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Anti-inflammatory property of *Rosmarinus officinalis L*

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2DE: Two-dimensional electrophoresis

5-HPETE: Hydroxyl-hexano-atetetraenoic acid

5-LOX: 5-lipoxygenase

AA: Arachidonic acid

ACAN: Aggrecan

AL: linoleic acid

APPs: Acute-phase proteins

BALF: Broncho-alveolar lavage fluid

CA: Carnosic acid

Ca2+: Calcium concentration

COX-1 and COX-2: Cyclooxygenase

CRP: C-reactive protein

DCs: Dendritic cells

ECM: Extracellular matrix

EORO: essential oil of *Rosmarinus Officinalis*

EU: European Union

FAP: Familial adenomatous polyposis

GDP: Guanosine diphosphate

GPCR: G protein-coupled receptors

GTP: Guanosine triphosphate

hsCRP: Highly sensitive CRP

HSPs: Heat shock proteins

IKK: IκB-kinase

IL-1β: Interleukin-1β

IL-6: Interleukin-6

IκB: Inhibitor of nuclear factor kappa B kinase proteins

JAK: Janus kinase signal transducer

LPS: lipo-polysaccharides

LTA4: leukotriene A4

LTB4: leukotriene B4

MAPK: Mitogen-activated protein kinase

MCP: Monocyte chemoattractant proteins

MIP: Macrophage inflammatory protein

MS: Mass spectrometry

NCDs: Non-communicable diseases

NF-κB: Nuclear factor kappa-B

NK: Natural killer

NKT: Natural killer T

NSAIDs: Non-steroidal anti-inflammatory drugs

Ova: Ovalbumin

PAMPs: Pathogen-associated molecular patterns

PAP: Proximal adaptor protein

PCR: Polymerase chain reaction

PGH2: Prostaglandin H2

PLA2: Phospholipase A2

PMNs: Polymorphonuclear neutrophils

PRRs: Pattern recognition receptors

RosA: Rosmarinic acid

SIRS: Systemic inflammatory response syndrome

Th1, Th17 cells: T helper cells

TLR4: Toll-like receptor 4

TNF-α: Tumor necrosis factor-α

TXA2: Thromboxane

WHO: World Health Organization

Introduction

Inflammation is a natural defense mechanism of higher organisms against any external attack (infection, injury, mechanical attack, etc.) **(Yougbaré et al., 2016).** In other words, the inflammatory response is an adaptive response generated in response to harmful stimuli. It requires fine regulation, generally beneficial; it leads to the elimination of possible pathogens and the return to homeostasis of the injured tissue **(Wollinger et al., 2016).**

There are different drugs to control and suppress inflammatory attacks; steroids, non-steroidal anti-inflammatory drugs and immunosuppressant are the practical examples of these drugs which are sometimes associated with very serious side effects **(Ghasemian et al., 2016).**

Worldwide, the uses of the non-steroidal anti-inflammatory drugs (NSAIDs) have increased. They are considered highly effective medications in controlling various conditions including inflammatory diseases. They are associated with various adverse effects including gastrointestinal bleeding and ulcer and renal toxicity though. These adverse effects are generally more potentiated when NSAIDs are co-prescribed with other drugs that share similar adverse effects and toxicities. Developing severe side effects from NSAIDs is more prone among elderly patients **(Al-Azayzih et al., 2020).** The frequency of side effects which associated with NSAIDs are varies among them. Common side effects are nausea, vomiting, diarrhea, constipation, decreased appetite, rash, dizziness, headache, and drowsiness. Other important side effects are: kidney failure (primarily with chronic use), liver failure, ulcers, and prolonged bleeding after injury or surgery **(Omudhome, 2020).** That is why it was necessary to search for natural alternatives to reduce these dangerous symptoms.

A number of natural products are used in various traditional medical systems to reduce the aches and pains associated with the inflammation without symptoms because they are completely natural remedies **(Biswas, 2009).** The different natural substances derived from plants have multiple interests in the traditional care system and in different industries such as food, cosmetology and dermo-pharmacy **(Hebi et al., 2016).** Screening of various bioactive compounds from medicinal plants has led to the discovery of new medicinal drugs which have efficient protection and treatment roles in various diseases **(Kumar et al., 2004; Mukherjee et al., 2007).** As a result, the development of natural resources is a concern that is becoming increasingly important in many countries **(Aboughe et al., 2015).**

Algeria, a country known for its natural resources, has a singularly rich and varied flora estimated at around 3000 plant species, 15% of which are endemic and belonging to several botanical families **(Dif et al., 2015).**

The Lamiaceae family is one of the most important families in the Algerian flora and the most used by traditional therapists. The species of this family are known to be active due to the bioactive compounds which they enclose **(Kechar et al, 2016).**

Rosmarinus officinalis popularly known as rosemary is a plant belonging to the family Lamiaceae and originated from the Mediterranean region **(González-Trujano, 2007).** It promotes several pharmacological effects due to the interaction between the molecules of the plant and the organic systems **(Gonçalves, 2019).**

A general research was conducted in order to identify the basic compounds, whether in the essential oil or the extract of the plant, in order to know the anti-inflammatory effect of rosemary plant and also the mechanism of action of these compounds at the molecular level.

Chapter 1 : Generalities on inflammation

1. Generalities on inflammation

1.1. Definition

Inflammation is a part of the body's defense mechanism. It is the process by which the immune system recognizes and removes harmful stimuli and begins the healing process. There are generally two types of inflammation: acute and chronic inflammation **(Fritsch et al., 2019; Michels da Silva et al., 2019; Zhang et al., 2019).** The inflammatory process is part of a mechanism of host defense against stimuli that cause injuries which can damage the health of the individual when this process is not controlled **(Dia VP et al., 2014).** Inflammation process has various mechanisms and numerous treatment methods consequently. Plenty of cytokines participate in enzyme activation (such as phosphor-lipase A2), mediator release, fluid extra-vasation and vasodilation, cell migration, and finally tissue damage which generally have been named inflammation **(Ghasemian et al., 2016).** At the tissue level, inflammation is characterized by redness, swelling, heat, pain, and loss of tissue function, which result from local immune, vascular and inflammatory cell responses to infection or injury **(Akira and Takeuchi, 2010).** Various pathogenic factors, such as infection, tissue injury, or cardiac infarction, can induce inflammation by causing tissue damage. The etiologies of inflammation can be infectious or non-infectious (Table 1) **(Chen et al., 2018).**

Table 1: Etiology of inflammation (Chen et al., 2018)

Non-infectious factors	Infectious factors
-Physical: burn, frostbite, physical injury, foreign bodies, trauma, lionizing radiation **-Chemical:** glucose, fatty acids, toxins, alcohol, chemical irritants (including fluoride, nickel and other trace elements) **-Biological:** damaged cells **-Psychological:** excitement	-Bacteria -viruses -other microorganisms

1.2. Types of inflammation

1.2.1. Acute inflammation

Tissue damage due to trauma, microbial invasion, or noxious compounds all induce acute inflammation. It starts rapidly, becomes severe in a short time and symptoms may last for a few days for example: cellulitis or acute pneumonia. Sub acute inflammation is the period between acute and chronic inflammation and May last 2 to 6 weeks **(Pahwa et al., 2020).**

1.2.2. Chronic inflammation

Chronic inflammation, as seen in non-communicable diseases (NCDs), does not present features that are obvious in acute inflammation **(Kotas and Medzhitov, 2015; Kawanishi et al., 2018; Suzuki, 2018).** Exogenous factors, such as pathogens, often initiate acute inflammation characterized by redness, swelling, fever, and pain. In contrast, endogenous materials or materials released endogenously caused by tissue damage, (endogenous ligands) bind to Pattern recognition receptors (PRRs) of the innate immune system to induce chronic inflammation **(Guo and Friedman, 2010; Kotas and Medzhitov, 2015 ; Zhong et al., 2019).** Chronic inflammation is also referred to as slow, long-term inflammation lasting for prolonged periods of several months to years. Generally, the extent and effects of chronic inflammation vary with the cause of the injury and the ability of the body to repair and overcome the damage **(Pahwa et al., 2020).**

1.3. Inflammatory cells

1.3.1. Lymphocytes

Lymphocytes are the only cells in the body capable of specifically recognizing and distinguishing different antigens **(Mackay and Von Andrian, 2000).** They are integral to the development of a complete innate and adaptive immune response. One important function of lymphocytes is to generate adaptive immune responses and to develop a memory compartment for future responses. Many lymphocytes can participate in allergic inflammation, including T helper (Th1, Th17 cells), CD8+ T cells, B cells, γ/δ T cells, natural killer (NK) cells and natural killer T (NKT) cells **(Davis and Rothenberg, 2016).**

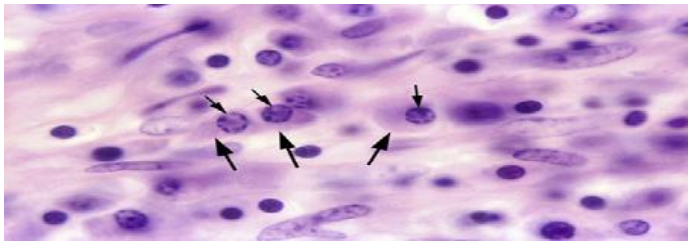

Figure 1: Sub-acute inflammation, rich in lymphocytes (Davis and Rothenberg, 2016). Many of them are plasma cells (large arrows) whose nuclei are indicated by small arrows. hemateineosin. Objective x25.

1.3.2. Mast cells

Mast cells are exclusively tissue cells distributed throughout the body that are not found in the blood in normal situation. They are further characterized by a rich intra- cytoplasmic content in secretory granules of variable sizes. These granules allow rapid identification. Mast cells because they can fix toluidine blue and cause it to change color to purple. Mast cells are also defined by the

expression of the Stem Cell Factor receptor (CD117 or c-Kit) and the high affinity receptor for type E immune-globulins **(Voehringer, 2013).**

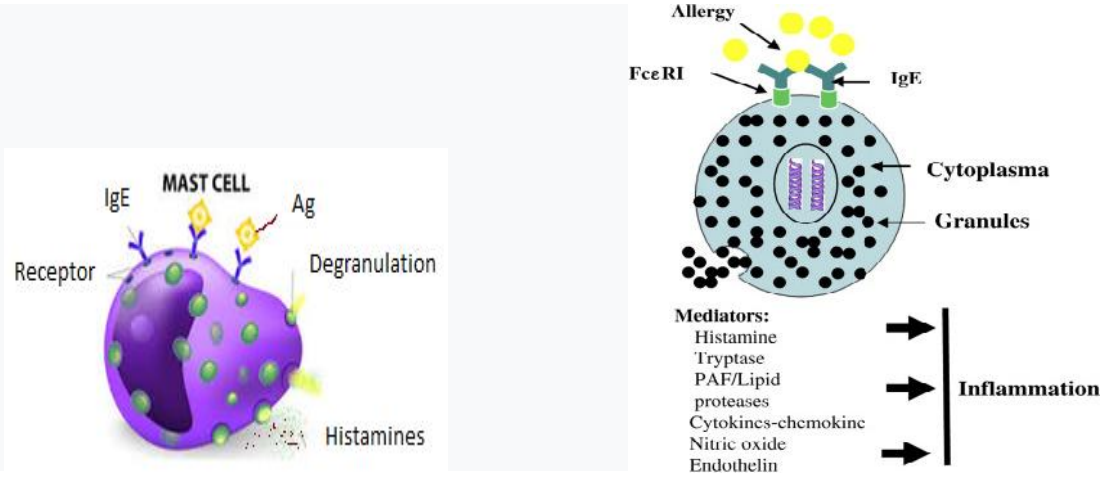

Figure 2: Schematic diagram of a mast cell activation and its products Voehringer, 2013). The cell is activated by Ag, which leads to the release of a host of mediators that lead to inflammation.

1.3.3. Basophils cells

Basophils are circulating granulocytes that typically mature in the bone marrow, circulate in the blood as mature cells, and can be recruited into sites of immunological or inflammatory responses, but are not found in normal tissues **(Arock et al., 2002).** They are crucial effectors in T helper 2 (Th2)-cell-dependent, IgE-associated allergic disorders and immune responses to parasites **(Gould et al., 2003; Prussin and Metcalfe, 2003; Min et al., 2004).** Also basophils are a major source of histamine **(de Paulis et al., 2006).**

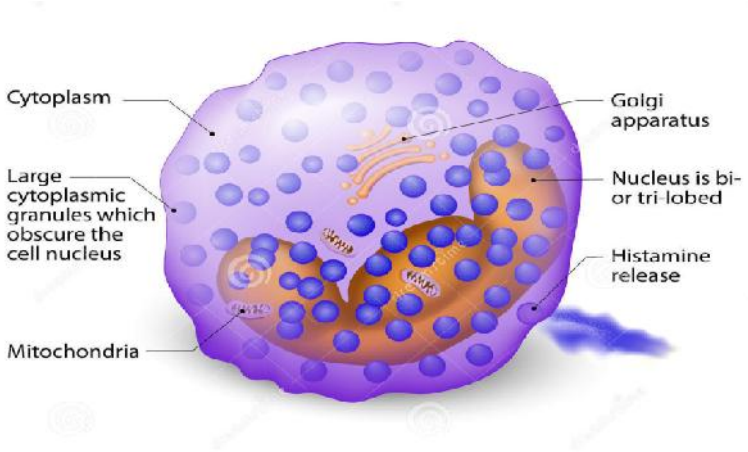

Figure 3: Diagram represents basophil cell and its contents.

1.3.4. Antigen-presenting cells

Antigen-presenting cells (macrophages, monocytes and dendritic cells) are specialized to capture and process microbial and other antigens, present them to lymphocytes, and provide signals that stimulate proliferation and differentiation of lymphocytes **(Beutler, 2004).** Macrophages and monocytes are primarily phagocytic cells and cytokine production, antigen presentation, migration, vascular functions, and immune-regulation, but once activated they become larger and produces a wide range of chemical mediators that drive and orchestrate chronic inflammation **(Bonizzi and Karin, 2004; Flynn, 2011).** Dendritic cells (DCs) play an important role in antigen capture and the induction of T-cell responses, especially in naiive T cells **(Hart, 1997).** They are present in lymphoid organs, the skin, the gastrointestinal and respiratory tracts, and most parenchymal organs. These cells capture protein antigens and transport them to the draining lymph nodes **(Sallusto and Lanzavecchia, 2002).**

1.3.5. Neutrophils

Neutrophils are bone marrow-derived granulocytes and account for the largest proportion of cells in most inflammatory sites. Activated neutrophils have the capacity to release a variety of products at inflammatory sites, which may induce tissue damage. These products include those of primary (azurophilic), secondary (or specific) and tertiary granules, including proteolytic enzymes, oxygen radicals and lipid mediators (LTB4, PAF and thromboxane A2). Neutrophil granules contain more than 20 enzymes; of these, elastase, collagenase and gelatinase have the greatest potential for inducing tissue damage **(Reeves et al., 2002; Lazaar et al., 2011).**

1.3.6. Inaate lymphoid cells (ILC)

Innate lymphoid cells (ILC) are a newly described component of the immune system. They contribute to the establishment of a rapid immune response following attacks to which the body may be confronted, whether they are of viral, bacterial, parasitic or cancerous origin. ILCs are made up of natural killer (NK) cells, lymphoid tissue inducer cells (LTI), ILC1, ILC2 and ILC3 **(Cherrier, 2014).**

1.3.7. Platelets

Platelets are produced in the bone marrow, the same as the red cells and most of the white blood cells. Platelets are produced from very large bone marrow cells called Mega-karyocytes. They are only about 20% of the diameter of red blood cells. The principal function of platelets is to prevent bleeding. Also involved in the response to inflammation and got a wide range of immune responses **(Yeaman et al., 2010; Elzey et al., 2011).**

1.3.8. Epithelial cells

Epithelial cells play roles in the regulation of inflammation by production of several families of anti-inflammatory molecules, including cytokines (IL-10, TGF-b), protease inhibitors (SLPI, SERPINA1 (a1-antitrypsin), SERPINB1, TIMP-1), inhibitory arachidonic acid metabolites (PGE2, PGI2, lipoxin A4) and others (CC10, SP-A, etc.). Epithelial cells also express anti-inflammatory or immunosuppressive cell surface molecules including B7-H1, B7-DC, IL- 13RA2 and FASL **(kim et al., 2005; Janes et al., 2006; Matsumura et al., 2007; Park et al., 2007).** Many of these molecules are induced by pro-inflammatory cytokines and Th2 cytokines, suggesting that they may be regulated by negative feedback pathways that dampen inflammatory signaling. An imbalance of pro-inflammatory responses and anti-inflammatory responses in the epithelium may induce several inflammatory diseases **(Yasumatsu et al., 2006; Park et al., 2007).**

1.3.9. Fibroblasts

The fibroblast populations in chronic inflammation and malignancy are heterogeneous. Fibroblasts are identified by their spindle-shaped cell morphology **(Kinchen et al., 2018).** They have a role in the formation of tunnels and inflammation **(John et al., 2019).**

1.4. Soluble mediators of the inflammatory response

1.4.1. Cytokines

Cytokines act as molecular messengers to control of, different cell types involved in the amplification and regulation of immune and inflammatory responses. A single cytokine may affect a number of different cell types or targets and may have both autocrine and paracrine signaling effects depending on the target **(Turner et al., 2014).**

1.4.2. Chemokines

In general, chemokines serve as chemoattractants for monocytes (RANTES), monocyte chemoattractant proteins (MCP 1–5), eosinophils (eotaxins 1–3), basophils (MCP 4–5), and lymphocytes (macrophage inflammatory protein (MIP)-1α and β). They control the recruitment of effector leukocytes in infection, inflammation, tissue injury, and tumors and direct cellular migration, activate macrophages and *polymorphonuclear* neutrophils (PMNs), and modulate wound healing through promotion of angiogenesis and the stimulation of fibrosis **(Sell, 2001).**

1.4.3. Acute-phase proteins

Inflammation typically triggers an acute-phase response, which results in changes in blood proteins known as acute-phase proteins (APPs). Production of APPs occurs primarily in the liver, and increased (positive APPs) or decreased (negative APPs) production and release occur in response to cytokine signals from the site of inflammation. These proteins alter homeostasis in

order to initiate or support defensive and/or adaptive processes that contribute to healing in the short term, but can lead to chronic inflammation, metabolic disturbances, and tissue damage with prolonged stimulation **(Evans and Duncan, 2003).** Because these proteins are regulated in response to inflammatory signals and change rapidly as conditions change, they are good markers of inflammation **(Everds et al., 2013).**

1.4.4. Complement system

The complement system is a complex network of proteins that participate in the acute inflammatory response through their enzymatic activity, effects on mediator release, chemotaxis and vascular permeability, and the ability to enhance phagocytosis through opsonization of microbes **(Murphy and Weaver, 2016).**

1.5. Inflammatory response mechanisms

The inflammatory response is the coordinate activation of signaling pathways that regulate inflammatory mediator levels in resident tissue cells and inflammatory cells recruited from the blood **(Lawrence, 2009).** Although inflammatory response processes depend on the precise nature of the initial stimulus and its location in the body, they all share a common mechanism, which can be summarized as follows:

1) Cell surface pattern receptors recognize detrimental stimuli
2) Inflammatory pathways are activated
3) Inflammatory markers are released
4) Inflammatory cells are recruited. **(Chen et al., 2018).**

1.5.1. Pattern recognition receptor activation

An inflammatory response is initiated by pattern recognition receptors (PRRs) which recognize structural components: the pathogen-associated molecular patterns (PAMPs) that can trigger the inflammatory response through activation of pattern-recognition receptors (PRRs) expressed in both immune and non-immune cells, and the molecules released from damaging cells as damage-associated molecular patterns (DAMPs). DAMPs are released forms of damaged cells, and parts of DAMPs such as degraded matrix molecules, leukocyte degranulation substances, and heat shock proteins (HSPs) are considered danger signals that induce inflammatory responses **(Chen et al., 2004; Brusselle and Bracke, 2014; Gudkov and Komarova, 2016; Hung and Suzuki, 2017).** Among PRRs, Toll-like receptor 4 (TLR4) are a family of highly conserved mammalian PRRs that participate in the activation of the inflammatory response **(Janeway and Medzhitov, 2002).** Also plays key roles in recognizing lipo-polysaccharides (LPS) and mediates signaling to produce pro-inflammatory cytokines. The excessive stimulation of PRRs leads to an

overproduction of pro-inflammatory cytokines and can cause systemic inflammatory response syndrome (SIRS) **(Kotas and Medzhitov, 2015; Hung and Suzuki, 2017).**

1.5.2. Activation of inflammatory pathways

Inflammatory stimuli activate intracellular signaling pathways that then activate production of inflammatory mediators. Primary inflammatory stimuli, including microbial products and cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), mediate inflammation through interaction with the TLRs (TLR_4), IL-1 receptor (IL-1R), IL-6 receptor (IL-6R), and the TNF receptor (TNFR) **(Kaminska, 2005).** Receptor activation triggers important intracellular signaling pathways, 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).**

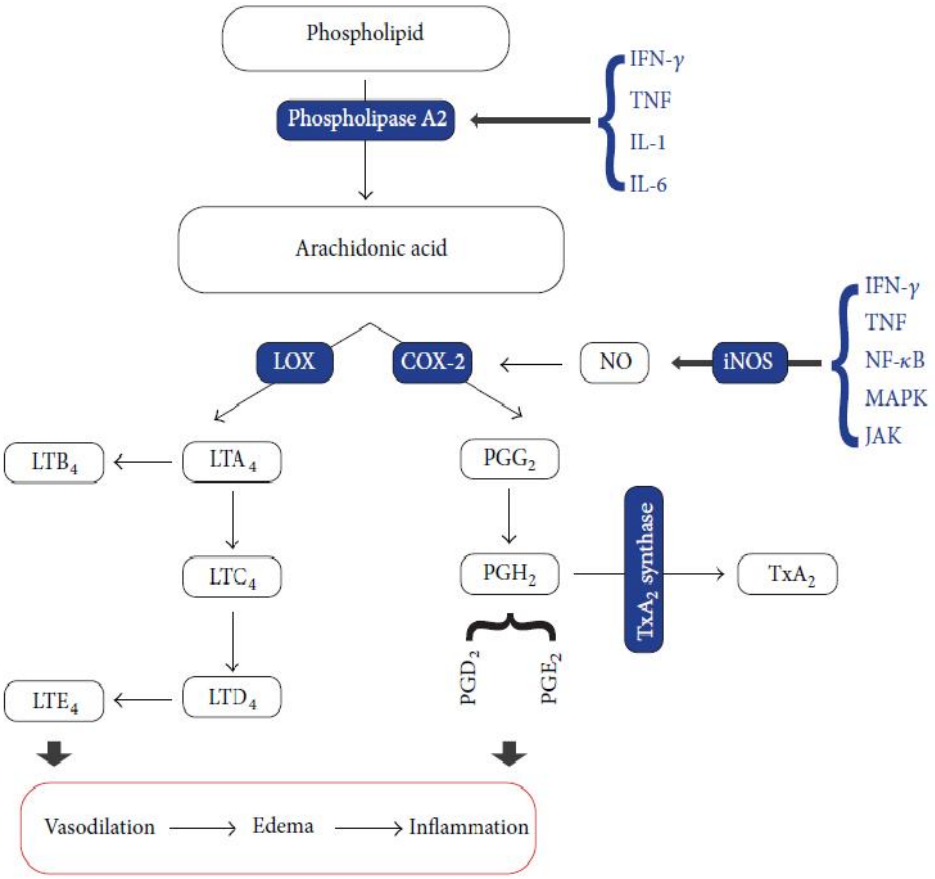

Figure 4: Inflammation pathway (Ghasemian et al., 2016). COX, cyclooxygenase; LOX, lipoxygenase; PG, prostaglandin; LT, leukotriene; TX, thromboxane; NO, nitric oxide; iNOS, inducible NO synthase; IFN, interferon.

1.5.2.1. NF-κB pathway

The NF-κB transcription factor plays important roles in inflammatory, immune response, survival, and apoptosis processes **(Girard et al., 2009).** The NF-κB family includes five related

transcription factors: P50, p52, RelA (p65), RelB, and c-Rel **(Moynagh, 2005; Hoffmann and Natoli and Ghosh, 2006).** NF-κB activity is induced by a range of stimuli, including pathogen-derived substances, intercellular inflammatory cytokines, and many enzymes **(Pasparakis and Luedde and Schmidt-Supprian, 2006; Basak et al., 2007).** Under physiological conditions, IκB (Inhibitor of nuclear factor kappa B) kinase proteins present in the cytoplasm inhibit NF-κB.

This pathway regulates pro-inflammatory cytokine production and inflammatory cell recruitment, which contribute to the inflammatory response (Figure 5) **(Kadhim et al., 2001).**

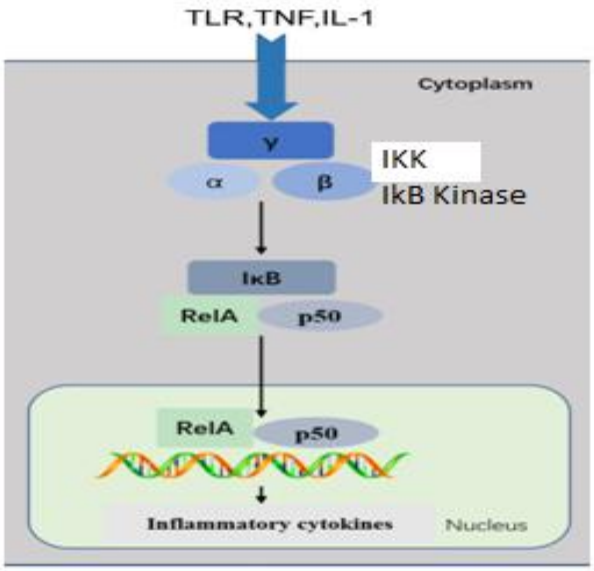

Figure 5: NF-κB pathway (Chen et al., 2018). This pathway is triggered by TLRs and inflammatory cytokines, such as TNF and IL-1, leading to activation of RelA/p50 complexes that regulate expression of inflammatory cytokines. NF-κB signaling requires IKK sub-units which regulate pathway activation through IκB phosphorylation.

1.5.2.2. 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 **(Pearson, 2001; Kaminska B, 2005).** The mammalian MAPKs include extracellular-signal-regulated kinase ERK1/2, p38 MAP Kinase, and c-Jun N-terminal kinases (JNK) **(Kim and Choi, 2010).** 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).** ERKs are generally activated by mitogens and differentiation signals, while inflammatory stimuli and stress activate JNK and p38 **(Sabio and Davis, 2014).** MKK1 and MKK2 activate ERK1/2, MKK4 and MKK7 activate JNK, and MKK3 and MKK6 activate p38. Activation of the MAPKs, including Erk1/2, JNK, leads to phosphorylation and activation of p38 transcription

factor present in the cytoplasm or nucleus, which initiates the inflammatory response **(Raingeaud, 1996; Pearson, 2001)** (Figure 6).

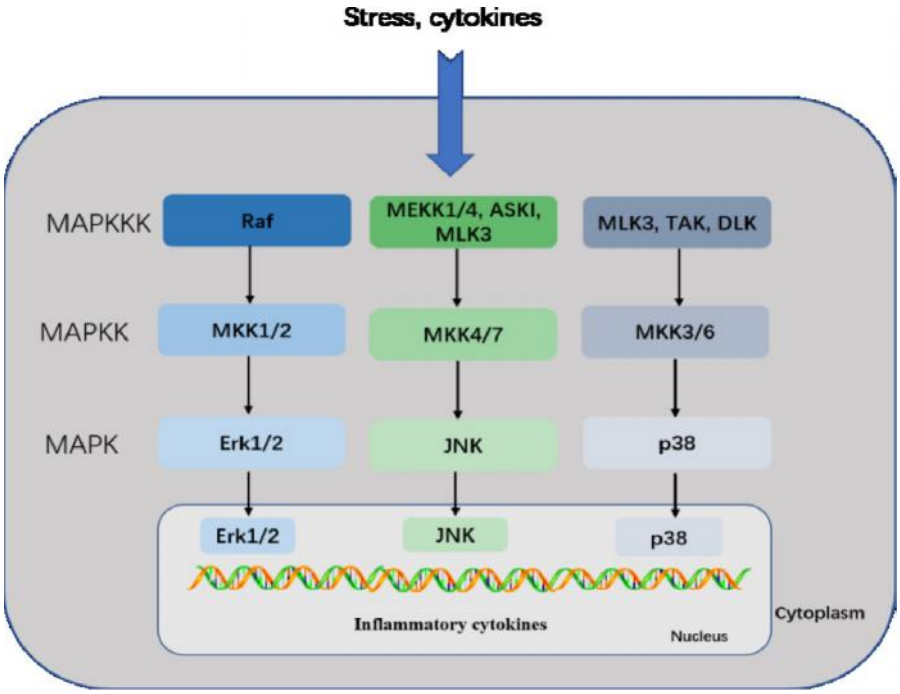

Figure 6: MAPK pathway (Chen et al., 2018). This pathway mediates intracellular signaling initiated by extracellular stimuli, such as stress and cytokines. MAPKKKs phosphorylate and activate MAPKKs, which in turn phosphorylate and activate MAPKs. The mammalian MAPK family includes Erk1/2, JNK, and p38. In the Erk1/2 pathway, Erk1/2 is activated by MKK1/2, which is activated by Raf kinase. In the JNK pathway, JNK is activated by MKK4/7, which is activated by MEKK1/4, ASK1, and MLK3. In the p38 pathway, p38 is activated by MKK3/6, which is activated by MLK3, TAK, and DLK. Activated MAPKs phosphorylate various proteins, including transcription factors, resulting in regulation of inflammatory responses.

1.5.2.3. JAK-STAT pathway

The highly conserved JAK-STAT pathway involves diverse cytokines, growth factors, interferons, and related molecules, such as leptin and growth hormone **(O'Shea et al., 2015).** Receptor-associated JAKs are activated by ligands and phosphorylate one other, creating docking sites for STATs, which are latent, cytoplasmic transcription factors. Cytoplasmic STATs recruited to these sites undergo phosphorylation and subsequent dimerization before translocation to the nucleus **(Walker and Smith, 2005).** Tyrosine phosphorylation is essential for STAT dimerization and DNA binding **(Ivashkiv and Hu, 2003).** STAT proteins translocated into the nucleus bind target gene promoter regions to regulate transcription of inflammatory genes (Figure 7) **(Boengler et al., 2008).**

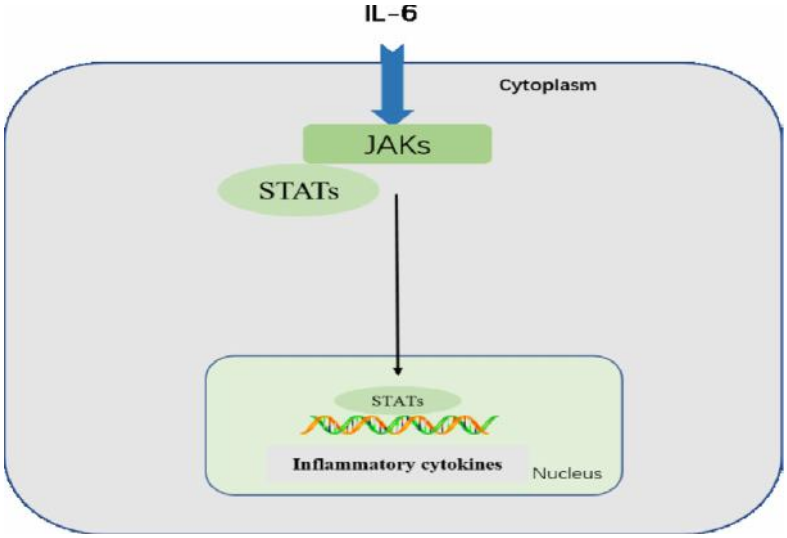

Figure 7: JAK-STAT pathway (Chen et al., 2018). Following IL-6 binding, signal is transduced by a receptor to activate the JAKs, which then activate STATs. STATs are de-phosphorylated in the nucleus, leading to activation of downstream cytokines.

1.7. Molecular methods for evaluating the inflammatory response

Recently "omics" technologies have been used to detect inflammation markers associated with inflammation in human and animal studies. Consistent with conventional measures of markers, serum and plasma are commonly used matrices for detection of circulating proteins by two-dimensional electrophoresis (2DE) and mass spectrometry (MS). These techniques can provide a more complete picture of the inflammatory process, since they can separate and measure active proteins, precursors, metabolites, and degradation products **(Shen et al., 2006; He et al., 2008).** Genomic techniques, especially polymerase chain reaction (PCR) and microarray, have been used to measure the expression of cytokines, chemokines, adhesion molecules, and ligands. In addition to evaluating individual molecules, pathway analysis provides vital information on the mechanism and signaling events of inflammation and inflammatory disease **(Barber, 2015).**

1.8. Treatment and management

Non-steroidal anti-inflammatory drugs (NSAIDs) are used primarily to treat inflammation, mild to moderate pain, and fever. Specific uses include the treatment of headaches, arthritis, sports injuries, and menstrual cramps.

The following list is some example of NSAIDs available in USA and Algeria:

- Aspirin is used to inhibit the clotting of blood and prevent strokes and heart attacks in individuals at high risk for strokes and heart attacks.
- Celecoxib (Celebrex) is used for treating familial adenomatous polyposis (FAP) to prevent the formation and growth of colon polyps.

- Diclofenac (Cambia, Cataflam, Voltaren-XR, Zipsor, Zorvolex)
- Ibuprofen (Motrin, Advil)
- Indomethacin (Indocin)
- Naproxen (Aleve, Anaprox, Naprelan, Naprosyn)
- Oxaprozin (Daypro)
- Piroxicam (Feldene)
- Ketorolac (Toradol) is only used for short-term treatment of moderately severe acute pain that otherwise would be treated with narcotics **(Omudhome, 2020).**

Many dietary and lifestyle changes may be helpful in removing inflammation triggers and reducing chronic and acute inflammation as listed below. The most effective is weight loss **(Pahwa et al., 2020).**

- Low-glycemic diet: diet with a high glycemic index is related to high risk of stroke, coronary heart disease, and type 2 diabetes mellitus. It is beneficial to limit consumption of inflammation-promoting foods like sodas, refined carbohydrates, fructose corn syrup in a diet **(Pahwa et al., 2020).**
- Reduce intake of total and saturated fat and Trans fats*:* some dietary saturated and synthetic trans-fats aggravate inflammation, while omega-3 polyunsaturated fats appear to be anti-inflammatory. Processed and packaged foods that contain trans fats such as processed seed and vegetable oils, baked goods (like soybean and corn oil) should be reduced from the diet **(Pahwa et al., 2020).**
- Fruits and vegetables*:* blueberries, apples, brussels sprouts, cabbage, broccoli, and cauliflower, that are high in natural antioxidants and polyphenols and other anti-inflammatory compounds, may protect against inflammation **(Pahwa et al., 2020).**
- Fiber: high intake of dietary soluble and insoluble fiber is associated with lowering levels of IL-6 and TNF-alpha **(Pahwa et al., 2020).**
- Nuts*:* such as almonds is associated with lowering risk of cardiovascular disease and diabetes **(Pahwa et al., 2020).**
- Green and black tea polyphenols: tea polyphenols are associated with a reduction in C-reactive protein (CRP) in human clinical studies **(Pahwa et al., 2020).**
- Turmeric: a constituent of turmeric causes significant patient improvements in several inflammatory diseases especially in animal models **(Pahwa et al., 2020).**
- Fish oil: the richest source of the omega-3 fatty acids. Higher intake of omega-3 fatty acids is associated with lowering levels of TNF-alpha, CRP, and IL-6 **(Pahwa et al., 2020).**

- Mung bean*:* rich in flavonoids (particularly vitexin and isovitexin). It is traditional food and herbal medicine known for its anti-inflammatory effects **(Pahwa et al., 2020).**
- Micronutrients: magnesium, vitamin D, vitamin E, zinc and selenium). Magnesium is listed as one of the most anti-inflammatory dietary factors, and its intake is associated with lowering of highly sensitive CRP (hsCRP), IL-6, and TNF-alpha activity. Vitamin D exerts its anti-inflammatory activity by suppressing inflammatory mediators such as prostaglandins and nuclear factor kappa-light-chain-enhancer of activated B cells. Vitamin E, zinc, and selenium act as antioxidants in the body **(Pahwa et al., 2020).**
- Sesame Lignans: Sesame oil consumption reduces the synthesis of prostaglandin, leukotrienes, and thromboxanes and is known for its potential hypotensive activity **(Pahwa et al., 2020).**
- Physical Exercise: In human clinical trials, it is shown that energy expenditure through exercise lowers multiple pro-inflammatory molecules and cytokines independently of weight loss **(Pahwa et al., 2020).**

1.8.1. Treatment of inflammation using medicinal plants

Medicinal plants and their secondary metabolites are gradually being used in the treatment of diseases as complementary medicine for the treatment of inflammation.

This list presents some herbs whose anti-inflammatory effects have been evaluated in clinical and experimental studies:

- *Curcuma longa* (Turmeric)
- *Zingiber officinalis* (Ginger)
- *Rosmarinus officinalis* (rosemary)
- *Borago officinalis* (Borage)
- *Oenotherabiennis* (evening primrose)
- *Harpago phytumprocumbens* (devil's claw)
- *Boswellia serrata* (Indian Olibanum)
- *Rosa canina* (dog rose) **(Ghasemian et al., 2016).**

Chapter 2 :

Rosmarinus Officinalis

2. *Rosmarinus officinalis*

2.1. Generalities

Medicinal plants have an important role on pharmacological research, the medical treatment and drug development, not only when the bioactive compounds are directly used as therapeutic agents, but also when they are used as raw material for drug synthesis or as a base model for new lead compounds **(Swain, 1972; Ahmad et al., 2006).**

Rosmarinus officinalis, commonly called rosemary in English; رزماري in Persian, Romero in Spanish, Romarin in French and اكليل **الجل** in Arabic), belongs to the lamiaceae family; which is one of the largest and most distinguished families of flowering plants, including about 236 genera and 6900–7200 species worldwide (Figure 8), it is a plant very well known in western countries and widely cultivated in the Mediterranean regions **(Al-sereiti, 1999; Naghibi et al., 2005; Raja, 2012; Wollinger et al., 2016).** Rosemary is a dense bush, branched, evergreen and blue–white flower, reaching a height of about 1 m. It is characterized by leaves with 1–4 cm long and 2–4 mm with curved edges, dark green upper side and very characteristic smell. **(Begum et al., 2013; Comissao Permanente da Farmacopeia Portuguesa, 2003).** The wild area in which *R. officinalis L* occurs includes Europe, Asia and Africa, but only in the areas around the Mediterranean Sea and in many islands, particularly Sicily, Sardinia, Corsica, Baleari and Elba **(Pintore et al., 2002).**

R. officinalis are directly or indirectly linked to the inflammatory process; for example, chronic inflammation has a critical role in rheumatoid arthritis and others inflammatory rheumatic diseases **(Benatti and Pedersen, 2015).**

Rosemary (*R. officinalis L.)* is used fresh, dried or as the essential oil **(Bauer et al., 2008).** It contains a great quantity of essential oil (up to 1%) finds extensive use in traditional medicines. **(Oury 1984).**The extracts obtained from *R. officinalis* are used as a natural antioxidant, improving the shelf life of perishable foods **(Habtemariam, 2016).** In fact; the European Union (EU) has approved the rosemary extract (E392) as a safe and effective natural antioxidant for food preservation **(Food Standards Agency, 2016).** Its leaves are a great source of its properties, and are composed of terpenoids, flavonoids, phenols and essential oils. Each component has its own pharmacological properties, which make it an excellent raw material for products with multiple therapeutic functions **(Satyal et al., 2017).**

In the past 20 years, there has been a clear tendency to rise in the number of articles regarding *R. officinalis* L. The interest in this plant is translated into the high amount of research performed since 2010, an average of 120 each year, a number that tends to increase.

Figure 8: Photography of *R.officinalis* (Andrade 2018)

2.2. Traditional use

Plants can be used as therapeutic resources in the form of herbal infusion, pharmaceutical preparations such as extracts, tablets or capsules by extracting and purifying active compounds **(Rates, 2001; Mohamed et al., 2012).** Rosemary is a very rich source of bioactive phenols which are mainly responsible for the bioactivity of the plant; the reason for its use in traditional medicine for centuries **(Ribeiro-Santos et al., 2015).**

R. officinalis, widely found in Western Mediterranean countries, is well known for its many uses in cooking, Herb soaked and its pharmacological properties. The essential oil obtained from the leaves of the plant is also used to prepare phenolic extracts, which are natural remedies for the traditional treatment of a number of common diseases **(Bellumori et al., 2016).** These phenolic acids, such as rosmarinic acid, have antibacterial, antiviral, antioxidant and anti-inflammatory Properties **(Naghibi et al., 2005).**

It being a highly appreciated medicinal plant to prevent and cure colds, rheumatism, pain of muscles and joints **(Calvo et al., 2011 and Zhang et al., 2014).** It is nowadays one of the most popular sources of natural bioactive compounds, and in fact, this plant exerts various pharmacological activities such as anti-bacterial **(Bozin et al., 2007),** anti-diabetic **(Bakirel et al.,2008)**, anti-inflammatory **(Takaki et al., 2008; Yu et al., 2013),** anti-tumor **(Cheung, 2007; Yesil-Celiktas, 2010)**, and anti-oxidant **(P´erez-Fons, Garz´on, Micol, 2010).**

Table 2: some of traditional uses of *R officinalis L* in some countries.

Uses	Geographical Area	References
Kidney stones, high blood-sugar levels	Middle east	Abu-Al-Basal,2010
Allergies, dermatological-ailments. gastro-intestinal-disorders.	Morocco	Jamila and Mostafa, 2014
Appetite loss	South-Africa	Asowata-Ayodele et al., 2016
Menstrual problems, fever, stomach ache, hypertension	Algeria	Benarba, 2016
Throat antiseptic, hypotension, rheumatism, boldness	Center of Portugal	Comiss˜ao Permanente da Farmacopeia Portuguesa, (2003).
Sore throat, stomach aches, Dandruff, fortifier,anti-inflammatory agent	South Italy	Montesano et al., 2012
Dandruff, fortifier, anti-inflammatory agent	Ecuadorian Andes	CerónMartínez, 2006
Stomach ache, menstrual pain, cough	Guatemalan Caribbean	Girón et al., 1997
Sinusitis, depression, dyspnea, flu, inflammations, cardiovasculardiseases	Center of Brazil	Borges et al., 2019

2.3.Botanical classification

This classification is made according to **(Begum et al., 2013).**

Kingdom:	Plantae
Sub kingdom:	Tracheobionta
Super division:	Spermatophyta
Division:	Magnoliophyta
Sub-branch:	Angiosperms
Class:	Magnoliopsida
Sub class:	Asteridae
Order:	Lamiales
Family:	Lamiaceae
Genus:	*Rosmarinus L*
Species:	*Officinalis*
Binomial nomenclature:	*Rosmarinus officinalis* L.

2.4. Chemical and bioactive compounds of *R. Officinalis*

In order to obtain the biologically active compounds from *R Officinalis* L, it is necessary to obtain the plant's extracts and/or essential oils, and perform a phytochemical characterization. The extraction methods are applied to the plant most active portions (leaves, roots, stems or flowers), using selective solvents and standard procedures **(Badal McCreath and Delgoda, 2016).**

The qualitative and quantitative studies on bioactive compounds isolated from plants depend greatly on proper choice of extraction method, which plays a crucial role in obtaining satisfactory results. The most important factors affecting the extraction process are related to the properties of the plant, the applied solvent, temperature, pressure and time of extraction **(Handa, 2008; Azmir et al., 2013).** After analysis of the collected articles, the most used extraction methods to obtain the bioactive compounds from *R. officinalis* are maceration, hydro-distillation, distillation and Soxhlet by supercritical fluid extraction.

2.4.1. *Rosmarinus Officinalis* essential oils

Essential oils are made up of very low molecular weight aromatic molecules **(Degryse et al., 2008).** They are liquid at room temperature but also volatile, which differentiates them from so-called fixed oils. They are liposoluble and soluble in the usual organic solvents as well as in alcohol, entrainable in water vapor but very little soluble in water. They are mostly colored, alterable and sensitive to oxidation; therefore, their conservation requires darkness and humidity **(Couic-Marinier et al., 2013).**

2.4.1.1. Essential oils composition

The study of the chemical composition of essential oils reveals that they are complex and eminently variable mixtures of constituents belonging exclusively to two groups: Terpene compounds such as mono and sesqui-terpenes; and aromatic compounds derived from phenyl-propane, much less frequent like cinnamic alcohol **(Bakkali et al., 2008; Couic-Marinier et al., 2013).**

Table 3: Major compounds of *Rosmarinus officinalis* L essential oil and some of the biological activities attributed to them.

Compound	Biological activity	Reference
1,8-cineole	Anti-inflammatory	Juhás et al., 2009
	Anti-depressive	Faria et al., 2011 and Machado et al., 2013
	Antialgic	Vilela et al., 2016
	Antioxidant	Takayama et al., 2016
	Smooth muscle relaxant activity	Bajalan et al., 2017 Selmi et al., 2017 Souza et al., 2005
Alpha- pinene	Anti-inflammatory	Nam et al., 2014
	Antifungal	Bae et al., 2012
	Antioxidant	Lin et al., 2016 and Mekonnen et al., 2016
	Antibacterial	Takayama et al., 2016
Camphor	Anti-inflammatory	Silva-Filho et al., 2014 Fahin et al., 1999 and Faria et al., 2011
	Antialgic	Melo et al., 2011
	Anti-mutagenic	Takayama et al., 2016
	Antioxidant	Bajalan et al., 2017

Several factors can affect the essential oil composition: the collecting season, geographical area, extraction method, plant variety, among others. The oil composition, in its turn, affects its biological activities **(Borges et al., 2019).** EORO from Morocco and Tunisia often shows a high content of 1,8-cineole, while EORO from Spain shows low content of this molecule, and yields a high concentration of camphor and borneol instead. EORO from France, in its turn, has a high concentration of verbenone **(Muñoz-Centeno, 2002; Republic Of South Africa, 2009).** This proves that there is a chemical composition variation due to the geographical area where the plant is collected. **Tawfik, (1998)** reported that EORO obtained from leaves showed higher extraction yield during the flowering phase (1.43%) compared to vegetati00ve phase (1.23%), and plants collected

in summer showed almost doubled yield compared to those collected in winter, evidencing chemical composition variation is due to plant phonological stage.

I.2.4.2. EORO anti-inflammatory activity and action

Faria et al., (2011) tested EORO (doses ranging from 100 to 1000 mg/kg, p.o) in rat models of carrageenan-induced paw edema. As results, the ED50 – determined as 300 mg/kg, significantly inhibited edema formation similarly to indomethacin treated group (positive control, 10 mg/kg, p.o) in a dose-dependent manner.

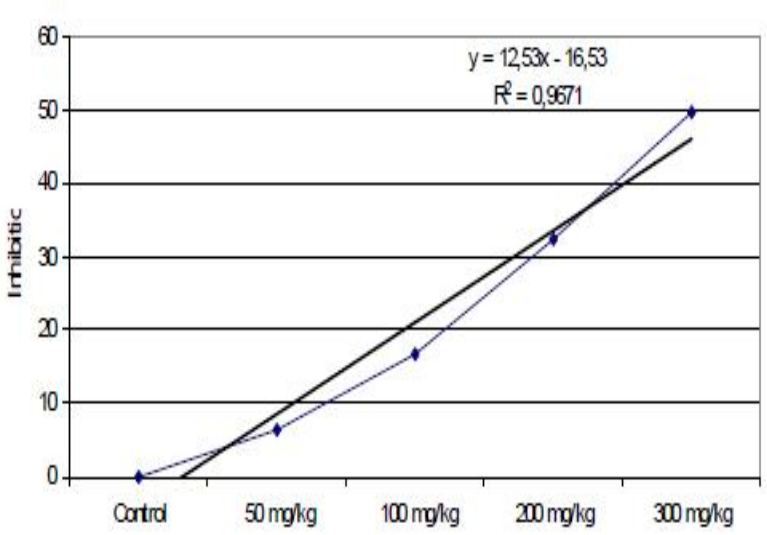

Figure 9: Determination of the effectiveness dose 50 (ED50) (Faria et al., 2011). Each point represents the average of eight animals, expressed as inhibition percentage. ED50 = 300 mg/kg (p.o).

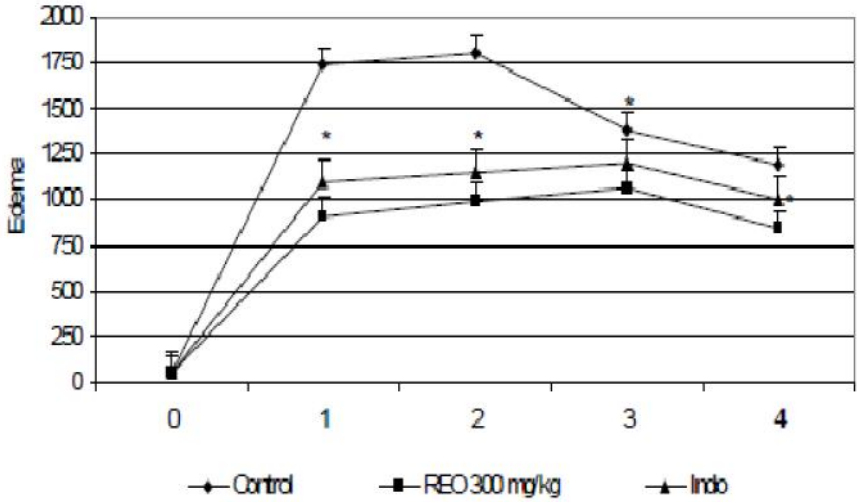

Figure 10: Effect of the oral administration of REO (300 mg/kg) and indomethacin (10 mg/kg) in rat paw edema induced by carrageenan (Faria et al., 2011).

Interestingly, in this study, the treatment with EORO had 64% less gastric damage compared to the group treated with indomethacin; this is highly relevant because the continuous use of non-steroidal anti-inflammatory drugs leads to gastric damage and peptic ulcer **(Drini, 2017).**

Moreover, **Takaki et al., (2008)** evaluated EORO (doses ranging from 250 to 500 mg/kg, p.o) anti-inflammatory activity by appraising exudate's volume and leukocyte migration in carrageenan-induced pleurisy and carrageenan-induced paw edema, both in rats. EORO treatment significantly inhibited carrageenan-induced edema formation 1-4 hours after carrageenan treatment compared to the control group; also, significantly reduced the volume of pleural inflammatory exudates and the number of migrated cells.

EORO was also evaluated in the form of a nano-emulsion by **Borges et al., (2017)** who compared the anti-inflammatory activity of pure EORO, and formulated as a nano-emulsion, in carrageenan-induced rat paw edema. EORO and its nano-emulsion were orally administered 30 minutes before carrageenan treatment.

The former was effective at 300 mg/kg **(**ED50 reported by **Faria et al., (2011)**) and inhibited 50% of edema formation; the latter was administered at 498 µg/kg and inhibited 46% of edema formation. That is highly relevant, considering that similar results were obtained with a 600 times smaller dose of EORO when administered as a nano-emulsion.

Borges et al., (2018), further studied this same dose of EORO nano-emulsion in carrageenan-induced abdominal edema in zebrafish; compared to the non-treated group, the treatment with EORO's nano-emulsion inhibited 78% of edema formation, which was more significant than the inhibition of Diclofenac at 0.5 mg/kg and Dexamethasone at 0.5 mg/kg.

A. Anti-inflammatory action of 1,8-cineole

The molecule 1,8-cineole (also known as eucalyptol) was identified in various genera of plant oils such as *Eucalyptus*, *Rosmarinus, Psidium, Croton* and *Salvia* **(Juergens, 2014).**

Zhao et al., (2014) tested 1, 8-cineole *in vivo* in LPS-induced acute pulmonary inflammation and reported that the treatment reduced the amount of proteins and inflammatory cells in the broncho-alveolar fluid. Moreover, the authors reported significantly decreased levels of the pro-inflammatory cytokines TNF-α and IL-1β, increased levels of the anti-inflammatory cytokine IL-10 in lung tissues, reduced expression of NF-κB's subunit p65, reduced expression of TLR4 (PAMP receptor involved in inflammation signaling), and lastly, reduced activity of myeloperoxidase (Borges., 2019).

B. Anti-inflammatory action of α-pinene

The α-pinene is a bioactive mono-terpene abundantly found in essential oils. To this compound, anti-inflammatory activity was attributed in several essential oils.

There are a lot of studies using EORO in which α-pinene is one of the major components which showed anti-inflammatory effect on carrageenan-induced rat paw edema test **(Xiao et al., 2014; Tümen et al., 2018).**

Lourens et al., (2004) and **Kohoude et al., (2017)** found in their study that α-pinene was capable to inhibit 5-lipoxygenase activity, an indicator of its possible anti-inflammatory mechanism. The 5-lipoxygenase enzyme catalyzes formation of LTA4 in the arachidonic acid pathway. They also said that the treatment with α-pinene decreased the levels of IL-4, IgE, TNF-α, ICAM-1 and MIP-2.

Nam et al., (2014) has found that administration of α-pinene also inhibited eosinophils infiltration and decreased mast cells presence in nasal mucosa. *In vitro*, it inhibited NF-κB activity in human mast cells

C. Anti-inflammatory action of camphor

Studies associate camphor with the anti-inflammatory activity; **Zhang et al., (2017)** found that EORO root significantly decreased expression of pro-inflammatory cytokine TNF-α, decreasing also the expression of COX2 in TPA-induced mouse ear edema assay.

El Jemli et al., (2017) analysed essential oil of *Tetraclinis articulata* which shows high camphor concentration. The oil was reported to inhibit carrageenan-induced edema in rats at the dose (200 mg/kg). The results suggested that the anti-inflammatory effect of the essential oil may be due to inhibition of cyclo-oxygenase, and therefore, the formation of its products, considering that arachidonic acid metabolites produced by COX plays a fundamental role in the inflammatory response.

2.4.3. Mechanism of action of the anti-inflammatory activity of EOROs

2.4.3.1. Inhibition of arachidonic acid cascade enzymes

In the study of **Takaki et al., (2008),** the idea of authors was that the anti-inflammatory effect of EORO is due to the presence of 1,8-cineole. Moreover, **Juergens, (2014)** proposed the inhibition of 5-Lipoxygenase (5-LOX) and COXs by 1,8-cineole, preventing the formation of inflammatory arachidonic acid metabolites, such as LTB4 and PGE2 (Figure 9).

An additional way of direct interference with the arachidonic acid cascade was proposed by **Borges et al., (2017),** which showed through a molecular modeling study (docking) of EORO molecules that camphor had the highest number of interactions with therapeutic targets of inflammation, such as COX-2 (Figure 9). Nonetheless; only *in silico* study supports this claim.

Cutillas et al., (2018) reported the inhibition of LOX by samples of EORO (150 µg/ml) *in vitro*. In this study, camphor had the higher inhibition capacity. Lastly, **Kohoude et al., (2017)** proposed the inhibition of 5-LOX by α-pinene (Figure 11).

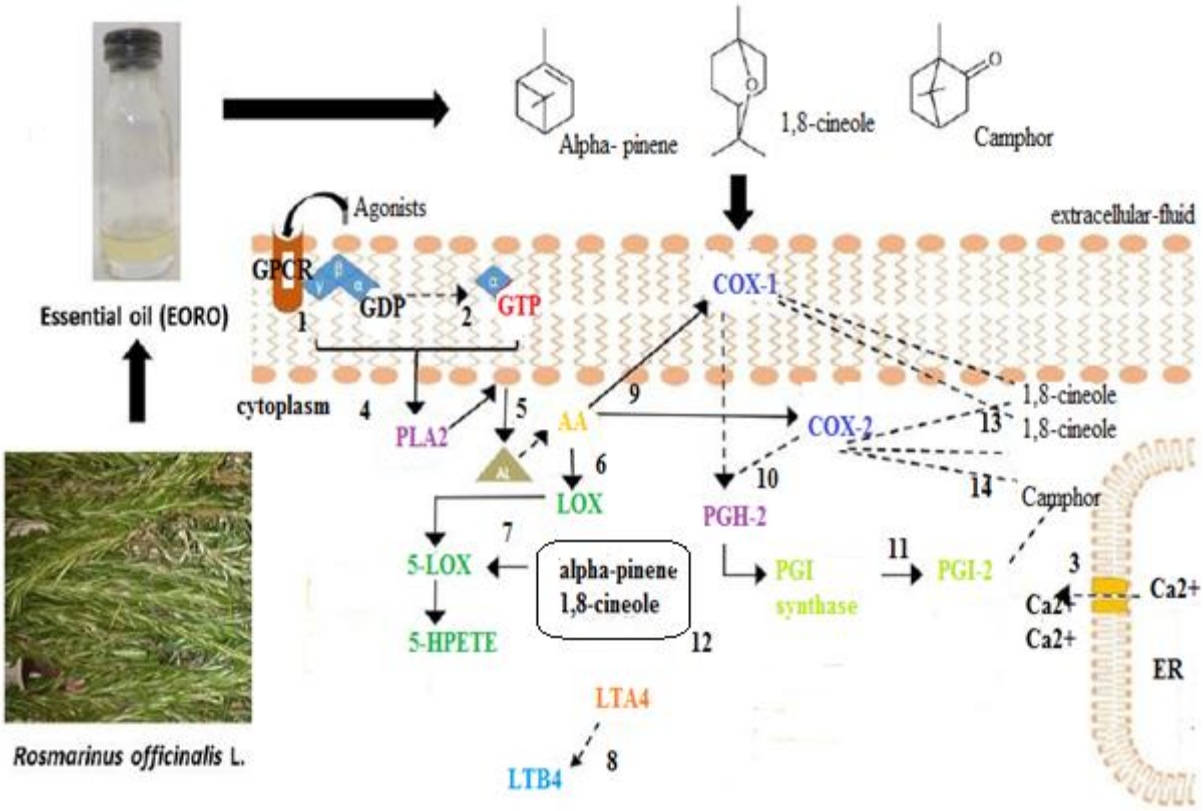

Figure 11: Arachidonic acid cascade pathway and mechanism of action as proposed by some authors for camphor, α-pinene, and 1,8-cineol isolated or combined with myrcene (Borges et al., 2019).: 1: G protein-coupled receptors (GPCR) are stimulated by agonists; 2: Guanosine diphosphate (GDP) is activated into guanosine triphosphate (GTP); 3: Calcium ions concentration (Ca2+) increases in the cytoplasm; 4: These processes activate phospholipase A2 (PLA2); 5: PLA2 acts on membrane phospholipids releasing linoleic acid (AL), which is transformed into arachidonic acid (AA); 6: AA is oxidized by Lipoxygenase (LOX); 7: 5-lipoxygenase (5-LOX) converts hydroxyhexanoatetetraenoic acid (5-HPETE) to leukotriene A4 (LTA4); 8: LTA4 is converted to leukotriene B4 (LTB4), acting on macrophages stimulating the production of proinflammatory cytokines; 9: AA is oxidized by cyclooxygenase (COX-1 and COX-2); 10: COXs form prostaglandin H2 (PGH2); 11: From PGH2 the catalysis of enzymes results in prostaglandins (PGE2, PGF2, PGI2, PGD2) and thromboxane (TXA2); 12: 1,8-cineol and α-pinene block the action of 5-LOX by preventing the formation of proinflammatory cytokines; 13: 1,8-cineol alone or combined with myrcene acts on the blockade of COX-1 and COX-2; 14: Camphor has a high number of possible interactions with PGI2 and COX-2.

2.4.3.2. Inhibition of NF-κB

Melo et al., (2011) reported the anti-inflammatory activity of EORO both *in vitro* (chemotaxis) and *in vivo* (leukocyte migration). They found that the presence of terpenes, and their potential to inhibit NF-κB transcription may contribute to EORO anti-inflammatory potential (figure 12). The results are in accordance to NF-κB inhibition since this transcription factor is involved in the synthesis of chemokines (hence in chemotaxis) and adhesion molecules (hence in leukocyte migration).

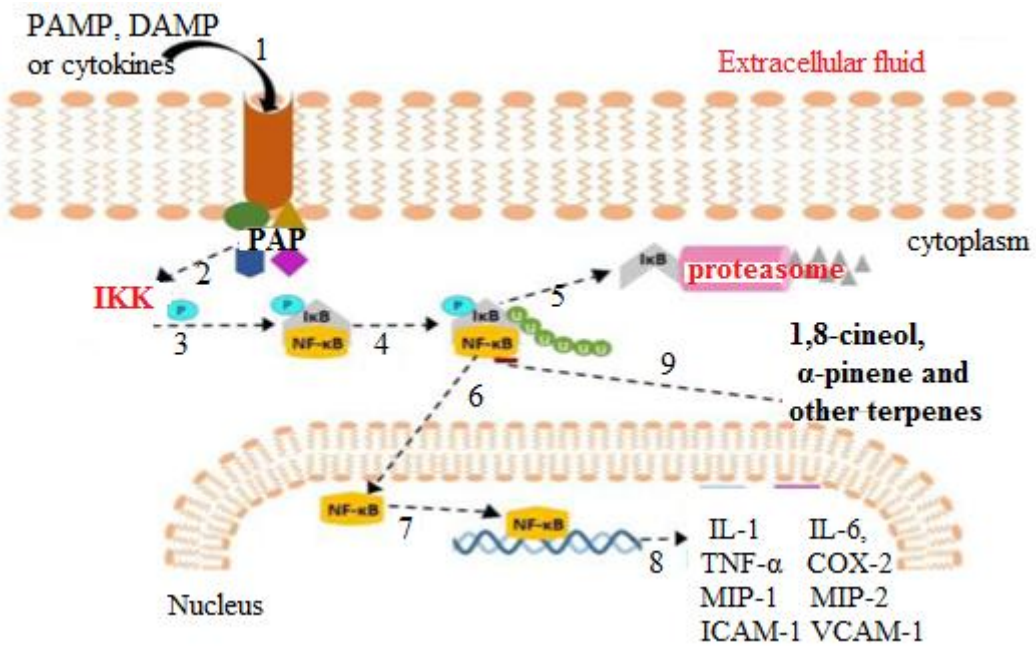

Figure 12: Mechanism of action of 1,8-cineol, α-pinene and other terpenes in NF-κB signaling pathway (Borges et al., 2019).

1: The pathogen-associated molecular pattern (PAMP), damage-associated molecular pattern (DAMP) or cytokine receptor is activated by its correspondent agonist molecule; 2:Receptor activation stimulus is transducted by coupled proximal adaptor protein (PAP), which in turn activates the IκB-kinase (IKK) by phosphorylation; 3: Activated IKK phosphorylates the inhibitor of κB (IκB), bounded to *nuclear factor-κB* (NF-κB); 4: Phosphorylation of IκB signalize its consequently polyubiquitination (u); 5: IκB polyubiquitination causes its degradation by proteasome; 6: Without its inhibitor, NF-κB is able to translocate into the nucleus; 7: In the nucleus, NF-κB binds to DNA, acting as transcription factor of several pro-inflammatory mediators; 8: NF-κB transcription products includes, among others, IL-1, IL-6, TNF-α, COX-2, MIP-1, MIP-2, ICAM-1 and VCAM-1; 9: The 1,8-cineole, α-pinene and other terpenes, act by preventing NF-κB translocation into nucleus, and the consequently formation of pro-inflammatory mediators.

2.4.4. *Rosmarinus Officinalis* extract

The rosemary extract is mainly composed of phenolic compounds, namely flavonoids, diterpenoids (carnosic acid, carnosol, and rosmanol derivatives), triterpenoid (betulinic acid), and lignans (medioresinol derivatives). Carnosic acid was the predominant phenolic compound (figure 13) **(Samuelsson and Bohlin, 2001; Ulbricht et al., 2010; Begum, 2013; Aumeeruddy-Elalfi et al., 2016; Pedro Mena et al., 2016).**

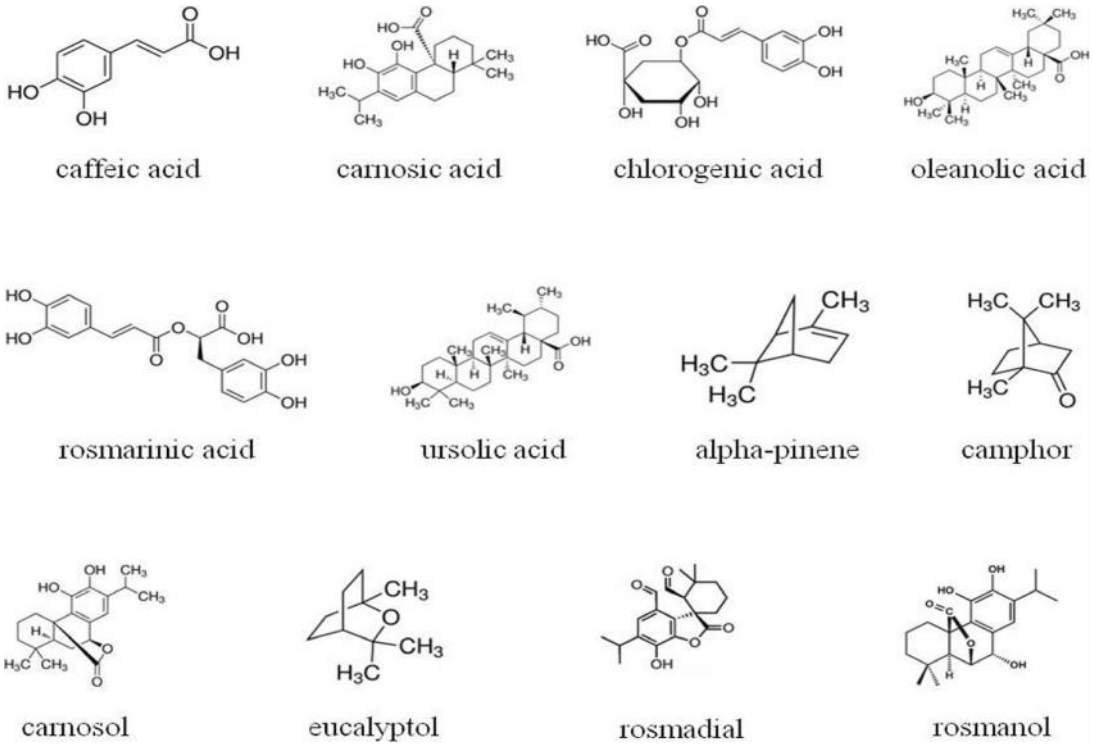

Figure 13: Poly-phenols present in *R. officinalis L* (Gonçalves et al., 2019).

2.4.5. Anti-inflammatory activity of *R. Officinalis* extract

Rosemary's extract has shown gastro-protective action against gastric ulcer, even better than Omeprazole; this advantage is because of inhibition activity of rosemary in neutrophils infiltration and reduction in pro-inflammatory mediators: TNF-α and IL-1 **(Amaral et al., 2013).** Histological analysis of the sciatic nerve made by **Di cezare et al., (2016)** revealed that terpenoid-enriched *R. Officinalis* extract prevented axon and myelin derangement, edema, and inflammatory infiltrate. The obtained results reinforced the traditional use of *R. Officinalis* as an effective treatment for inflammatory disorders and pain relief. These results also suggest that the ethanolic extract of *R. Officinalis* might be potential candidates in treating neurological disorders accompanied by inflammation and neuropathic pain by modulating neuro-inflammation. According to these results, it could be suggested that the extract might have an important role against oxidative and inflammatory markers including IL-1b, PGE-2, NO, COX-2, and MMP2.

2.4.5.1. Rosmainic acid anti-inflammatory activity

Rosmarinic acid (RosA) has many biological activities, including antiviral, antibacterial, antioxidant, anti-mutagenic, and anti-inflammatory activities **(Elufioye and Habtemariam, 2019).** Arthritis is an inflammatory disease that involves damage to one or more joints. It has more than one hundred types, the most common of which are osteo-arthritis (OA) and rheumatoid arthritis (RA) **(Petchi et al., 2013).** At the cellular and molecular level collagen 2 (COL2) and aggrecan

(ACAN) are the main components of cartilage extracellular matrix (ECM) **(Luo et al., 2017).** A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4 and ADAMTS-5 are responsible for ACAN depletion in osteo-arthritic cartilage **(Gendron et al., 2007).** The inflammatory cytokine interleukin-1-beta (IL-1b) also exerts an important role in ECM degradation **(Tu et al., 2017).**

An effect of RosA on OA has been reported in rat chondrocytes by **Hu et al., (2018).** In this experiment, chondrocytes were isolated from rat cartilage and incubated with RosA in the presence of IL-1b. RosA was found to inhibit IL-6 secretion and inhibit the gene and protein levels of ADAMTS-4 and ADAMTS-5. Moreover, RosA also inhibited the ACAN and COL2 gene expression induced by IL-1b. The results indicate that RosA can degrade ECM in OA and may have a therapeutic effect on OA. Another study of **Connelly et al., (2014)** found that drinking high-RosA spearmint tea can be a potential complementary treatment for OA pain relief. The study indicated that taking high RosA tea for 16 weeks per day could significantly improve stiffness and physical disability scores in adults with knee OA and could significantly reduce pain.

Asthma is a common chronic airway disease described as acomplicated interaction between airway obstructions, bronchial hyper-responsiveness (BHR), and airway inflammation **(Manuyakorn et al., 2013).**The study of **Hur et al., (2007)** found that RosA can induce apoptosis in activated T cell subsets in RA patients by the mitochondrial pathway. The results showed that RosA induced CD3+CD25+ activated T cell apoptosis in 57.1% of RA patients in a dose-dependent manner, RosA inhibited MMP destruction, reduced Bcl-2 expression, and induced Cyt c release from mitochondria to the cytoplasm. **Liang et al., (2016)** have found that RosA inhibits ovalbumin (Ova)-stimulated airway inflammation in a mouse model of asthma. In this experiment, RosA significantly inhibited the increase in inflammatory cells and Th2 cytokines in broncho-alveolar lavage fluid (BALF), decreased total IgE and Ova-specific IgE concentrations, and significantly improved airway hyper-responsiveness (AHR). Histological analysis showed that RosA significantly reduced the number of inflammatory cells and excessive mucus secretion in the airways. Pretreatment with RosA led to a significant regulation of NF-kB and MAPK activation. Therefore, this study suggested that RosA may be a promising candidate for asthma treatment. The protective effect of RosA may be exerted via the inhibition of ERK, JNK, and p38 phosphorylation and the activation of NF-kB.

(Sahu et al., 1999) confirms the anti-inflammatory potential of *R. officinalis* in molecular scope; according to them, rosmarinic acid could disturb complement system activation easily by inhibiting C3b attachment at a very low dose (34 μM).

Moreover, **Ghasemzadeh et al., (2016)** conducted a research to investigate the potential anti-inflammatory properties of ethanolic extract of *R. officinalis* (100, 200, and 400 mg/kg, IP) and

rosmarinic acid (10, 20, and 40 mg/kg, IP) in a rat model of sciatic nerve chronic constriction injury (CCI) -induced neuropathic pain. In this study, the effects of 14days, intra-peritoneal prescription of ethanolic extract of rosemary and rosmarinic acid on the lumbar spinal cord expression of oxidative stress and inflammatory markers including PGE-2, IL-1b, COX2, NO, and MMP2

2.4.5.2. Carnosic acid

Carnosic acid (CA) is a natural phenolic di-terpene originally isolated from *R. officinalis* plant and has been identified as one of the principal active components. To date, CA has been well proved as a potent antioxidant that is applied in food, health, and cosmetics industries **(Birtic et al., 2015).** Recently, its potential anti-inflammatory activity has attracted great attention. Efforts directed at mechanisms of CA-mediated anti-inflammation found that CA reduced reactive oxygen species (ROS) production, attenuated nuclear factor (NF)-kB and p38/ERK1/2 MAP kinase signaling activation **(Schwager et al., 2016; Shibata et al., 2016; Thummuri et al., 2017; Xia et al., 2017; Yang et al., 2017).**

Wang et al., in their work published in (**2018)** founds that CA attenuates the secretion of various inflammatory mediators in lipopolysaccharide LPS-Challenged RAW264.7 macrophage cells and prevents inflammatory genes expression in the same cells (Figures 14 and 15). Also, they found that CA restrained the activation of ERK, JNK, and p38 MAPKs in LPS-challenged RAW264.7 cells and suppress LPS-induced IKKb/IkB-a/NF-kB signaling activation (figures 16 and 17).

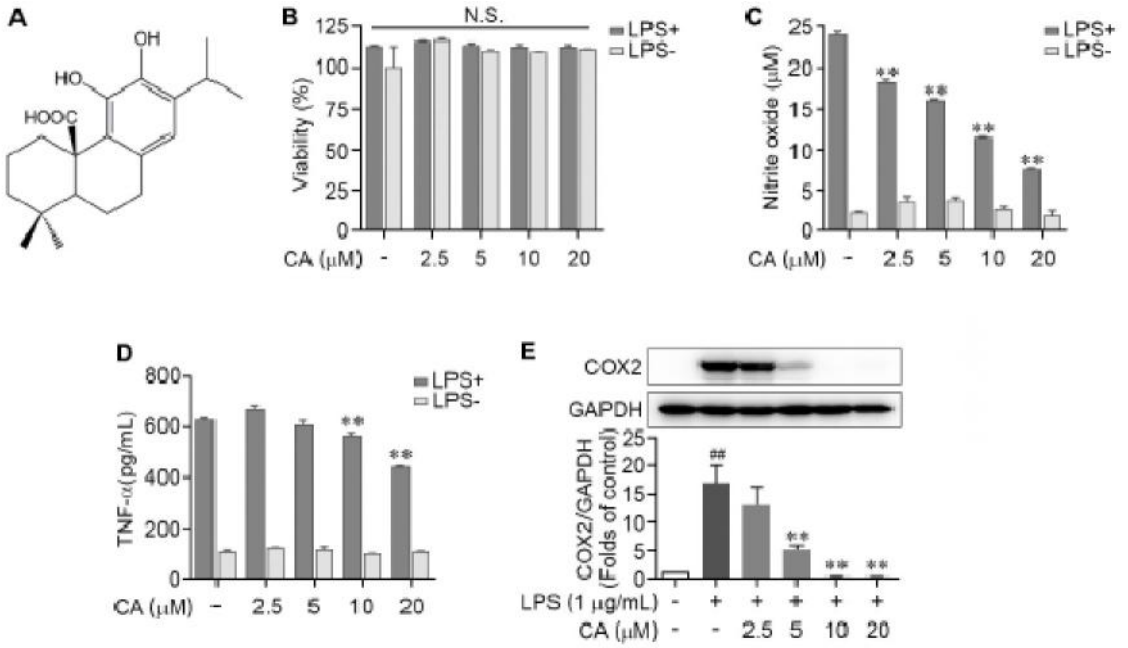

Figure 14: Carnosic acid down-regulated the levels of pro-inflammation mediators in LPS-induced RAW264.7 cells (Wang et al., 2018).

(A) Chemical structure of carnosic acid (CA). (B, C) RAW264.7 cells were treated with various concentration of CA (2.5, 5, 10, and 20 mM) in the absence or presence of LPS (1 mg/ml) for 24 h. Then the cell viability (B) and nitric oxide production (C) were determined by MTT and Griess methods, respectively. (D) RAW274.7 cells were treated with CA and LPS as in (B, C) for 4 h, then the TNF-a level was detected by ELISA. (E) RAW264.7 cells were treated with 1 mg/ml of LPS containing CA (2.5, 5, 10, and 20 mM) or not for 24 h. The protein expression of COX2 was detected by western blot assay.

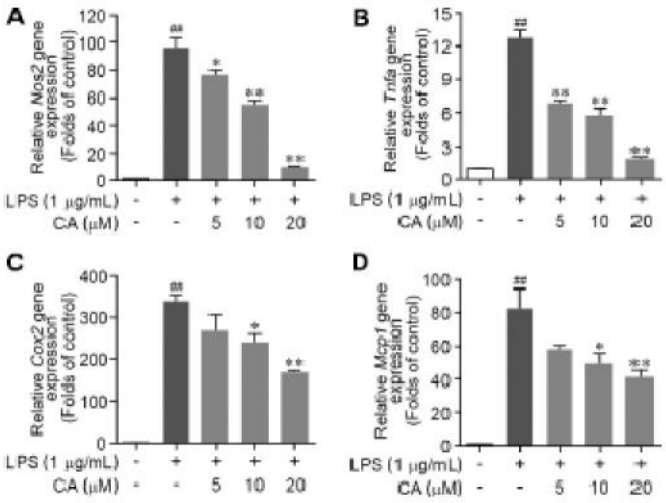

Figure 15: Carnosic acid down-regulated the levels of pro-inflammation gene expression in LPS-stimulated RAW264.7 cells (Wang et al., 2018).

(A–D) Cells were treated with LPS (1 mg/ml) for 6 h with or without CA (5, 10, and 20 mM). The relative mRNA expressions of Nos2 (A), Tnfa (B), Cox2 (C), and Mcp1 (D) were detected by real-time PCR analysis, respectively.

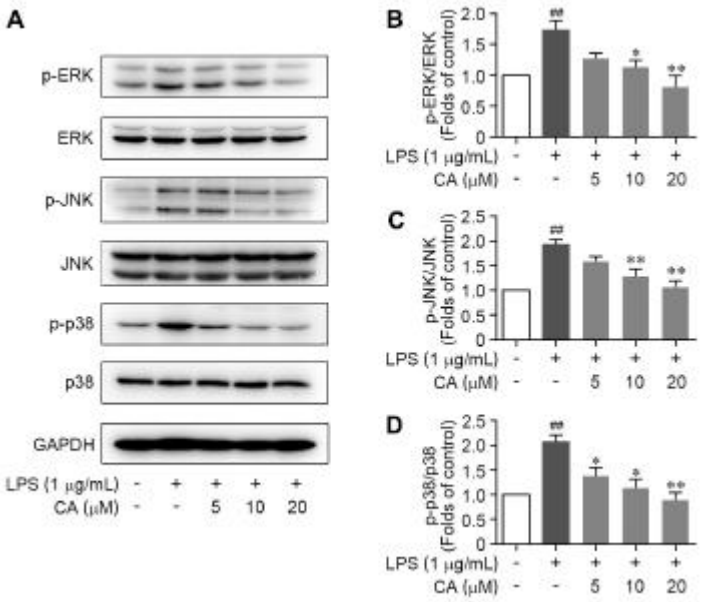

Figure 16: CA restrained the activation of ERK, JNK, and p38 MAPKs in LPS-challenged RAW264.7 cells (Wang et al., 2018).

Cells were treated with LPS (1 mg/ml) with or without CA (5, 10, and 20 mM) for 1 h.
(A) Phosphorylations of ERK, JNK, and p38 protein were determined by western blot assay. (B–D) Quantitative analysis for relative phosphorylation levels of ERK (B), JNK (C), and p38 MAPK (D) was performed by normalizing to the control group.

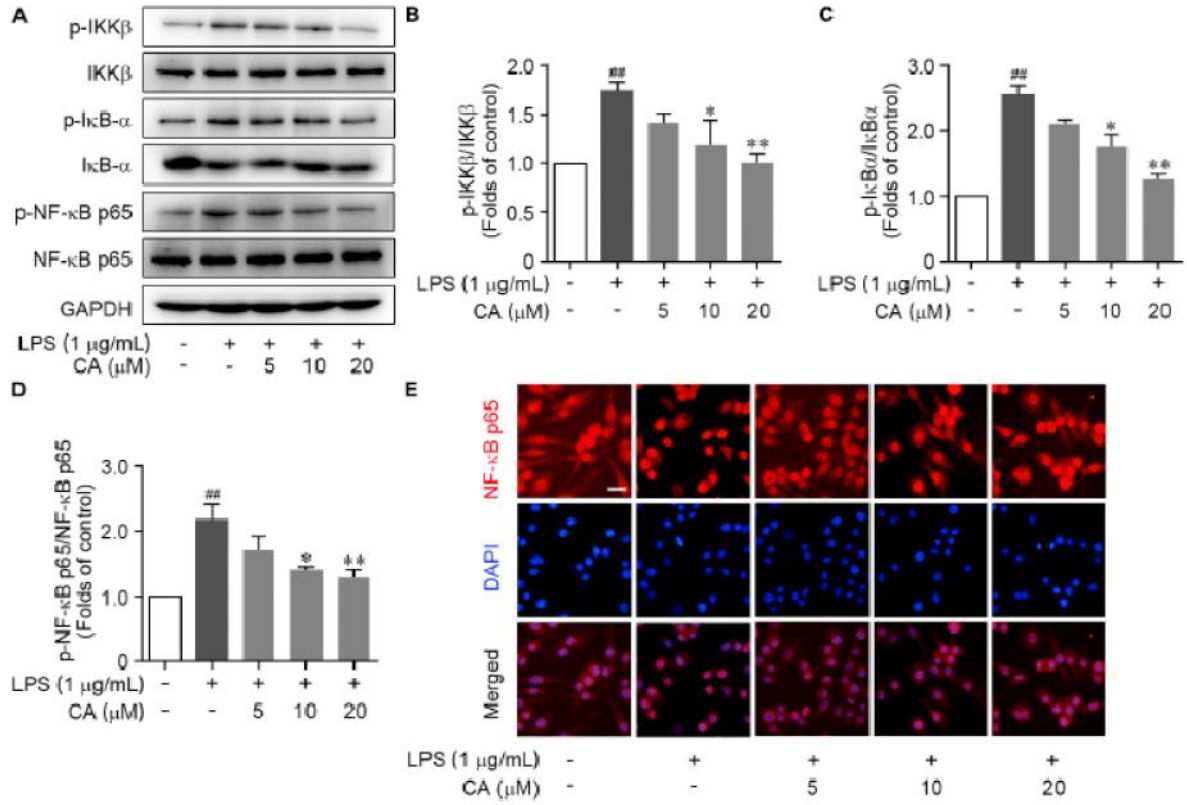

Figure 17: CA suppressed LPS-induced IKKb/IkB-a/NF-kB signaling activation in RAW264.7 cells (Wang et al., 2018). Cells were treated with LPS (1 mg/ml) with or without CA (5, 10, and 20 mM) for 1 h.(A) Phosphorylation and total expressions of IKKb, IkBa, and NF-kB p65 were determined by western blot assay.(B–D) Quantitative analysis for relative phosphorylation levels of IKKb (B), IkB-a (C), and NF-kB p65 (D) was performed by normalizing to the control group.(E) The nuclear translocation of NF-kB p65 was detected by immune-fluorescence assay. Representative images were displayed with NF-kB p65 (red) and nucleus (blue). Typical apoptotic neurons were labeled with white arrows. Scale bar = 40 mm.

2.4.5.3. Luteolin

Kong et al., (2019) conclude in their work that luteolin has an anti-inflammatory effect on rat lung tissue in a model of acute pneumonia. The results demonstrate that the anti-inflammatory mechanism of luteolin is, at least in part, due to the inhibition both of cAMP‑phosphodiesterases activity and expression of adhesion molecules in microvascular endothelial cells (cAMP-PDE) and phosphodiesterases (PDE4) activity as well as the expression of vascular cell adhesion molecule (VCAM-1) (*in vitro*) and intracellular cell adhesion molecule (sICAM-1) (*in vivo*) in endothelial cells.

Conclusion

Inflammation is an acute reaction to infection and tissue lesion to prevent damage to the body. Any defect may occur in the regulation or in this phenomenon pathways will cause excessive inflammation that lead to chronic or systemic inflammatory diseases. In the past few decades, the prevalence of inflammatory diseases has been on the rise, especially in developed countries.

Presently, the field of inflammation study is rapidly developing in the direction of herbal research to find safe and effective drugs. Medicinal plants are a reliable source of active ingredients with a multitude of therapeutic properties. A large number of aromatic plants represent a source of chemical compounds endowed with anti-inflammatory activity. However, it is not clear if any of these supplements can be effectively and safely recommended to reduce steroidal or non-steroidal anti-inflammatory drug usage despite its symptoms, which are often dangerous, thus, more research is required.

R. officinalis has a promising future in the medical field, especially in the treatment and prevention of various inflammatory diseases. Scientific experiments on its bioactive compounds, isolated from its essential oil or extract have proven their efficacy against inflammation. Considering this, more reliable trials are needed in the future to evaluate the *R. officinalis* active phyto-compounds safety and efficacy in treating different pathological conditions.

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Thème :
Anti-inflammatory property of *Rosmarinus Officinalis L*

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Abstract:

Inflammation is a natural defensive phenomenon for the body that may turn into a disease due to a defect in its mechanism of work. Today the inflammatory diseases of all kinds have become widespread in our society, especially for the elderly peoples. The search for safe treatment methods has become very necessary, especially taking into account that the available drugs treatments no longer provide satisfactory results at the therapeutic level for patients, but may make the matter worse due to its many side effects, and therefore returning to mother nature is the best solution.

Rosmarinus Officinalis L or rosemary is a plant belongs to the Lamiaceae family. It was considered as a source of effective compounds from its essential oil and extract, which scientific research has proven to be very effective in treating inflammatory diseases. In this report, a group of plant compounds and their mechanism of action against inflammation were reviewed. A group of studies dealing with this topic have also been covered.

Based on these available scientific and experimental data, it can be said that this plant is very effective in influencing inflammatory conditions. Therefore, the area of interest in it should be expanded experimentally to study its therapeutic properties more broadly.

Key words: Inflammation; NSAIDs; *Rosmarinus Officinalis L;* Phyto-compounds; essential oil; extract.

Résumé:

L'inflammation est un phénomène défensif naturel pour l'organisme qui peut se transformer en maladie en raison d'un défaut de son mécanisme de travail. Aujourd'hui, les maladies inflammatoires de toutes sortes se sont généralisées dans notre société, en particulier chez les personnes âgées. La recherche de méthodes de traitement sûres est devenue très nécessaire, d'autant plus que les traitements médicamenteux disponibles ne donnent plus de résultats satisfaisants au niveau thérapeutique pour les patients, mais peuvent aggraver la situation en raison de ses nombreux effets secondaires, et donc revenir à la nature mère est la meilleure solution.

Rosmarinus Officinalis L ou romarin est une plante appartenant à la famille des lamiacées. Il était considéré comme une source de composés efficaces à partir de son huile essentielle et de son extrait, dont la recherche scientifique a prouvé son efficacité dans le traitement des maladies inflammatoires. Dans cette recherche, nous passons en revue le groupe des composés de la plante et leur mécanisme d'action contre l'inflammation. De plus, plusieurs 'études traitons ce sujet ont été approuvées.

Sur la base de ces données scientifiques et expérimentales disponibles, on peut dire que cette plante est très efficace pour influencer les conditions inflammatoires. Par conséquent, son domaine d'intérêt devrait être élargi expérimentalement pour étudier ses propriétés thérapeutiques plus largement.

Mots clés: Inflammation; *Rosmarinus Officinalis L;* Phyto-compounds; huile essentielle ; extrait ; mécanisme d'action.

الملخص:

الالتهاب هو ظاهرة طبيعية دفاعية للجسم قد يتحول إلى مرض بسبب حدوث خلل في آلية عمله. هذا و قد أصبحت الأمراض الالتهابية بجميع أنواعها منتشرة بشكل كبير في مجتمعنا خاصة لذا كبار السن، وبالتالي أصبح البحث عن طرق علاجية آمنة أمرا ضروريا للغاية خاصة إذا أخدنا بعين الاعتبار أن العلاجات المتاحة من أدوية لم تعد توفر نتائج مرضية على الصعيد العلاجي للمرضى، بل قد تزيد الأمر سوءا بسبب أعراضها الجانبية الكثيرة ولهذا فالعودة للطبيعة الأم هو أفضل حل.

نبتة إكليل الجبل هي مصدر لمركبات فعالة من زيوت أساسية ومستخلص النبتة والتي أثبتت الأبحاث العلمية على فعاليتها الكبيرة في علاج أمراض الالتهاب. في هذا البحث نستعرض مجموع المركبات النباتية والية عملها ضد الالتهاب .كما تم التطرق إلى مجموعة من الأبحاث التي تناولت هذا الموضوع، وبناءا على هذه المعطيات العلمية والتجريبية المتاحة يمكن القول إن هذه النبتة جد فعالة في التأثير على حالات الالتهاب ولذا وجب توسيع دائرة الاهتمام بها من الناحية التجريبية لدراسة خصائصها العلاجية بشكل موسع أكثر.

الكلمات المفتاحية: **الالتهاب؛ أمراض التهابية؛ أدوية؛ نبتة إكليل الجبل؛ زيوت أساسية؛ مستخلص؛ آلية عمل؛ أبحاث.**