Inflammatory cytokines are classified as the following:

7.1.4.1. Tumor necrosis factor (TNF)

Tumor Necrosis Factor (TNF) is a major mediator of inflammation among cytokines released by immunologic cells specifically by monocytes (Wong *et al*., 2017). TNF also has an important role in autoimmunity, cancer, infectious disease, and graft-versus-host disease (Vanamee and Faustman, 2018). During an inflammatory response, TNF induces vasodilation through the expression of COX2 (Rossi and Zatti, 1964), and induces the expression of pro-coagulant proteins that can cause intravascular thrombosis (Oren *et al*., 1963).

TNF-α causes a wide range of additional effects, including activation of NK cells (Wherry *et al*., 1991), proliferation of cytotoxic T-cells (Kasahara *et al*., 2003), and T-cell apoptosis (Vinay and Kwon, 2009). However, an uncontrolled or chronic secretion of TNFα, may mediate various chronic inflammatory diseases (Aggarwal *et al*., 2006).

7.1.4.2. Interleukins

Interleukins (ILs) are another major class of cytokines which play a pivotal role in immune modulation (Riccardi *et al*., 2018). Pro-inflammatory interleukins include IL-1 which is implied in the stimulation of the acute phase response. Besides the induction of other pro-inflammatory mediators, IL-1 also up-regulates cell adhesion molecules (CAM) that are crucial to an effective defense mechanism. In addition to IL1, IL-6 is another chief molecule during acute inflammation and its uncontrolled production leads to many inflammatory diseases (Balkwill and Mantovani, 2010; Tasneem *et al*., 2019).

IL-10 and IL-13 are anti-inflammatory interleukins (Berczi and Szentivanyi, 2003).

7.1.4.3. Interferons

Interferons (IFNs) are a class of cytokines that have a role in the antiviral immune response due to their property to interfere with viral replication in the host (Petreski *et al*., 2021;

Riccardi *et al*., 2018). They are divided based on their receptor usage, structural and biological activity into three distinct types (Type I, Type II, and Type III) (Jha *et al*., 2015).
Type I IFN enhances the action of dendritic cells and monocytes (McNab *et al*., 2015). Type II IFN inhibits viral replication, induces a pro-inflammatory CD4+ T cell response (Th1), regulates macrophage activation, and improves antigen recognition (Tannahill *et al*., 2013). Type III IFN induces antiviral activity in cells and upregulates MHC class I (Palsson-Mcdermott and O'Neill, 2013).

7.1.4.4. Chemokines

Chemokines are a family of small proteins that are described as chemotactic cytokines of the immune system (Riccardi *et al*., 2018). They are known to be secreted by macrophages, endothelium, and other cell types (Johnston and Tobias, 2017) after stimulation by cytokines or microbial products (Riccardi *et al*., 2018).
During an inflammation, chemokines mediate the recruitment of leukocytes such as neutrophils and monocytes into inflammatory sites and their degranulation (Petreski *et al*., 2021; Riccardi *et al*., 2018). These cells follow chemokine gradients to the site of inflammation to control the damage (Infantino *et al*., 2011).

7.1.5. Reactive oxygen species (ROS)

In the context of inflammation, ROS serves as a second messenger. They can initiate and amplify inflammation by the up-regulation of several different genes involved in the inflammatory response, such as those of pro-inflammatory cytokines and adhesion molecules (Asdonk *et al*., 2012). ROS can also help induce pro-inflammatory cytokine synthesis under the influence of endotoxin and TNF-α binding (Gupta *et al*., 2011).

7.1.6. Nitric oxide

Nitric oxide (NO) is considered as a biological messenger molecule and is involved in diverse biological processes including vasodilation, bronchodilation, antimicrobial defense, and regulation of inflammatory-immune response (Peyrefitte *et al*., 2006).
NO has effective participation in the host response to infection and exhibits both anti-inflammatory and pro-inflammatory effects (Miller *et al*., 1993; Sharma *et al*., 2007). At low concentration, NO has pro-inflammatory actions by vasodilation and neutrophil recruitment. However, at high concentrations, NO has anti-inflammatory role by down-regulation of adhesion molecules and inducing apoptosis in inflammatory cells (Yuan *et al*., 2017).

7.2. Plasma-driven mediators

The inflammatory response is also mediated by plasma proteins. These plasma-derived mediators are produced in the liver and, once released into the bloodstream; they can contribute to important functions of coordinating various events during inflammation like defending the host against pathogens, and bridging innate and adaptive immune responses (Riccardi *et al*., 2018).

7.2.1. Complement system

The complement system comprises more than 30 serum proteins and cell surface receptors that play an integral role in opsonization, phagocytosis, chemotaxis, and active cell lysis (Carroll, 2004). Thus, mediating early host defense responses. On the other hand, the complement is also involved in the control of inflammatory responses (figure 4) (Burmester *et al*., 2003).

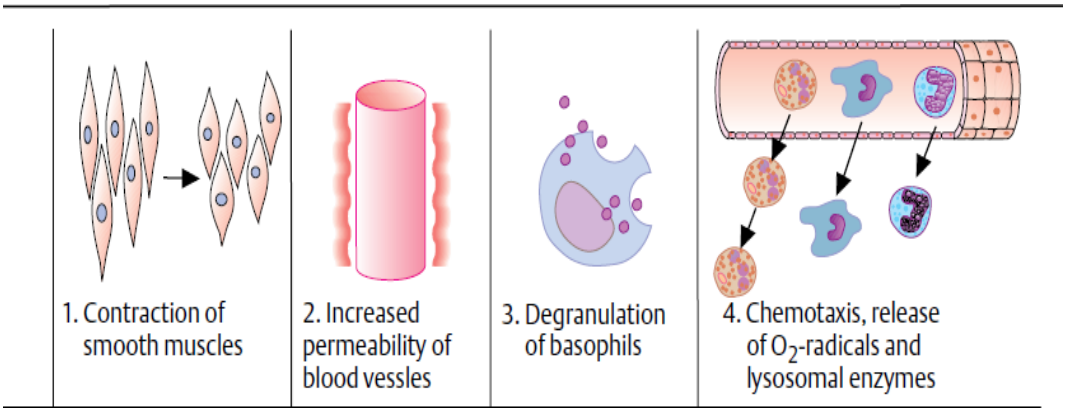

Figure 4. Inflammatory effects of complement factors (Burmester *et al*., 2003). Activated complement proteins are able to induce the contraction of smooth muscles, increase vascular permeability, make mast cells release histamine, and work as chemotactic elements.

7.2.2. Blood coagulation system

Activated coagulation factors affect specific receptors on inflammatory cells and endothelial cells and, thereby, modulate the inflammatory response. Coagulation factors are mostly pro-inflammatory; fibrinogen, fibrin, and also fibrin degradation products can affect leukocytes migration and cytokines production (Chan *et al*., 2013).

7.2.3. Kallikrein-Kinin system

The kallikrein-kinin system is an endogenous metabolic cascade widely involved in blood pressure control, coagulation, inflammation and pain. The activation of this system induces the release of vasoactive kinins, potent pro-inflammatory peptides (Mortimer *et al*., 2016). Similar to histamine and serotonin, it can increase the synthesis of prostaglandins and produces pain locally (Hsieh, 2014).

7.3. Acute-phase proteins

ILs work synergistically with other cytokines to stimulate the transcription and release of a class of proteins named acute-phase proteins from hepatocytes (Jiang *et al*., 2011). Acute phase proteins are those proteins whose serum concentrations change significantly in response to inflammation (Johnston and Tobias, 2017). Overall, the role of these proteins is to enhance protective host functions by minimizing tissue damage and promoting repair processes after infection, trauma, or stress (Ceron *et al*., 2005; Crisman *et al*., 2008; Dhainaut *et al*., 2001). In addition to these functions, acute phase proteins may be used as diagnostic or prognostic markers for early identification of inflammation and prediction of outcomes (Crisman *et al*., 2008; Kajikawa *et al*., 1999; Paltrinieri, 2008).

7.3.1. Negative acute phase proteins

Negative acute phase proteins are proteins active in regulating homeostasis that decrease in concentration by at least 25% during an inflammatory response (Ceciliani *et al*., 2002; Crisman *et al*., 2008). Albumin is the primary negative acute phase protein in most species, in addition to transferrin, apolipoprotein A, retinol-binding protein, cortisol-binding protein, and transthyretin (Dhainaut *et al*., 2001; Paltrinieri, 2008).

7.3.2. Positive acute phase proteins

Positive acute phase proteins show an increase in plasma concentration by at least 25% during an inflammatory response (Ceciliani *et al*., 2002; Crisman *et al*., 2008). Their levels increase in response to pro-inflammatory cytokines and remain elevated as long as inflammatory stimuli persists (Paltrinieri, 2008; Sasaki *et al*., 2003).

7.3.2.1. C reactive protein

C reactive protein (CRP) is a positive acute phase protein and an important analyte that provides diagnostic information on inflammatory status in human beings (Ceciliani *et al*.,

2002). Bacteria-bound CRP promotes activation of complement, contributing to host defense (Ceron *et al*., 2005) and regulates leukocyte infiltration (Ferri *et al*., 2007).

7.3.2.2. Serum amyloid A

Serum amyloid A is produced in macrophages, endothelial cells, and hepatocytes. Free serum amyloid A stimulates the production of pro-inflammatory cytokines mainly from neutrophils (Ribeiro *et al*., 2003). Serum amyloid A is a chemoattractant for T-cells, monocytes, and neutrophils (Ceciliani *et al*., 2002; Xu *et al*., 1995). It mediates some anti-inflammatory effects by decreasing prostaglandin E2 (PGE2) production, platelet activation, and oxidative bursts of neutrophils (Ceciliani *et al*., 2002; Linke *et al*., 1991).

8. The inflammatory response

The inflammatory response processes share a common mechanism; starting from the recognition of the alarm signals by cell surface pattern receptors, then the activation of inflammatory pathways (figure 5a,b,c), the release of inflammatory markers (figure 5d), and finally the recruitment of inflammatory cells (figure 5e). The last phase of inflammation is its resolution (figure 5f) (Ashley *et al*., 2012).

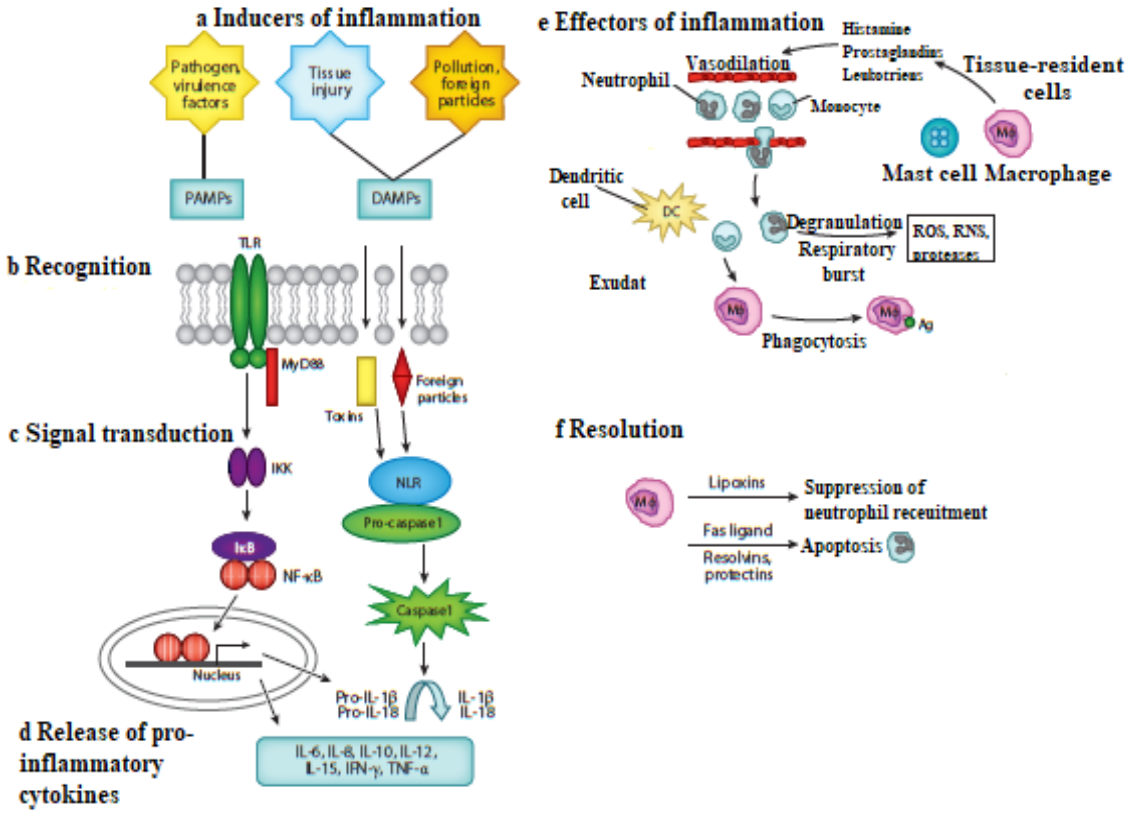

Figure 5. The inflammatory cascade (Ashley *et al*., 2012). a. exposure to triggering factors such as pathogen invasion or cell damage induces an inflammatory reaction which can trigger

intracellular signaling pathways via **b**. antigen recognition using pattern recognition receptors, such as toll-like receptors 4 (TLR4). **c.** signaling cascades, through transcription factors like Nuclear Factor kappa B (NF-κB) and Mitogen Dependent Protein Kinase (MAPKs), are activated which further trigger **d**. an over-expression of pro-inflammatory genes leading to the release of pro-inflammatory cytokines that **e**. accelerate the recruitment of leukocytes to the site of injury. **f**. restoration of homeostasis and tissue repair.

8.1. Alarm signals

The first step of the inflammatory cascade involves recognition of infection or cellular damage which is achieved by the detection of alarm signals (Ashley *et al*., 2012); an evolutionarily conserved system used to alert the body (Bianchi, 2007; Minton, 2009). The warning molecules, either exogenous or endogenous, incite intracellular signaling cascades (Johnston and Tobias, 2017).

8.1.1. Pathogen-associated molecular patterns (PAMPs)

Pathogen associated molecular patterns (PAMPs) are highly conserved microbial molecules, recognized as foreign to the host (Bianchi, 2007; Moller *et al*., 2005). Such microbial structures include lipopolysaccharide (LPS), lipoteichoic acid, peptidoglycan, and microbial oligonucleotides (Johnston and Tobias, 2017).

8.1.2. Danger associated molecular patterns (DAMPs)

In contrast to PAMPs, danger associated molecular patterns (DAMPs) or alarmins are endogenous molecules such as fibrinogen that signal tissue or cell damage initiated by infectious or non infectious agents (Gudkov and Komarova, 2016).

PAMPs can trigger the inflammatory response through activation of pattern-recognition receptors (PRRs) expressed in both immune and non immune cells (Brusselle and Bracke, 2014; Gudkov and Komarova, 2016). Some PRRs also recognize DAMPS (Gudkov and Komarova, 2016).

8.2. Pattern recognition receptors activation

Pattern recognition receptors PRR are expressed on the cell surface or within the intracellular compartment (Ahmad-Nejad et al., 2002; Medzhitov, 2001). They initiate the complex cellular responses that result in inflammation (Johnston and Tobias, 2017). The classes of PRR families include the toll-like receptors (TLRs) (Takeuchi and Akira, 2010), a very diverse family that participate in the activation of the inflammatory response (Janeway

and Medzhitov, 2002) and the progression of certain inflammatory diseases like atherosclerosis (Tasneem *et al*., 2019). TLRs are the most well studied of the known PRRs (Yamamoto and Takeda, 2010). They play a central role in the release of inflammatory cytokines from the innate immune system in response to microbial structures. Toll-like receptor 4 (TLR4), in particular, is a major receptor for lipopolysaccharide (endotoxin). TLR4 activation increases expression of numerous pro-inflammatory mediators and modulates the further expression of other toll-like receptors (Johnston and Tobias, 2017).

8.3. Inflammatory pathways activation

The inflammatory stimuli activate intracellular signaling pathways that then activate production of inflammatory mediators. Primary inflammatory stimuli mediate inflammation through interaction with the TLRs, IL-1 receptor (IL-1R), IL-6 receptor (IL-6R), and the TNF receptor (TNFR) (Kaminska, 2005) leading to receptor activation which triggers important intracellular signaling pathways (figure 6) (Pua *et al*., 2020), including the mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), and Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathways (Hendrayani *et al*., 2016; Henríquez-Olguín *et al*., 2015).

8.3.1. Mitogen-activated protein kinase (MAPK) pathway

MAPKs are a family of serine/threonine protein kinases that direct cellular responses to a variety of stimuli, including osmotic stress, mitogens, heat shock, and inflammatory cytokines (such as IL-1, TNF-α, and IL-6), which regulate cell proliferation, differentiation, cell survival and apoptosis (Kaminska, 2005; Pearson *et al*., 2001).

The mammalian MAPKs include extracellular-signal-regulated kinase ERK1/2, p38 MAP Kinase, and c-Jun N-terminal kinases (JNK) (Kim and Choi, 2010). ERKs are mainly activated by mitogens and differentiation signals, meanwhile JNK and p38 are activated by inflammatory stimuli and stress (Sabio and Davis, 2014).

Each MAPK signaling pathway comprises at least three components: a MAPK, a MAPK kinase (MAPKK), and a MAPK kinase kinase (MAPKKK). MAPKKKs phosphorylate and activate MAPKKs, which in turn phosphorylate and activate MAPKs (Dhillon *et al*., 2007; Kim and Choi, 2010). Activation of the MAPKs, including Erk1/2 and JNK, leads to phosphorylation and activation of transcription factors p38 present in the cytoplasm causing their translocation into the nucleus, which initiates the expression of inflammatory genes (Pearson *et al*., 2001; Raingeaud *et al*., 1996).

8.3.2. The NF-κB Pathway

The NF-κB family includes five related transcription factors: P50, p52, RelA (p65), RelB, and c-Rel (Hoffmann *et al*., 2006; Moynagh, 2005). NF-κB activity is induced by a range of stimuli, including pathogen-derived substances, intercellular inflammatory cytokines, and many enzymes (Basak *et al*., 2007; Pasparakis *et al*., 2006).

Under physiological conditions, IκB proteins present in the cytoplasm inhibit NF-κB (Kadhim *et al*., 2001). PRRs use similar signal transduction mechanisms to activate IκB kinase (IKK). IKK regulates NF-κB pathway activation through IκB phosphorylation (Lawrence, 2009) which results in its degradation by the proteasome and the subsequent release of NF-κB for nuclear translocation and gene transcription activation (Hayden and Ghosh, 2012). This pathway regulates pro-inflammatory cytokine production and inflammatory cell recruitment, which contribute to the inflammatory response (Chen *et al*., 2018).

8.3.3. The JAK-STAT Pathway

The highly conserved JAK-STAT pathway involves diverse cytokines, growth factors, interferons, and related molecules, such as leptin and growth hormone, and is a signaling mechanism through which extracellular factors can control gene expression (O'Shea *et al*., 2015). The binding of mediators to the cytokine receptors and their interaction at cytoplasmic domain causes phosphorylation of JAKs and STATs. Activated STATs form a dimer, and these dimers then translocate into the nucleus and modulate the expression of specific cytokine-responsive genes (Boyle *et al*., 2015). Therefore, JAK/STAT signaling allows for the direct translation of an extracellular signal into a transcriptional response (Chen *et al*., 2018).

Dysregulation of NF-κB, MAPK, or JAK-STAT activity is associated with inflammatory, autoimmune, metabolic diseases, and cancer (Oeckinghaus *et al*., 2011).

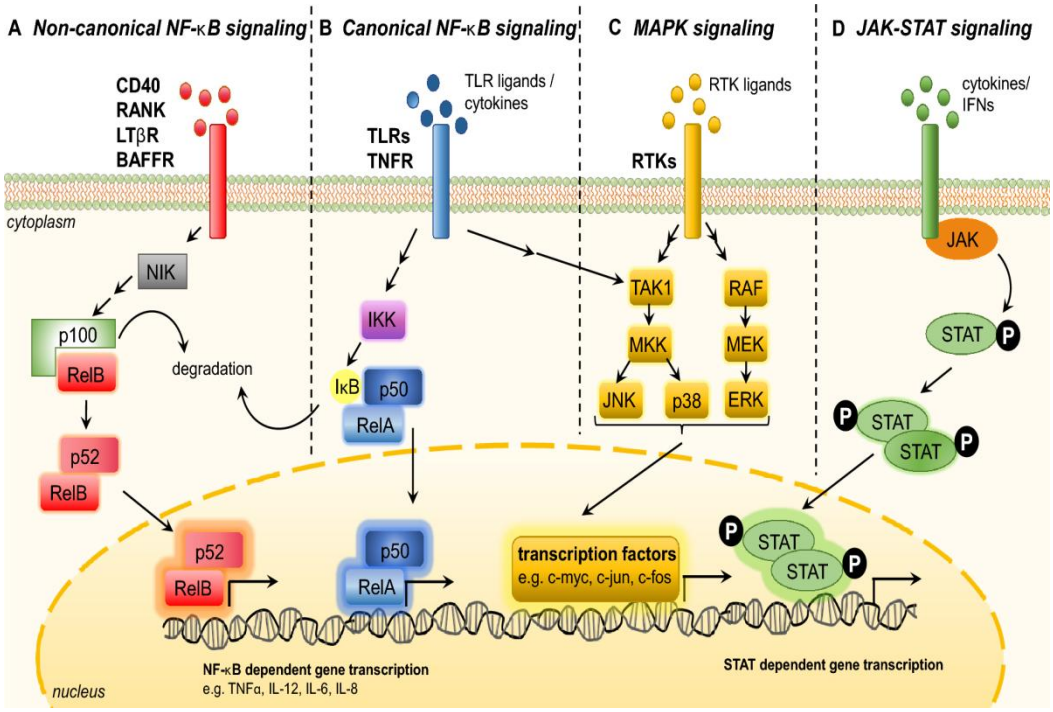

Figure 6. Major signaling pathways regulating inflammation (Pua *et al*., 2020).

9. Treatment of inflammation

Anti-inflammatory drugs can interfere with the pathophysiology of inflammation, seeking to minimize tissue damage and provide greater patient comfort (Nunes *et al*., 2020). The major classes of anti-inflammatory drugs are steroidal (Kawai and Akira, 2011) and nonsteroidal (Van-Furth, 2013).

9.1. Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs worldwide (Virshette *et al*., 2019). They are synthetic organic compounds that have been developed to suppress inflammation (Fink, 2010) mainly utilized to treat acute and chronic pain resulting from an inflammatory process (Lima and Alvim, 2018). This class of medicines contains primarily inhibitors of the cyclooxygenase enzymes, most precisely COX-2 responsible for the biosynthesis of PGs which triggered inflammation, thereby preventing the amplification of the pain stimuli (Albert *et al*., 2002; Herdman *et al*., 2001). NSAIDs such as acetylsalicylic acid, indomethacin, ibuprofen, and piroxicam have been used clinically for the treatment of inflammation (Sandoval *et al*., 2017).

9.2. Corticosteroid drugs

These are anti-inflammatory agents that prevent phospholipid release and undermine eosinophil action and number of other mechanisms involved in inflammation (Nordqvist, 2012). Glucocorticoids interfere with the inflammatory processes by inhibiting the migration of leukocytes to the site of inflammation, modulating the various functions of effector cells, and decreasing the production of inflammatory mediators (Burmester *et al*., 2003).
Among the different indications they are used in treatment for asthma and autoimmune inflammatory response (Nunes *et al*., 2020).

However, the prolonged use of anti inflammatory drugs is associated with various side effects; for example, steroidal drugs cause adrenal atrophy (Phalitakul *et al*., 2011), osteoporosis, suppression of response to infection or injury (Craig and Stitzel, 2004). On the other hand, NSAIDs cause peptic ulcers and bronchospasm due to blockade of both the physiological and inflammatory prostaglandins and concurrent production of leukotrienes (Abdulkhaleq *et al*., 2018).

9.3. Herbal therapy

Taking into account both the adverse effects and the high cost of synthetic steroidal and non-steroidal drugs (Burchum and Rosenthal, 2014; Izuhara *et al*., 2011), the search for new anti-inflammatory agents from herbal sources is getting popular with the objective to obtain greater safety, better efficacy, and a more economical way to treat inflammation (table 2) (Nunes *et al*., 2020).

Table 2. Anti-inflammatory activity of some medicinal plants (Nunes *et al*., 2020).

Botanical name	Plant/Family	Parts used	Constituent compounds
Acacia catechu	Mimosaceae	Bark, wood, flowering tops, gum	Tannin, gum, catechuic acid
Caesalpinia crista	Caesalpiniaceae	Seeds, root, leaf, root bark	Oleic, linoleic, palmitic, stearic acid, phytosterols
Erythrina variegate	Papilionaceae	Leaves, bark, roots, flower	2-Hydroxygenistein, genistein
Ficus carica	Moraceae	Fruit, root	Alkaloids, ascorbic acid, caffeic acid, niacin, linoleic acid, lutein, β-carotene, pantothenic acid, β-amyrin
Ocimum basilicum	Laminaceae	Whole plant	Acetic acid, ascorbic acid, aspartic acid, apigenin, arginine
Solanum nigrum	Solanaceae	Whole plant	Solenin, solasodine
Thespesia populneoides	Malvaceae	Whole plant	Populneol, gossypol, kaempferol, quercetin-5 glucoside, calycopterin, kaempferol-5-glucoside, kaempferol-3-gluoside

CHAPTER Ⅱ:
LAVANDULA STOCHEAS AS A MEDICINAL PLANT

Due to the tremendous potentials of *Lavandula stoechas* as a medicinal plant along with the recent growing interest towards natural remedies and medicinal plant-derived products in alternative medicine, this plant has been in the spotlight for its potentially beneficial usage in the treatment and the management of inflammation (Akbar, 2020).

1. Generalities

The Mediterranean region has a diverse vegetation cover that has been long considered as an important source of medicinal plants including the *Lavandula* genus which is one of the most popular medicinal and aromatic plants in this region (Bousta and Farah, 2020). The genus *Lavandula* which belongs to the *Lamiaceae* family comprises approximately 39 species, many hybrids, and nearly 400 registered cultivars (Upson and Andrews, 2004). This genus is represented in the Algerian flora by six species**,** including *Lavandula stoechas* (*L. stoechas*) (Lis-Balchin, 2002) which is locally known as "El Halhal" (table 3) (Lim, 2014).

Table 3. Different nomenclatures of lavender (Lim, 2014).

Arabic	Halahal (حلحال), khouzama (خزامى), Ustukhuddus, Ustukhuddus (أستخدوس), Moqif Rwah (موقف الأرواح), Washa'I Al-Shaikh (وشاح الشيخ).
Berber	Amezzir, Timerza, Imezzir.
English	French Lavender, Italian Lavender, Spanish Lavender, Top Lavender.
French	Lavande, lavande Maritime, lavande Papillon, lavande Stéchade, lavande Stéchas, Stoechas Arabique, lavande à toupet.
Spanish	Lavándula, Arca, Astecados, Azaya, Cantahueso, Cantuerca, Cantueso, Morisco,Cap D'ase, Estecados, Tomillo, Tomillo Borriquero.
Turkish	Karabaşotu.
Chinese	Xun Yi Cao.

2. Taxonomical classification

L. stoechas belongs to a plant family called "the mint family" or *Lamiaceae*; taxonomical classification of the plant is shown in figure 7 (Tison and Foucault, 2014).

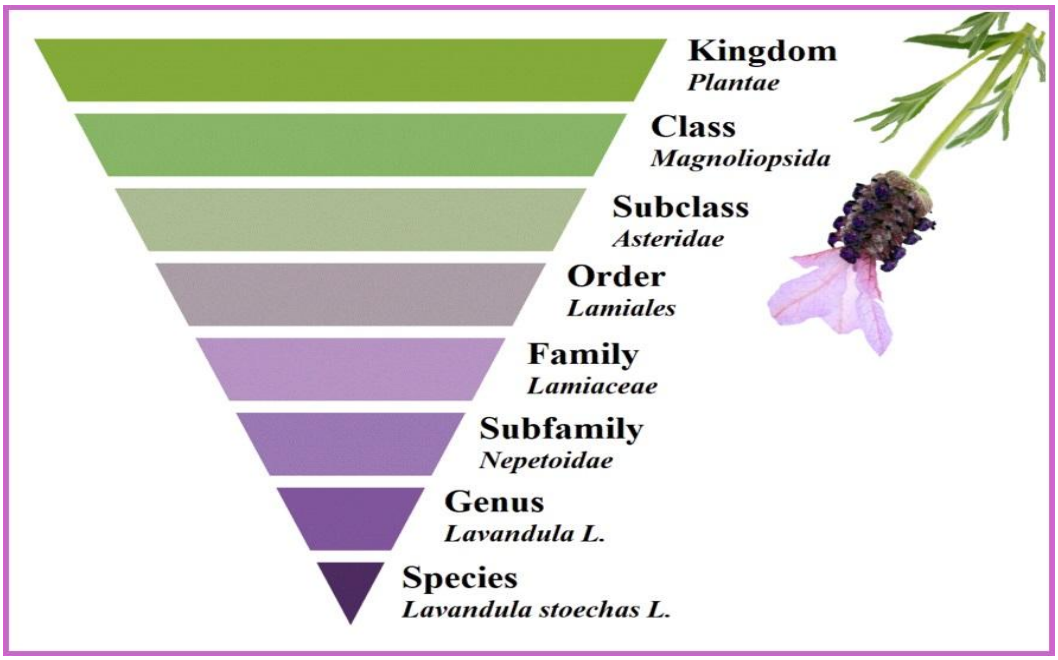

Figure 7. Taxonomy of *Lavandula stoechas* (Tison and Foucault, 2014).

3. Morphological description

L. stoechas is an evergreen shrub that usually grows to 30–100 cm tall, with 1-4 cm long greyish and tomentose leaves (figure 8) (Lim, 2014). The fragrant flowers, which appear in late spring and early summer, are pink to purple or violet, occur on spikes of 2 cm long at the top of slender, leafless stems of 10–30 cm long, and are situated in the axils of downy, heart-shaped bracts (Akbar, 2020; Miraj, 2016).

Figure 8. *Lavandula stoechas* (Lim, 2014).

4. Agro-ecology

In its native range, *L. stoechas* thrives in full sun exposure and dry hills, garrigue, maquis shrubland, or open woodlands, and on well-drained limestone or granite soils. It requires dry or moist soil and is drought resistant (Lim, 2014).

5. Origin and geographical distribution

The natural geographical distribution of lavender ranges from the Canary Islands to Cape Verde Islands and Madeira, across the Mediterranean basin, the Arabian Peninsula, and all the way to tropical North Africa, and Central and Southeast India (Lis-Balchin, 2002).

L. stoechas can be found on the three continents: Africa, Europe, and Asia. It is native to countries bordering the Mediterranean basin (figure 2) (Bousta and Farah, 2020), including Algeria, Morocco, Tunisia, Spain, Greece, France, Italy, and Turkey (Boukhatem *et al*., 2020; Cavanagh and Wilkinson, 2002; Hajhashemi *et al*., 2003). However, it has been introduced and cultivated in other areas like the Americas and Australia (Lim, 2014).

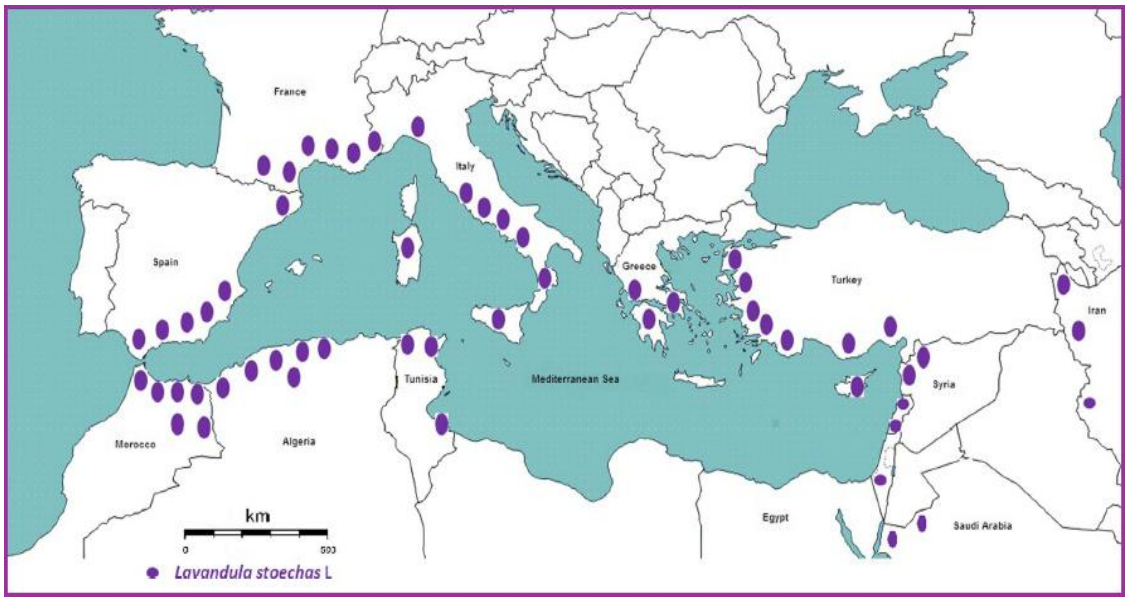

Figure 9. Geographic distribution of *Lavandula stoechas* (Bousta and Farah, 2020).

6. Traditional uses

The aromatic and medicinal properties of lavender have been used cosmetically and medicinally since ancient times and throughout history by the Greeks, Romans, and even Ancient Egyptians. *L. stoechas* is one of the most commonly used healing plants in Mediterranean countries (table 4) (Bousta and Farah, 2020). Moreover, it has been used

traditionally in Algerian folk medicine as an antiseptic and stimulant agent (Baba Aissa, 1991; Mahmoudi, 1990).

Table 4. Ethnomedicinal uses of *Lavandula stoechas* in some Mediterranean countries (Bousta and Farah, 2020).

Countries	Plant parts used	Traditional uses	Preparation form	References
Algeria	Aerial part	Analgesic, antiseptic, and stimulant agent	Infusion	(Mahmoudi, 1990; Sarri *et al*., 2014)
Morocco	Aerial part	Rheumatism, digestive system, cystitis, nephritis, pain and inflammation, and antispasmodic	Decoction	(El-Hilaly *et al*., 2003; Ez zoubi *et al*., 2016)
Spain	Flowered aerial part	As herbal tea and for making liqueur	Infusion	(Tardío *et al*., 2006)
Greece	Leaves	Anti-diabetes, menstrual pains, kidney stones, and hypertension	Infusion and essential oils	(Skoula *et al*., 1996)
Turkey	Inflorescence and areal part	Antiseptic, sedative, wound healing, epilepsy, asthma, expectorant, urinary tract infections, cardiovascular diseases	Infusion	(Baytop, 1999; Bulut and Tuzlaci, 2015)
Palestine	Areal part	Migraine and epilepsy	Decoction	(Gilani *et al*., 2000)

7. Chemical composition

7.1. Chemical composition of *L. stoechas* essential oil

Several studies on chemical constituents of *L. stoechas* essential oil (LSEO) from wild and cultivated plants have demonstrated the presence of various compounds, including fenchone, camphor, and 1,8-cineole (figure 10; A, B, C) (Benabdelkader *et al*., 2011) which are the most commonly identified major compounds.

Moreover, LSEO could be separated into two main chemotypes; fenchone/camphor and fenchone/1,8-cineole (Skoula *et al*., 1996). This significant variation of the LSEO composition depends on different factors like geographical origins, environmental conditions, parts of the plant used for extraction, and extraction techniques (Da Porto *et al*., 2009; Marcum and Hanson, 2006; Muñoz-Bertomeu *et al*., 2007).

The main components of LSEOs from Algeria include monoterpenes with fenchone, camphor, 1,8-cineole, sesquiterpenes as the second most abundant components with viridiflorol (figure10; D), and other trace elements such as p-methylacetophenone, mcymen-8-ol, anecrodyl acetate, epicubebol, cubebol, and d-amorphene. Therefore, LSEOs were poor in sesquiterpene hydrocarbons and monoterpene hydrocarbons (Benabdelkader *et al*., 2011).

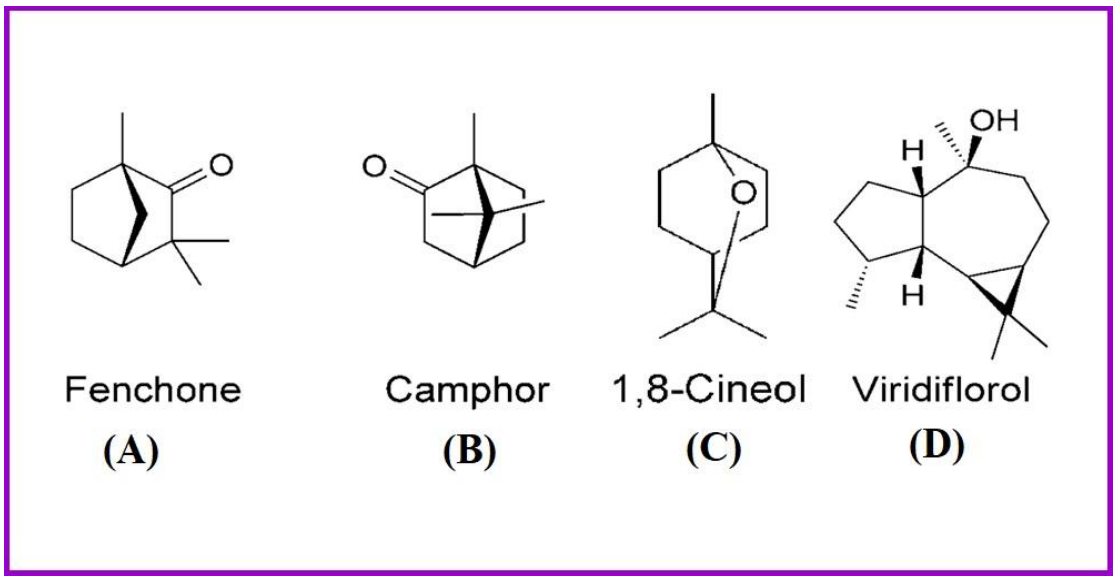

Figure 10. Structures of the main compounds of the Algerian LSEOs (Benabdelkader *et al*., 2011).

7.2. Chemical composition of *L. stoechas* extract

Many studies on *L. stoechas* revealed the presence of several chemical families in its hydroethanolic extract such as catechic tannins, flavonoids, sterols and terpenes, coumarins, leucoanthocyans, and mucilages (table 5) (Ezzoubi *et al*., 2016).

Table 5. Phytochemical screening of hydroethanolic extract of *L. steochas* (Ezzoubi *et al*., 2016).

Phytochemical	Hydroethanolic extract
Tannins	+
Catechic tannin	+
Gallic tannin	-
Flavonoids	+
Sterols and terpenes	+
Coumarins	+
Quinones	-
Leucoanthocyans	+
Cardiac glycosides	+
Mucilages	+

Presence of compounds: (+) = present; (-) = absent

The major flavonoids identified in *L. stoechas* were apigenin 7-glucoside, luteolin, luteolin 7-glucoside and luteolin 7-glucuronide (Xaver and Andary, 1988). Lavanol was also isolated from *L. stoechas* (Manzoor-I- Khuda and Khan, 1967). Acetylated glucosides, apigenin 7-O-glucoside, and luteolin 7-O-glucoside were found in the aerial parts of *L. stoechas* (Upson *et al*., 2000).

8. Biological and pharmacological activities

According to several ethnobotanical and phytopharmacological studies, LSEOs and other extracts have been shown to be a potent therapeutic agents used in treating several diseases including epilepsy, headaches (Ulubelen *et al*., 1988; Ulubelen and Olcay, 1989), flu-like

symptoms (Benítez *et al*., 2010; González-Tejero *et al*., 1992), cough and asthma (Benítez et *al*., 2010) and has analgesic and antiseptic properties (Ulubelen *et al*., 1988; Ulubelen and Olcay, 1989). It has also been reported to have hypoglycemic and anti-hyperglycemic activity (Benítez *et al*., 2010; González-Tejero *et al*., 1992; Mustafa *et al*., 2019), and to be cholesterol lowering agent (Benítez *et al*., 2010). *L. stoechas* is also characterized by (Benabdelkader *et al*., 2011; Bouayyadi *et al*., 2015), its antibacterial (Bousta and Farah, 2020), antifungal, insecticidal, anti-leishmanial (Bouyahya *et al*., 2017), antioxidant (Baptista *et al*., 2015; Celep *et al*., 2018), anticonvulsant, antispasmodic, sedative (Gilani *et al*., 2000), and anti-inflammatory properties (Algieri *et al*., 2016; Kulabas *et al*., 2018). According to Algieri *et al*. (2016), *L. stoechas* has an anti-inflammatory effect with values similar to those recorded by a steroidal anti-inflammatory drug.

CHAPTER III:
MECHANISMS OF ACTION OF THE ANTI-INFLAMMATORY ACTIVITY OF LAVANDULA STOECHAS

The richness of *L. stoechas* in bioactive molecules, such as monoterpenoids and flavonoids confers anti-inflammatory properties to this medicinal plant, and therefore it can serve as a potential therapeutic agent for anti-inflammatory drugs development (Benabdelkader *et al*., 2011; Kulabas *et al*., 2018).

In this chapter, we summarize current knowledge about the mechanistic aspects of the anti-inflammatory activity of these bioactive molecules of LSEO and extracts from published experimental studies.

1. The mechanistic aspects of the anti-inflammatory activity of LSEO

1.1. The anti-inflammatory mechanisms of action of 1,8-cineole

1,8-cineole, also known as eucalyptol, is a natural bicyclic monoterpene comprising the majority of the volatile oil in various plant genera, including *L. stoechas* (Quintans *et al*., 2019). It has been effective in the treatment of rheumatic disorders, as well as in inflammatory diseases of the respiratory tract, sinusitis, bronchitis, asthma, and chronic obstructive pulmonary disease (COPD) (Habich and Repges, 1994; Wittmann *et al*., 1998).

In vivo and *in vitro* studies have established that 1,8-cineole has a potent anti-inflammatory profile (Brown *et al*., 2017). 1,8-cineole caused a significant reduction in carrageenan-induced inflammatory paw edema in Wistar rats (Santos and Rao, 2000).

1.2.1. The effects of 1,8-cineole on inflammatory mediators

Various studies suggested that 1,8-cineole modulates important pathways that regulate the release of pro and anti-inflammatory cytokines (Quintans *et al*., 2019).

1,8-cineole was impressively shown to modulate the key chemical mediators of inflammation by down-regulating the production of pro-inflammatory cytokines such as TNF-α, IL-1β (Bastos *et al*., 2011; Kennedy-Feitosa *et al*., 2016; Zhao *et al*., 2014), and up-regulating the release of anti-inflammatory cytokines such as IL-10 (Kennedy-Feitosa *et al*., 2016; Zhao *et al*., 2014).

Numerous studies further reported that 1,8-cineole significantly inhibited the production of TNF-α, IL-1β, IL-4, IL-5 in lymphocytes and TNF-α, IL-1β, IL-6 and IL-8 in monocytes with the strongest degree of TNF-α and IL-1β inhibition (Juergens *et al*., 2004; Khan *et al*., 2013).

1.2.2. The effects of 1,8-cineole on signaling pathways

Different studies demonstrated that 1,8-cineole could inhibit NF-κB transcription by preventing its translocation into the nucleus. Furthermore, 1,8-cineol may inhibit nuclear translocation of NF-κB's subunit p65, and AP-1, as well as NF-κB target gene expression through two potential targets which are Inhibitor of kappa Bα (IκBα) and c-Jun N-terminal kinase (JNK) in LPS-stimulated cells (figure 11) (Greiner *et al*., 2013).

1,8-cineole may additionally suppress the expression of pro-inflammatory genes by inhibiting another transcription factor known as Egr-1 which regulates many genes involved in inflammation including TNF-α gene expression (Greiner *et al*., 2013; Pawlinski *et al*., 2003; Zhou *et al*., 2007).

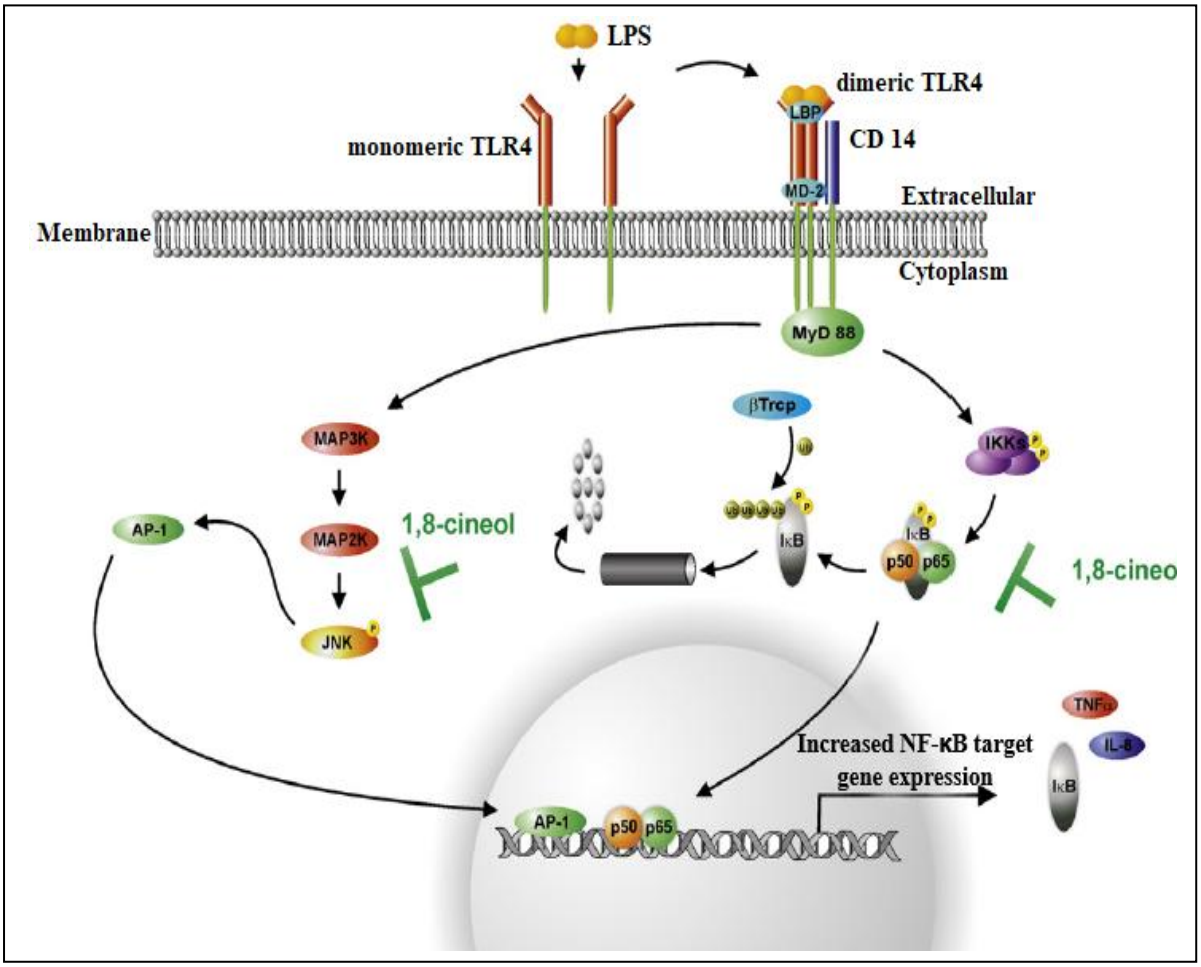

Figure 11. Schematic representation of the potential mode of action of 1,8-cineol (Greiner *et al*., 2013). Treatment with 1,8-cineole causes a reduced expression of TLR4. Reduced expression of NF-κB's subunit p65 strongly reduces translocation of NF-κB p65 into the nucleus. Increased protein levels of IκBα and lack of its degradation in an IKK independent way reduce protein levels of phosphorylated c-Jun N-terminal kinase (JNK) and AP-1. Reduced AP-1 nuclear translocation.suppresses DNA binding activity of p65 and AP-1. Reduced expression of transcription factor NF-κB and pro-inflammatory NF-κB target genes.significantly reduces activity of NF-κB.

1.2.3. The effects of 1,8-cineole on inflammatory cells

On the cellular level, 1,8-cineole reduced inflammatory cells infiltration including neutrophils, eosinophils, macrophages, and lymphocytes in bronchoalveolar fluid, as well as myeloperoxidase (MPO) activity (Bastos *et al*., 2011; Kennedy-Feitosa., 2016).

1.2.4. The effects of 1,8-cineole on AA-metabolism

1,8-cineole has shown very promising results in targeting the AA pathway via inhibiting 5-LOX and COX-2 and thereby impairing the production of AA-derived eicosanoids; leukotrienes and prostaglandins (Juergens *et al*., 2014) precisely, the production of leukotriene B4 (LTB 4), prostaglandin 2 (PGE 2), and thromboxane B2 (TxB 2). Furthermore, the inhibition of phosphlipase A2 (PLA2) has been reported (Juergens *et al*., 2014; Juergens *et al*., 1998).

1.2.5. The effects of 1,8-cineole on oxidative stress

1,8-cineole has shown *in vitro* anti-oxidative capacity (Juergens *et al*., 2014; Juergens *et al*., 2009). It significantly inhibited the production of ROS; O_2^- ion formation and H_2O_2 by partial blockade of SOD activity (Juergens *et al*., 1998).

The anti-oxidative action of 1,8 cineole with its strong ROS scavenging activity blocks oxygen radicals and their transformation into cytokine inducing H_2O_2. Thus, potentially contributing to the anti-inflammatory action of this compound by interfering with oxidative mediator production (Juergens *et al*., 2014).

1.2. The anti-inflammatory mechanisms of action of camphor

Camphor is a natural terpenoid ketone compound that is mainly present in *Cinnamomum camphora* (Siegel and Wason, 1986), which can also be found in other plant species including *L. stoechas*, and in some essential oils with anti-inflammatory activity (Abu-Darwish *et al*., 2016).

1.2.1. The effects of camphor on inflammatory mediators

Camphor may act by inhibiting pro-inflammatory cytokines. Moreover, isolated camphor inhibited the production of IL-1β, IL-4, and TNF-α (Vonaparti., 2008). Likewise, many other studies performed with camphor-rich extracts and EOs of *Cinnamomum camphora* and

Artemisia fukudo noted that they inhibited pro-inflammatory cytokines, such as IL-1β, IL-6, TNF-α, and PGE2 in macrophage cultures (Cassatella, 1995; Ribeiro *et al*., 2010).

The camphor-rich essential oil from the roots of *Curcuma kwangsiensis* significantly decreased the expression of the pro-inflammatory cytokine TNF-α and the inflammatory enzyme COX-2 in TPA-induced mouse ear edema assay (Zhang *et al*., 2017).

1.2.2. The effects of camphor on signaling pathways

The treatment with camphor-rich oil of *Artemisia argy* suppressed the production of inflammatory mediators such as NO, PGE2, ROS, IL-6, TNF-α, and IFN-β, and down-regulated mRNA expression of iNOS and COX-2 without directly affecting their activity in LPS-induced macrophages. Though the treatment did not inhibit the activation of MAPKs or NF-κB, inhibited JAK2 and STAT1/3 phosphorylation was further reported suggesting a down-regulation of the JAK/STAT signaling (Chen *et al*., 2017).

1.2.3. The effects of camphor on inflammatory cells

In a study that assessed the anti-inflammatory activity of isolated camphor, the authors demonstrated that it reduced leukocytes migration and also reported a significantly reduced croton oil-induced ear edema in rat and MPO activity. Further, *In vitro* treatment with camphor significantly reduced neutrophil migration without affecting their viability.

Pure camphor showed an anti-inflammatory profile and no significant cytotoxicity at low doses. However, irritant effects occur at higher doses (Silva-Filho *et al*., 2014).

1.2.4. The effects of camphor on oxidative stress

Extracts and EOs from *Cinnamomum camphora* and *Ocotea odorifera*, which both contain camphor, exhibit antioxidative activity, hence showing potential inhibition of free radical formation, such as NO and ROS, and likely contributing to anti-inflammatory activity (Lee *et al*., 2006). *In vivo*, the camphor-rich EO of *Tetraclinis articulate* induced significant antioxidant properties through scavenging activity in carrageenan-induced rat paw edema. The authors also reported a possible inhibition of COX (El Jemli *et al*., 2017).

Despite the fact that camphor has evidenced potent anti-inflammatory properties, a precise mechanism of action cannot be determined.

2. The mechanistic aspects of the anti-inflammatory activity of *L. stoechas* extract

2.1. The anti-inflammatory mechanisms of action of luteolin

Luteolin (3',4',5,7-hydroxyl-flavone) (figure 12) is a naturally occurring compound belonging to the flavones, a subclass of flavonoids, which is found in many medicinal plants. Luteolin and its glycosylated form luteolin-7-glucoside (L7G) are present in *L. stoechas* (Gabrieli and Kokkalou, 2003). It reportedly possesses anti-inflammatory activities (Shanmugam *et al*., 2016).

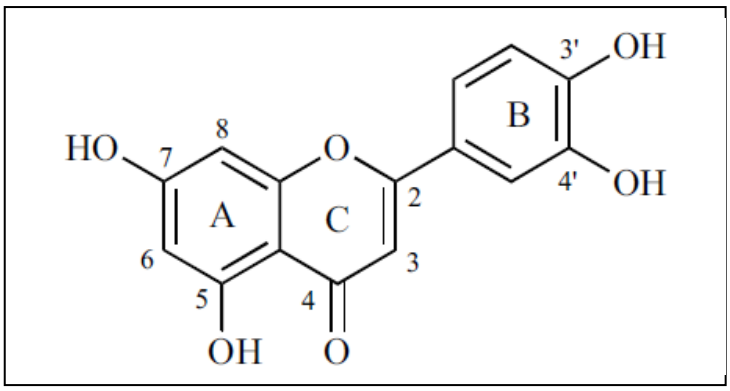

Figure 12. Luteolin (3',4',5,7-hydroxyl-flavone).

2.1.1. Regulation of inflammatory mediators

In vitro and *in vivo* studies reported that luteolin exerts its anti-inflammatory effects partly by regulating inflammatory mediators. Luteolin inhibits pro-inflammatory cytokines IL-1β, IL-2, IL-6, IL-8, IL-12, IL-17, TNF-α, and IFN-β along with eicosanoids; prostaglandin, and leukotriene and increase the level of anti-inflammatory cytokine IL-10. Luteolin inhibited TNF-α and IL-6 production in a dose-dependent manner in rats-derived macrophages (Wu *et al*., 2013).

Luteolin has been reported to act partly by inhibiting inducible nitric oxygen synthase (iNOS), iNOS expression, and NO production (Seelinger *et al*., 2008). Luteolin also acts as a ROS scavenger, an inhibitor of ROS production, and an activator of antioxidant enzymes (Seelinger *et al*., 2008). It was reported that luteolin significantly attenuated intracellular ROS generation by TNF-α-induction in a dose-dependent manner (Xia *et al*., 2014).

The anti-inflammatory activity of luteolin derivative luteolin-7-glucoside has also been noted. It inhibited leukotriene C4 (LTC4) production in a dose-dependent manner (Jin *et al*., 2011), increased the level of the anti-inflammatory compound, and decreased the level of PGE2 in normal human keratinocytes (Palombo *et al*., 2016).

2.1.2. Alterations in signaling pathways

Luteolin exerts its effects by altering the NF-κB, MAPK/AP-1, and JAK-STAT signaling pathways, as summarized in figure 13 (Aziz *et al*., 2018).

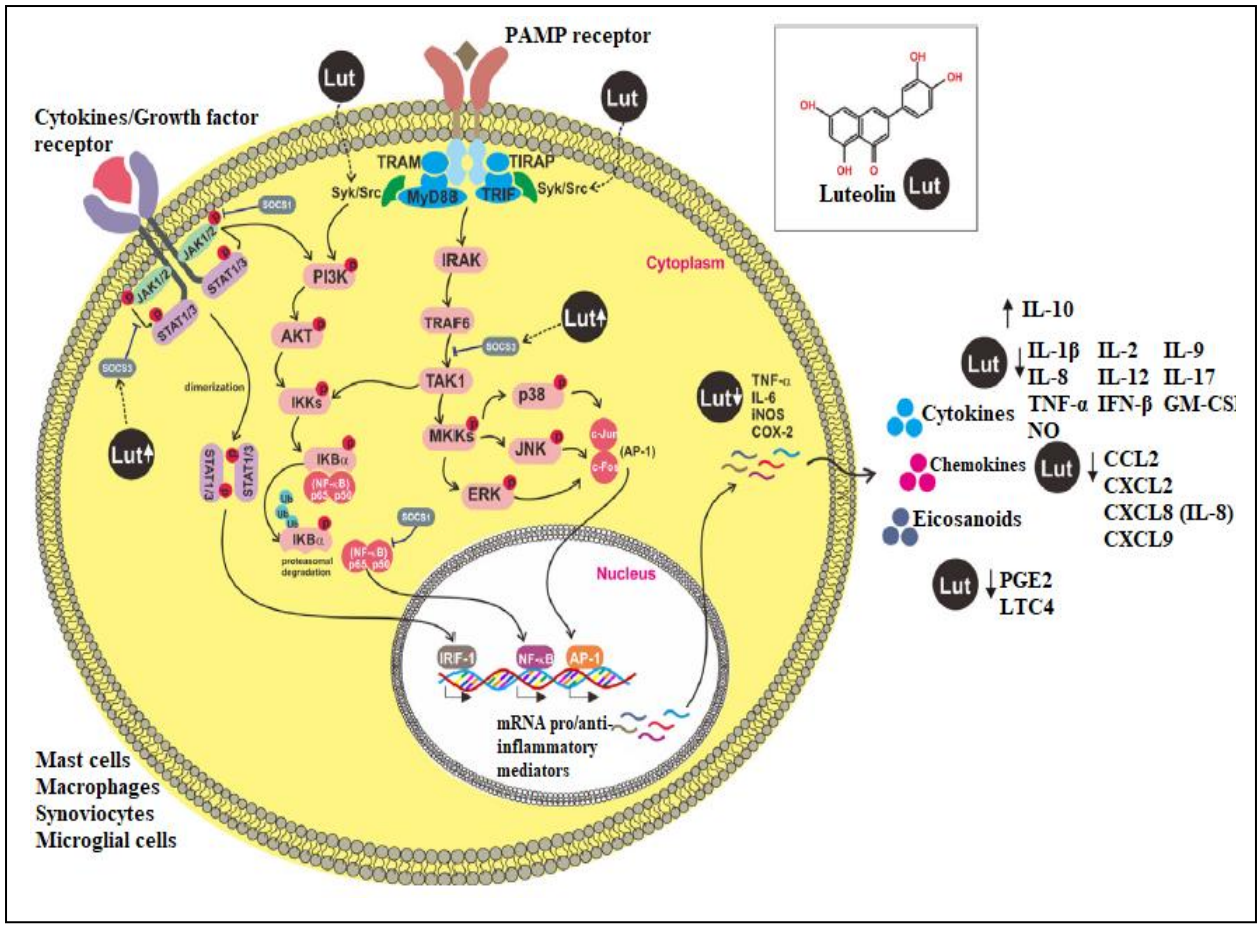

Figure 13. Schematic illustration of various luteolin-targeted inflammatory signaling pathways (Aziz *et al*., 2018). Luteolin (Lut) targets Src, Syk, and SOCS3 activated by cytokines, growth factors, and PAMPs linked to the activation of NF-κB, AP-1, and IRF-1; essential transcription factors involved in the inflammatory responses such as the release of cytokines, production of inflammatory mediates, and secretion of chemokines. NF-κB, nuclear factor kappa B; AP-1, activator protein; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor-α; NO, nitric oxide; iNOS, inducible nitric oxygen synthase; ROS, reactive oxygen species; AKT, protein kinase B; MAPK, mitogen-activated protein kinase; ATP, adenosine triphosphate; Syk, spleen tyrosine kinase; Src, proto-oncogene tyrosine-protein kinase; IL-1β, interleukin-1β; CCL2, chemokine (C-C motif) ligand 2; CXCL2, chemokine (C-X-C motif) ligand 2; IFN-β, interferon-β; HMGB-1, high mobility group B-1; PGE2, prostaglandin E2; COX-2, cyclooxygenase enzyme-2; BMMCs, bone marrow-derived mast cells; LTC4, leukotriene C4; MIP, macrophage inflammatory protein; JAK, Janus tyrosine kinase; PI3K, phosphatidylinositide 3-kinases; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; IκB, inhibitor of kappa B; IKK, IκB kinase; PAMP, pathogen-associated molecular pattern; pseudorabies virus; IRF, interferon regulatory transcription factor; MyD88, myeloid differentiation primary response 88; TRIF, TIR-domain-containing adapter-inducing interferon-β; TBK1, TANK-binding kinase 1; JNK, c-Jun N-terminal kinase; SOCS, suppressor of cytokine signaling.

2.1.2.1. Effects of luteolin on NF-κB signaling

The anti-inflammatory effect of luteolin was found to be mediated by the inhibition of NF-κB activity by the reduced expression of TNF-α and COX-2 in the kidneys, thereby suppressing pro-inflammatory gene expression. (Domitrovic *et al*., 2013).

Luteolin significantly decreased the protein and the phosphorylated level of NF-κB p50 (Liu *et al*., 2016), and suppressed p50 nuclear localization in LPS-stimulated cells (Lee *et al*., 2015) without altering IκBα degradation (Lee *et al*., 2009; Nunes *et al*., 2017) or NF-κB activity (Chen *et al*., 2014). These results conflicted with another study which indicated that luteolin decreased NO production and iNOS expression by blocking NF-κB activity (Sung and Lee, 2015).

Other studies on luteolin and its derivatives revealed that luteolin suppressed p65, c-Jun phosphorylation, and both NF-κB and AP-1 activation, while luteolin-7-glucoside suppressed only p65 phosphorylation and NF-κB activation in LPS-stimulated cells (Park and Song, 2013).

Interestingly, luteolin decreased LPS-induced AKT phosphorylation (Li *et al*., 2012), leading to decreased expression levels of the inflammatory mediators (Park and Song, 2013). Thus, luteolin partly inhibits NF-κB activation by inhibiting the PI3K-AKT pathway. Luteolin also inhibited MyD88-dependent signaling (Lee *et al*., 2009).

2.1.2.2. Effects of luteolin on MAPK signaling

Luteolin reportedly modulates the MAPK pathway, as shown by the suppression of JNK and p38 kinase activation. Furthermore, treatment with luteolin resulted in inhibition of AP-1 nuclear translocation (Choi and Lee, 2010), pro-inflammatory cytokine production, and intracellular Ca^{2+} release through the inhibition of ERK and JNK activation. Though, p38 MAPK phosphorylation was not attenuated (Kang *et al*., 2010). Pretreatment with luteolin was also reported to inhibit IL-1β-induced IκB, ERK, and JNK phosphorylation (Lamy *et al*., 2015). However, several contradictory results have been obtained in different cell types and experimental models. Yu *et al*. (2015) reported that luteolin decreased p-p38 MAPK and p-JNK levels along with significantly increased ERK1/2 phosphorylation in ROS-induced MAPK activation.

Additionally, the ROS-scavenging activity of luteolin (Seelinger *et al*., 2008) attenuates ROS-induced MAPK activation (Yu *et al*., 2015).

2.1.2.3. Effects of luteolin on the JAK-STAT pathway

Luteolin exerts its anti-inflammatory activity at least in part by inhibiting the STAT1 and STAT3 signaling pathways (Xia *et al*., 2016). Luteolin markedly suppressed STAT1 and STAT3 phosphorylation (Liu *et al*., 2016), decreased STAT-binding activity, and the basal level of the transcriptional factor IRF-1. Moreover, treatment with luteolin increased the expression of suppressor of cytokine signaling 3 (SOCS−3) leading to inactivation of STAT1 (Kao *et al*., 2011) and thereby, decreased level of p-STAT1 (Nunes *et al*., 2017) and p-STAT3 (Xia *et al*., 2016). Interestingly, luteolin did not have a significant effect on JAK1, JAK2, or Tyk2 phosphorylation (Kao *et al*., 2011). Liu *et al*. (2016) proposed that by suppressing the STAT1/3 dependent NF-B pathway, luteolin attenuates the production of the proinflammatory mediators NO, iNOS, COX-2 whilst also decreasing the secretion of IL-6 and monocyte chemoattractant protein-1 (MCP-1).

2.2. The anti-inflammatory mechanisms of action of apigenin

Apigenin, (4′, 5, 7,-trihydroxyflavone) (Figure 14), is a naturally occurring flavone. It is found in many fruits, vegetables, and herbs (Lefort and Blay, 2013; Shukla and Gupta, 2010). The anti-inflammatory activity is among the reported properties of apigenin (Liu *et al*., 2017).

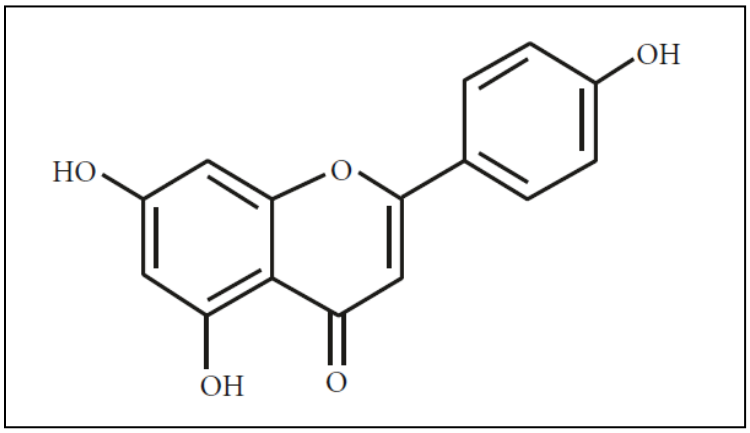

Figure 14. Apigenin (4′, 5, 7,-trihydroxyflavone).

2.2.1. Regulation of inflammatory mediators

Several experimental studies demonstrated that apigenin regulates various inflammatory molecules. Furthermore, *in vivo* and *in vitro* studies have shown that apigenin inhibited the expression of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α, (Farkas *et*

al., 2015; Hougee *et al*., 2005; Smolinski and Pestka, 2003; Zhang *et al*., 2014), as well as the expression of intracellular adhesion molecules (ICAM) (Zhang *et al*., 2014), and H_2O_2 (Farkas *et al*., 2015).

Apigenin was also reported to inhibit NO production, to strongly suppress the expression of iNOS and COX-2 (Choi *et al*., 2014; Zhao *et al*., 2014), and to attenuate LOX and COX-2 activities. Treatment with low concentrations of apigenin protects against ROS-induced oxidative damage in rat liver. However, at very high doses, apigenin can induce oxidative stress (Ali *et al*., 2017).

2.2.2. Alterations in signaling pathways

Apigenin has shown its role in modulating the inflammatory pathways by regulating the DNA binding capacity of different transcription factors including NF-κB, Fos-Jun, or AP-1 through the inhibition of protein kinases involved in signal transduction such as PKC, ERK, and MAPK, which leads to attenuated expression of several cytokine genes (Kim *et al*., 2004). The possible apigenin-induced anti-inflammatory activity is shown in figure 15 (Ali *et al*., 2017).

In an experimental study, it has been shown that apigenin significantly modulated NF-κB activity in the lungs (Cardenas *et al*., 2016). The inhibition of NF-κB is mediated by the inhibition of IκB kinase activity in mouse macrophages (Liang *et al*., 1999). Apigenin however did not affect the degradation of IκB proteins, nuclear translocation, and DNA binding activity of NF-κB p65 (Funakoshi-Tago et al., 2011).

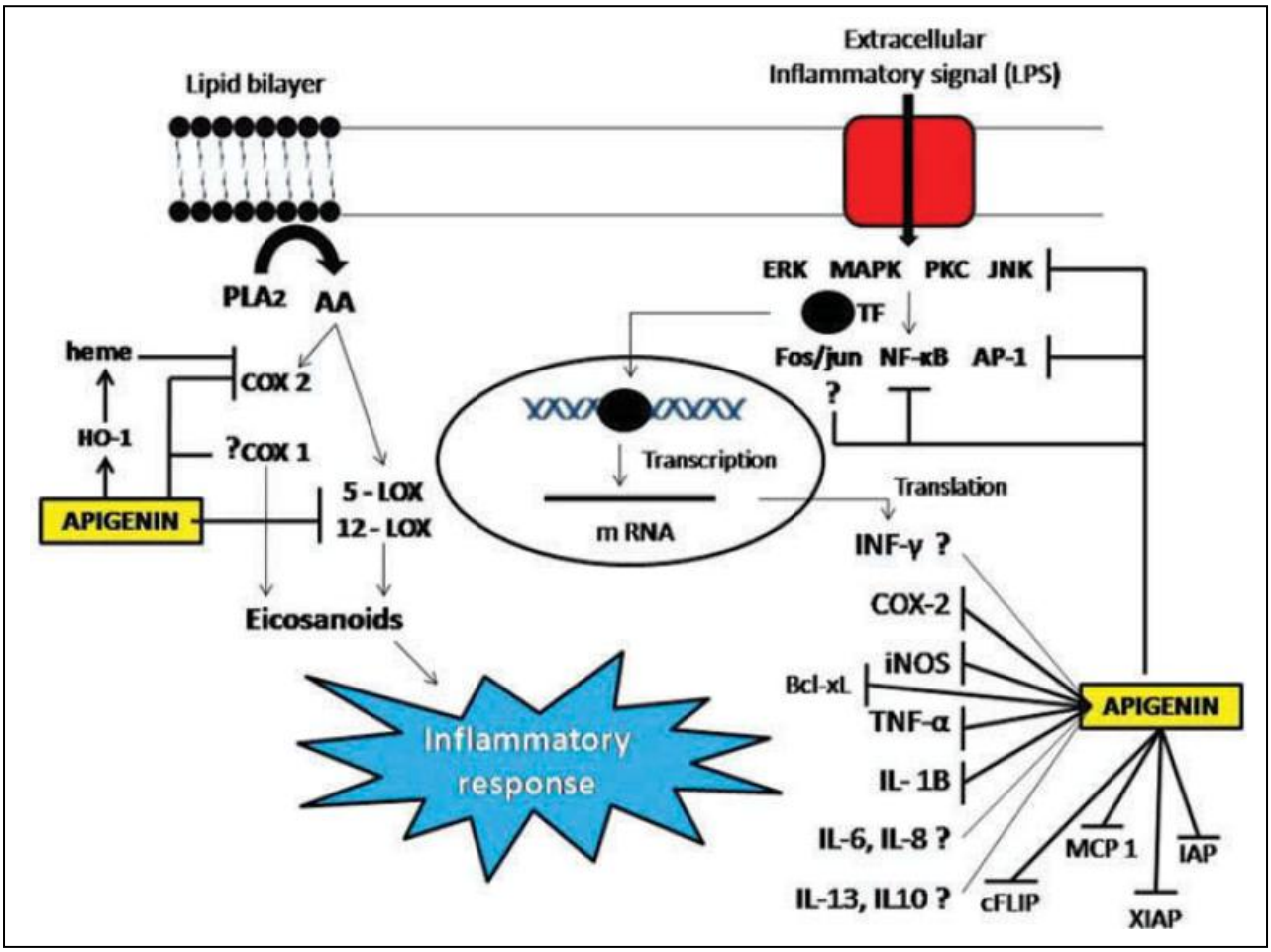

Figure 15. Potential anti-inflammatory effect of apigenin through the modulation of inflammatory molecules expression at both transcriptional and post-transcriptional levels (Ali *et al*., 2017). COX 1/2 (Cycloxygenase 1/2), LOX (Lipoxygenase), HO-1 (Haeme oxygenase 1), PLA (Phospholipase), IL (Interleukins), TNF-α (Tumor necrotic factor alpha), iNOS (inducible nitric oxide synthase), INF-γ (Interferon gamma), XIAP (X-linked inhibitor of apoptosis protein), c-FLIP (Cellular FLICE like inhibitory protein).

CONCLUSION

In conclusion, the field of plant-derived compounds is a topic of current interest and the focus of many ongoing studies due to its multitarget nature and less-to-none side effects. Therefore, medicinal plants such as *L. stoechas* provide a challenging field in the identification of new potent phytochemicals for the therapy of inflammatory-based disorders. Overall, the collective data reported from *in vitro* and *in vivo* as well as clinical trials validated the therapeutic potential of the major compounds from EOs and extracts isolated from *L. stoechas*.

Moreover, this study has drastically improved our understanding of not only the potency of *L. stoechas* against inflammation, but also the implied mechanisms of action of its active compounds. Various mechanisms can contribute to this beneficial effect through an improvement and down-regulation of the immune response.

The studied bioactive molecules reflect their diverse modes of action by the modulation of various pro and anti-inflammatory mediators (interleukins, TNF-α, IFN-γ, NO, prostaglandins, and leukotrienes), the inhibition of AA metabolism (COX-2, LOX, PLA2, and iNOS), and the modulation of various transcription factors implied in the expression of pro-inflammatory genes. However, further studies need to be undertaken to elucidate new insight into the development of novel anti-inflammatory formulations from this plant.

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The mechanistic aspects of the anti-inflammatory activity of *Lavandula stoechas*

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Abstract

Inflammation is a defensive mechanism against various harmful stimuli, which involves both the innate and the acquired immune responses. This response includes vascular and cellular events which are highly coordinated by different inflammatory mediators. It is aimed to repair and restore the normal homeostasis of the injured tissue. However, persistent or uncontrolled inflammation can lead to the development of chronic inflammation which may act as the central executor in the pathogenesis of many inflammatory diseases. Taking into consideration the adverse side effects of synthetic anti-inflammatory drugs, the search for new anti-inflammatory agents from herbal sources is desirable.

The recent growing interest towards natural remedies and medicinal plant-derived products in alternative therapies has shed some light on lavender including its different species such as our plant of interest, *Lavandula stoechas* which could serve as a potential source for anti-inflammatory bioactive molecules that could be further used for drug development.

The aim of this study was to evaluate the anti-inflammatory activity as well as the underlying molecular mechanisms of action of some bioactive molecules found in *Lavandula stoechas* essential oils and extracts.

Results from published experimental and clinical studies demonstrated the anti-inflammatory properties of *Lavandula stoechas* which was mainly due to its richness of bioactive compounds such as 1,8-cineole, camphor, luteolin, and apigenin. Additionally, these findings proposed that the anti-inflammatory mechanism of action of these phytochemicals is mediated through the modulation of various pro and anti-inflammatory mediators such as interleukins, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), nitric oxide (NO), as well as prostaglandins and leukotrienes. Additionally, they induce the inhibition of arachidonic acid (AA) metabolism, cyclooxygenase-2 (COX-2), lipooxygenase (LOX), inducible nitric oxide (iNOS), and various transcription factors implied in the expression of pro-inflammatory genes.

Finally, the identified components from *Lavandula stoechas* could be incorporated into future novel bioactive anti-inflammatory formulations and in the exploitation of targeted therapies used for the treatment of inflammatory diseases. However, further studies need to be undertaken.

Key words: Inflammation; *Lavandula stoechas*; Secondary metabolites; Terpenes; Flavonoids; 1,8-cineole; Camphor; Luteolin; Apigenin; Anti-inflammatory activity.

الملخص

الالتهاب هو آلية دفاعية ضد مختلف المحفزات الضارة، و تشمل كلا من الاستجابة المناعية الفطرية والمكتسبة. تتضمن هذه الاستجابة تطورات خلطية وخلوية و التي يتم تنسيقها بشكل كبير عبر وسطاء الالتهاب المختلفة حيث تهدف لإصلاح واستعادة التوازن الطبيعي للأنسجة المتضررة. إلا أن الالتهاب المستمر أو غير المعالج يمكن أن يؤدي إلى إلتهاب مزمن و الذي بدوره قد يكون المتسبب الرئيسي في العديد من الأمراض الالتهابية. و بالأخذ بعين الاعتبار الآثار الجانبية الضارة للأدوية المضادة للإلتهابات فإن البحث عن عوامل جديدة مضادة للالتهاب من المصادر النباتية أمر مستحب.

أدى الاهتمام المتزايد مؤخرًا بالطب البديل والمنتجات الطبية المشتقة من النباتات إلى تسليط الضوء على نبات الخزامى بأنواعه المختلفة و نخص بالذكر *Lavandula stoechas* والتي يمكن أن تكون مصدرا محتملا للجزيئات النشطة بيولوجيًا و المضادة للالتهابات حيث يمكن إستخدامها لتطوير الأدوية.

تهدف هذه الدراسة إلى تقييم الخصائص المضادة الإلتهاب وكذلك الآليات الجزيئية الكامنة وراء عمل بعض الجزيئات النشطة بيولوجيًا الموجودة في الزيوت العطرية ومستخلصات نبات *Lavandula stoechas*.

أظهرت نتائج الدراسات التجريبية والسريرية الخصائص المضادة للالتهاب لنبات *Lavandula stoechas* والتي ترجع أساسًا إلى ثرائها بالمركبات النشطة بيولوجيًا مثل1،8 سينيول ، الكافور ، اللوتيولين ، والأبيجينين. بالإضافة إلى ذلك، اقترحت نتائج هذه الدراسات أن آلية عمل هذه المركبات الكيميائية النباتية المضادة للالتهاب تتم من خلال تعديل العديد من الوسطاء المسببين أوالمانعين للالتهاب مثل الإنترلوكين وعامل نخر الورم ألفا (TNF-α) و interferon-gamma (IFN- γ) ، وأكسيد النيتريك (NO) ، وكذلك البروستاجلاندين والليوكوترين. بالإضافة إلى ذلك، فإنها تحفز على تثبيط أيض حمض الأراكيدونيك (AA) ، وانزيمات الأكسدة الحلقية-2 (COX-2) ، وليبوأكسيجيناز (LOX) ، وأكسيد النيتريك المحرض (iNOS) ، وعوامل النسخ المختلفة المستعملة في التعبير عن الجينات المسببة للالتهاب.

و بناء عليه، يمكن استعمال المكونات الفعالة من *Lavandula stoechas* في التركيبات العلاجية المستقبلية المضادة للالتهاب واستغلالها في العلاجات المستخدمة لعلاج الأمراض الالتهابية. ومع ذلك، تبقى هناك حاجة لإجراء مزيد من الدراسات المعمقة.

الكلمات المفتاحية : الإلتهاب، *Lavandula stoechas*، الأيضيات الثانوية، التربنويدات، الفلافونويدات، 1،8 سينيول، الكافور، اللوتيولين، الأبيجينين، الخصائص المضادة للإلتهاب.

Résumé

L'inflammation est un mécanisme défensif contre divers stimulus nocifs, qui implique à la fois les réponses immunitaires innées et acquises. Cette réponse comprend des événements vasculaires et cellulaires qui sont fortement coordonnés par différents médiateurs inflammatoires. Elle vise à réparer et à restaurer l'homéostasie normale du tissu lésé. Cependant, une inflammation persistante ou incontrôlée peut conduire au développement d'une inflammation chronique qui peut jouer un rôle central dans la pathogenèse de nombreuses maladies inflammatoires. Compte tenu des effets secondaires indésirables des médicaments anti-inflammatoires synthétiques, la recherche de nouveaux agents anti-inflammatoires à partir de sources végétales est désirable.

Récemment, l'intérêt croissant pour les remèdes naturels et les produits dérivés de plantes médicinales dans les thérapies alternatives a mis en évidence la lavande, avec ses différentes espèces telle que notre plante d'intérêt, *Lavandula stoechas*, qui pourrait servir de source potentielle de molécules bioactives anti-inflammatoires qui pourraient être encore utilisé pour le développement de médicaments.

Le but de cette étude était d'évaluer l'activité anti-inflammatoire ainsi que les mécanismes moléculaires d'action sous-jacents de certaines molécules bioactives trouvées dans les huiles essentielles et les extraits de *Lavandula stoechas*.

Les résultats d'études expérimentales et cliniques publiées ont démontré les propriétés anti-inflammatoires de *Lavandula stoechas* qui étaient principalement dues à sa richesse en composés bioactifs tels que le 1,8-cinéole, le camphre, la lutéoline et l'apigénine. En outre, ces résultats ont suggéré que le mécanisme d'action anti-inflammatoire de ces composés phytochimiques est médié par la modulation de divers médiateurs pro- et anti-inflammatoires tels que les interleukines, le facteur de nécrose tumorale alpha (TNF-α), l'interféron-gamma (IFN- γ), l'oxyde nitrique (NO), ainsi que les prostaglandines et les leucotriènes. De plus, ils induisent l'inhibition du métabolisme de l'acide arachidonique (AA), de la cyclooxygénase-2 (COX-2), de la lipooxygénase (LOX), de l'oxyde nitrique inductible (iNOS) et de divers facteurs de transcription impliqués dans l'expression de gènes pro-inflammatoires.

Enfin, les composants identifiés de *Lavandula stoechas* pourraient être incorporés dans la mise au point de futures nouvelles formulations anti-inflammatoires et dans l'exploitation de thérapies ciblées utilisées pour le traitement des maladies inflammatoires. Cependant, d'autres études doivent être réalisées.

Mots clés: Inflammation**;** *Lavandula stoechas*; Métabolites secondaires; Terpènes; Flavonoïdes; 1,8-cinéole; Camphore; Lutéoline; Apigenine; Activité anti-inflammatoire.