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Artemisia herba alba: a new perspective in asthma treatment?

By

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Dedications

To our families,

beloved ones

and all our friends.

Amel & Thanina

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Abstract

Asthma is considered to be the most prevalent chronic lung disease, with over 300 million asthmatics around the world including 1.5 million from Algeria. Bronchodilators and glucocorticoids are the main drugs used to alleviate and treat asthma as well as control exacerbations. However, side effects, costs and ineffectiveness (severe asthma) negatively impact the healthcare systems. As a consequence, looking for an alternative treatment has attracted more attention and led to an interest in herbal medicine.

The current work attempts to document and review the therapeutic potential of *Artemisia herba alba* in the treatment of asthma by searching different databases including PubMed, ScienceDirect, Google Scholar, and ResearchGate with the following key words: *Artemisia herba alba*, asthma, respiratory diseases, antioxidant, anti-inflammatory, and anti-asthmatic activities.

An analysis of the search data highlighted multiple interesting biomolecules with anti-inflammatory and anti-asthmatic activities that were found in noticeable levels in *A. herba alba*.

Our findings suggest that *Artemisia herba alba*, a source of bioactive molecules, could be a potential plant-based treatment in asthma. Further experimental investigations are needed to assess its effectiveness in the treatment of asthma.

Key word: Asthma, *Artemisia herba alba*, anti-inflammatory activity, anti-asthmatic activity.

Résumé

L'asthme est considéré comme la maladie pulmonaire chronique la plus répandue ; avec plus de 300 millions d'asthmatiques dans le monde dont 1,5 million en Algérie. Les bronchodilata teurs et les glucocorticoïdes sont les principaux médicaments utilisés pour atténuer et traiter l'asthme ainsi que pour contrôler les exacerbations. Cependant, leurs effets secondaires, coûts et inefficacité (asthme sévère) ont des répercussions négatives sur les services de santé. Par conséquent, la recherche d'un traitement alternatif a suscité plus d'attention et d'intérêt pour la phytothérapie.

Le travail actuel tente de documenter et d'examiner le potentiel thérapeutique d'*Artemisia herba alba* dans le traitement de l'asthme par une recherche bibliographique dans différentes bases de données : PubMed, Science Direct, Google Scholar, et ResearchGate. Cette recherche est basée sur des mots clés comprenant *Artemisia herba alba*, asthme, maladies respiratoires, activité antioxydante, activité anti-inflammatoire, et activité antiasthmatique.

L'analyse des données de recherche a mis en évidence plusieurs biomolécules intéressantes avec des activités anti-inflammatoires et antiasthmatiques rapportées avec des niveaux notables dans *A. herba alba*.

En conclusion, *Artemisia herba alba*, source de molécules bioactives, pourrait être un traitement potentiel à base de plantes dans l'asthme. D'autres investigations expérimentales sont nécessaires afin d'évaluer son efficacité dans le traitement de l'asthme.

Mots clé : Asthme, *Artemisia herba alba*, activité anti-inflammatoire, activité antiasthmatique.

Abbreviation List

ABTS: 2,20-azinobis-3-ethylbenzothiazoline-6-sulphonate radical

ACQ: Asthma control questionnaire

AERD: Aspirin-exacerbated respiratory disease

AHR: Airway hyper responsiveness

BAL: Bronchoalveolar lavage

BHT: Butylated Hydroxytoluene

DPPH: 2,2-diphenyl-1-picrylhydrazyl

ELISA: Enzyme linked immunosorbent assays

FEV1: Forced Expiratory Volume in 1 second

FRAP: Ferric reducing antioxidant power

FVC: Forced Vital Capacity

GINA: Global initiative for asthma

IFNγ: Interferon gamma

IGC : Inhaled glucocorticoids

IL-12 : Interleukin 12

IL-13 : Interleukin 13

IL-4 : Interleukin 4

IL-5 : Interleukin 5

iNOS : Induced nitric oxide synthase

LABA: Long-acting β2-agonists

LPS: Lipopolysaccharides

LTE4: Urinary leukotriene E4

LTRA: Leukotriene receptor antagonists

MCF7: Michigan Cancer Foundation - 7

NF-κB: Nuclear factor-kappa B

OVA: Ovalbumin

PCR: Polymerase chain reaction

PEV: Peak airflow limitation

ROS: Reactive oxygen species

SABA: Short-acting β2-agonists

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Introduction

Introduction

Asthma is an inflammatory lung disease usually associated with chronic bronchial inflammation and airway hyperresponsiveness (AHR). Among the history of respiratory symptoms in asthma, wheezing, shortness of breath, chest tightness and cough have been described as the frequent symptoms that can vary over time and intensity [1].

In 2015, about 300 million people were reported to have asthma around the world [2]. In Algeria, the available epidemiological studies are limited and relatively old [3]. However, according to Pr. H. Douagui, president of the Algerian society of clinical allergology and immunology (ASCAI), over 1.5 million of Algerians are asthmatic [4]. In fact, the prevalence of asthma in Algeria was 3.45% in a cross-sectional epidemiological survey conducted in north African regions [5]. Asthma morbidity is significant, with at least 250,000 deaths each year, making it the most prevalent chronic lung disease [2].

Most asthma treatments are considered as a symptomatic therapy using anti-inflammatory drugs, in particular, glucocorticoids (GCs) and bronchodilators such as short and long acting β2-adrenergic agonists [6]. GCs are considered as the most effective anti-inflammatory therapy that improves asthma control in most asthmatic patients. However, the high cost of the drugs [7] and adverse effects including adrenal insufficiency, weight gain, increased skin fragility, myopathy, osteoporosis, cataracts, and mood changes are associated with these treatments [8]. In patients with severe asthma and smoker asthmatics, decreased glucocorticoid responsiveness has been reported [9]. Moreover, the major difficulty in asthma management remains maintaining a stable state of control, particularly in severe asthma. Thus, the resort to medicinal plants as alternative or complementary therapies has been growing over recent decades.

Humans have been using plants as medicines since ancient times, due to their richness of multiple phytocompounds that prevent and cure several diseases and disorders [10]. In developing countries, about 80% of the population relies on traditional medicine [11]. Due to patients' economic conditions and the unavailability of medications, plants are the main medicinal source to treat infectious ailments [12].

Furthermore, it has been demonstrated that various compounds of different plant species such as polyphenols showed several biological activities that include anti-inflammatory, immune-modulatory, antioxidant, cardiovascular protective and anti-cancer, thus playing an important role as potential therapeutic tools in various acute and chronic disorders [13].

Introduction

Artemisia herba alba is an aromatic and medicinal herb of 30-50 cm height that grows commonly in Mediterranean region in North Africa, Spain, deserts of Sinai Peninsula, Middle East, Northwestern Himalayas, and in India. This plant is widely used in traditional medicine to treat diabetes, bronchitis, diarrhea, hypertension, and neuralgia [14,15]. *A. herba alba* is a rich source of polyphenol compounds; the levels of phenolic compounds, including flavonoids, seems to vary in quantity and quality depending on the harvest time [15].

In this context, we aim to review the main scientific literature that studied the *Artemisia herba alba* chemical profile, the composition of its specific biomolecules and their biological effects, particularly the anti-inflammatory, antioxidant and anti-asthmatic activities in order to relate these biomolecules to a potential asthma therapy.

Asthma

I. Asthma

I.1. Definition

Asthma is a lung disease usually associated with chronic bronchial inflammation and airway hyperresponsiveness. Wheezing, shortness of breath, chest tightness and cough have been described as the frequent symptoms that can vary over time and intensity [1]. These symptoms are triggered by many factors, including genetic predisposition in association with environmental factors such as inhaled allergens, smoke exposure, indoor and outdoor air pollution [16].

Asthma is characterized by airway infiltration of inflammatory immune cells, particularly eosinophils and mast cells, but also lymphocytes and neutrophils [17] with elevated serum immunoglobulin E (IgE) levels [18].

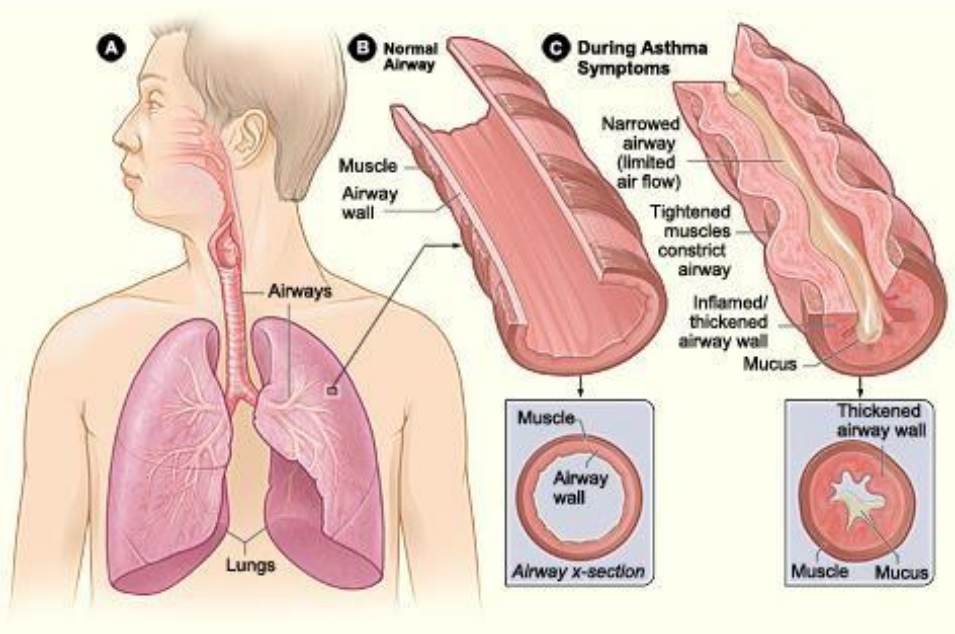


Figure 1. A) The location of the lungs and airways. **B)** A cross-section of a normal airway. **C)** A cross-section of an airway during asthma symptoms. Contributed by United States-National Institute of Health [19].

I.2. Classification

I.2.1. Asthma phenotypes

By definition, phenotypes are grouped by individuals with similar observable characteristics. Treating asthma based on phenotypes has been shown to be suboptimal [20]. In

fact, asthma phenotypes are associated with variable clinical features and asthma endotypes are associated with distinct signaling pathways [21].

a. Allergic asthma

This phenotype is easily identified. It is associated with a past and/or family background of allergic disease (eczema, allergic rhinitis, food or drug allergies), which often appears in childhood [1]. The diagnosis reveals a positive skin prick test, specific IgE antibodies in serum, eosinophilia in the peripheral blood and/or in induced sputum, bronchoalveolar lavage (BAL), and bronchial biopsies. It is also characterized by thickened reticular basal membrane and hypertrophic smooth muscle [22].

b. Non-allergic asthma

It is often more severe than atopic (allergic) asthma. This phenotype is also known as intrinsic [22] or non-atopic asthma and is not associated with allergy. However, sputum from patients with non-allergic asthma may contain neutrophilic, eosinophilic or only a few inflammatory cells [1].

c. Adult-onset asthma

It occurs for the first time in some adults particularly women [1]. Older asthmatics have higher morbidity and mortality rates related to their disease than younger patients. Additionally, sputum neutrophils may be increased in older compared to young patients [23].

d. Aspirin-intolerant asthma

It affects approximately 5–10% of adult asthmatics mainly women. It has been suggested to describe this condition as aspirin-exacerbated respiratory disease (AERD) [22], given that it is usually triggered by aspirin or other nonsteroidal anti-inflammatory drugs [24]. Moreover, this condition causes dysregulated arachidonic acid metabolism, blood or sputum eosinophil count, urinary LTE4, and more frequent exacerbation [21].

e. Asthma with obesity

In adults, obesity is defined as a body mass index (BMI) of 30 kg/m^2 or more [25,26]. This phenotype is noticed in some obese asthmatics with prominent respiratory symptoms and few eosinophilic cells in airway inflammation [1]. Obesity can worsen asthma through many mechanisms such as by reducing exhaled NO, decreasing airway eosinophils and increasing airway neutrophils [25].

f. Extensive remodeling asthma

Lack of inflammation despite of extensive airway remodeling is the main feature of this phenotype. It is also divided into many subtypes with different features including thickened small airways, alveolar detachment and loss of elastin, airway smooth muscle hypertrophy, goblet cell hyperplasia and mucus production, and reticular basement membrane thickening [22].

g. Exercise-induced asthma

Exercise-induced asthma is a phenotype where exercise triggers bronchial hyperresponsiveness [27]. This phenotype occurs in 40-90% of people with asthma and up to 20% of those without asthma. It describes a transient airway narrowing occurring during physical exertion. It can occur during or after exercise. There are multiple triggers including high intensity of aerobic exercise [28].

h. Cough variant asthma

This phenotype is a form of chronic cough and is defined according to the American College of Chest Physician guidelines as a cough lasting ≥ 8 weeks which is caused by airway eosinophilic inflammation and airway remodeling [29].

I.2.2. Asthma control

The clinical assessment of asthma control requires evaluation of several aspects including [30]:

- Symptoms such as dyspnea, wheezing, cough and chest tightness;
- Rescue bronchodilator use that induces poor asthma control, which is associated with increasing frequency, a shorter duration of effect, and incomplete relief of symptoms;
- Lung function, by measuring airflow obstruction variations performed clinically by spirometry which may include the forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV1) representing the volume of air a patient can exhale in a second. The result is expressed by percentage [31]; the aim of the asthma treatment is to reduce or eliminate these variations.

Table I. Global Initiative for Asthma definition of asthma control [32].

Levels of asthma control			
Characteristics	Controlled (All of the following)	Partly controlled (Any measure present)	Uncontrolled
Daytime symptoms	None (twice or less/ week)	More than twice/week	Three or more features of partly controlled asthma*
Limitations of activities	None	Any	
Nocturnal symptoms/ awakenings	None	Any	
Need for reliever/ rescue treatment	None (twice or less/ week)	More than twice/week	
Lung Function (PEF or FEV1) ≠	Normal	<80% predicted or personal best (if known)	

PEF: Peak Expiratory Flow
***** Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate
≠ Without administration of bronchodilator.
Lung function is not a reliable test for children 5 years and younger.

In addition, another asthma control tool is the asthma control questionnaire (ACQ) [33]. This questionnaire is administered to patients and the score determines whether their asthma is controlled or not [1].

The score range varies from 0 to 6 and is interpreted as follows [22]:

- 0 - 0.75 well controlled asthma
- 0.75 – 1.5 intermediate
- >1.5 poorly controlled asthma.

I.2.3. Asthma severity

Asthmatics with similar clinical symptoms may respond differently to the same treatment [21]. As a result, appropriate asthma treatment is often determined by asthma severity [24].

Table II. Classification of asthma severity [19].

Components of severity		Classification of Asthma Severity ≥ 12 years of age			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤ 2 days/week	>2days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤ 2 x/ month	3.4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting beta-agonist use for symptom control	≤ 2 days/week	>2days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Normal FEV1/FVC 8-19 yrs 85% 20-39 yrs 80% 40-59 yrs 75% 60-80 yrs 70%	Lung function	• Normal FEV1 between exacerbations • FEV1>80% predicted • FEV1/FVC normal	• FEV1>80% predicted • FEV1/FVC normal	• FEV1>60% but < 80% predicted • FEV1/FVC reduced 5%	• FEV1>60% predicted • FEV1/FVC reduced > 5%

FEV1: Forced Expiratory Volume in 1 second
FVC: Forced Vital Capacity

I.3. Pharmacological Treatment

Pharmacologic options are classified as either reliever (short-term benefit) or controller (longer-term benefit) medications [34].

I.3.1. Relievers

I.3.1.1. Short-acting β2-agonists (SABAs)

SABAs inhalers (commonly albuterol) are recommended as a monotherapy to treat acute symptoms in intermittent asthma [35]. These bronchodilators act on β2-receptors by relaxing bronchial smooth muscle which relieves symptoms [36]. However, nervousness, tremor, bronchospasm, tachycardia, headache, pharyngitis are the most common side effects of the SABAs [35].

I.3.1.2. Anticholinergics

Anticholinergics are muscarinic receptor antagonists that act as bronchodilators [37]. Ipratropium is used to treat reversible airway obstructions in acute and chronic asthma combined with β2 agonists. However, albuterol is more efficient than Ipratropium [38].

Bronchitis, dyspnea and headaches are the adverse effects of anticholinergics [35].

I.3.2. Controllers

I.3.2.1. Inhaled glucocorticoids (IGCs)

IGCs are the most used in daily preventative care [36] for asthma management due to direct airway inhalation [39]. The IGCs have the advantage of reducing airway swelling and inflammation and reduce the symptoms of dyspnea, cough, and nighttime awakening [36]. However, IGCs have many side effects, the common ones are dysphonia, oropharyngeal candidiasis, adrenal suppression, osteoporosis, and cataracts [40].

I.3.2.2. Leukotriene receptor antagonists (LTRAs)

LTRAs inhibit the action of cysteinyl leukotrienes, responsible for the airway smooth muscle constriction [35]. They are efficient in improving pulmonary function, increasing peak expiratory flow, decreasing daytime and nighttime symptoms, reducing the need for SABAs and decreasing the number of asthma flares [36]. They can be also used as an additional therapy with inhaled glucocorticoids, but only for patients older than 12 years old [41].

Patients treated with LTRAs may experience some side effects including headache, ear infection, pharyngitis, abdominal pain, nausea, rash, and angioedema [36].

I.3.2.3. Long-acting β2-agonists (LABAs)

LABAs are lipophilic agents that last for 12 hours in the airway tissue inciting constant bronchodilation. These agents are never used alone as they are related to severe exacerbations and asthma death. In fact, they are always combined with IGCs [37].

Arrhythmia, cardiac ischemia, hyperglycemia, hypopotassemia, increase of plasma free fatty acid and tachycardia are the most common side effects of LABAs [42].

I.1.1. Other Therapies

I.3.3.1. Oral glucocorticoids (OGCs)

OGCs are given as a short burst to briefly reduce pulmonary swelling and to prevent evolution of acute disease [36]. Indeed, they are prescribed for moderate to severe asthma exacerbations [41].

Patients usually present with glucose intolerance, gastrointestinal bleeding, hypertension, and mood changes with short term use, and adrenal insufficiency, ocular cataracts, glaucoma, and osteoporosis with long term use [43].

I.3.3.2. Biologic therapies

Biologic therapies are used for specific inflammatory pathways involved in asthma, in addition to anti-IgE therapy that has improved results in allergic asthmatics [44]. Anti-IL-5 therapy plays a maintenance role in patients with uncontrolled, persistent eosinophilic asthma regardless of high-dose IGCs [45]. These therapies reduce asthma exacerbations, improve lung function, reduce OGCs use, and improve quality of life in appropriately selected patients [44].

I.2. Herbal treatment in asthma

Considering the drug unavailability, side effects and high cost, it has become necessary to develop alternative treatments to manage asthma. Hence, medicinal plants are the most convenient substitute with interesting advantages (availability, traditional knowledge, low cost, therapeutic potential) to treat all socioeconomic classes [46].

Table III. List of select natural compounds with anti-inflammatory and/or anti-asthmatic effects [46].

Plant Name/product	Product form	Product Source	Active compounds	Compound class/type	Mechanism of Action
Nigella sativa	Oil	Seeds	Thymoquinone (2-isopropyl-5-methyl-1,4-benzoquinone)	Quinone	Decreases NO and IgE levels.
Curcuma longa	Essential oil extract and extract	Turmeric root	Curcumin	Polyphenol	Reduces the plasma level of the leukotriene C4, nitric oxide
Perilla frutescens	Isolated compound	Luteolin	(2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-chromenone)	Flavonoid	Inhibits the overproduction of mucus
Eucalyptus globulus	Isolated compound	Essential oil of Leaves	1,8-Cineol	Monoterpene	Reduces the expression of NF-κB target gene MUC2
Lepidium sativum	Crude extract	Seeds	Ascorbic acid, linoleic acid, oleic acid, palmitic acid, stearic acid	Vitamin and fatty acids	Promotes an anticholinergic effect, inhibits Ca2+ influx.
Naringin	Isolated compound	Common grapefruit	Naringin	Flavone	Attenuates bronchoconstriction by reducing calcium influx.

Artemisia herba alba

II. 1. Description of the plant

II.1.1. Ecology and botany of *Artemisia herba alba*

The genus *Artemisia* is one of the largest and most widely spread genera of the family Asteraceae. It is a varied and economically important genus with more than 500 species. Eleven species within can be found in Algerian flora [47].

Artemisia herba alba, known as desert wormwood, is an aromatic and medicinal herb of 30–50 cm height [14]. It is a greenish-silver perennial dwarf shrub that grows in arid and semi-arid climates. It is prominent in the Mediterranean region in North Africa, Spain, deserts of Sinai Peninsula, the Middle East, Northwestern Himalayas, and in India. The plant is green to light green, with strong, sturdy roots. The flowering period and harvesting is around May/June and continues until October in some areas [49].

Figure 2. Photograph of *Artemisia herba alba* [50].

II.1.2. Taxonomical classification

According to Lichtfouse (2020), *Artemisia herba alba* is classified as follows*:*

- Kingdom: Plantae,
- Division: Magnoliophyta,
- Class: Magnoliopsida,
- Family: Asteraceae,
- Genus: *Artemisia L.*,
- Species: *Artemisia herba alba Asso*

II.1.3. Therapeutic effect and traditional use

Artemisia herba alba is used in folk medicine as well as in European, North African, and Arabic traditional medicine [52]. Several ethnobotanical studies reported it as one of the most used medicinal plants in different countries, namely Algeria, Egypt, Jordan, and Tunisia [53–56].

Indeed, it is used for treating diabetes, bronchitis, diarrhea, hypertension, and neuralgias [12], and heart ailments and stomachache [55]. In addition, the plant is also used as an analgesic, anti-inflammatory for respiratory diseases, blood purifier, and anti-cancer drug [56].

As a traditional remedy, *A. herba alba* has been used as herbal tea [50] in decoction [55], and its essential oil was used as a disinfectant, anthelmintic and antispasmodic [57].

II.2. Chemical composition

The chemical composition of *A. herba alba* has been investigated in many studies demonstrating the importance of the plant as a rich source of polyphenol compounds including flavonoids, phenolic acids, monoterpenes, tannins, and anthocyanins contents [12,14,15]. Potassium and sodium were also found as mineral compounds in high concentrations in *A. herba alba* aqueous extract [58]. The yield of polyphenols found in *A. herbal alba* varies by geographic location, seasonal variations and subspecies [59] and growth season [60] depending on the solvents, as shown in Table IV.

Table IV. Polyphenol yields in *Artemisia herba alba* organic and aqueous extracts.

Polyphenol Yield					
Solvent	**Polyphenols**		**Flavonoids**	**Location**	**Reference**
Methanol	July	514.5 [a]	10.61 [g]	Djelfa, Algeria	[15]
	November	257.1 [a]	7.72 [g]		
	May	264.87 [a]	8.27 [g]		
Chloroform	160.47 [a]		41 [g]	Setif, Algeria	[61]
Ethyl acetate	320.43 [a]		76.55 [g]		
Aqueous	133.43 [a]		17.80 [g]		
Methanol/ Water	123.95 ± 4.30 [b]		19.74 ± 0.17 [h]	Sidi Bouzid, Tunisia	[12]
Methanol	25.34 ± 0.69 [c]		/	M'sila, Algeria	[62]

Water	113.6 ± 8.0 [d]	/	Bénikhdache, Tunisia	[58]
Ethyle Acetate	87.50 [e]	96.45 [g]	Gabes, Tunisia	[14]
Water	40.00 [e]	60,59 [g]		
Water/ethanol	13.06 ± 0.40 [e]	11.31 ± 0.51 [i]	Laghouat, Algeria	[63]
Methanol	5.61 ± 0.90 [e]	44.75 ± 3.46 [i]	Matmata, Tunisia	[64]
Aqueous extract	83.59 ± 0.96 [f]	25.7 ± 0.95 [g]	Oum el Bouaghi, Algeria	[65]
Pure methanol	8.38 ± 0.75 [e]	16.15 ± 1.44 [j]	Kef, Tunisia	[66]
	14.03 ± 1.33 [e]	32.58 ± 4.21 [j]	Boukorine, Tunisia	
	16.80 ± 1.86b [e]	43.59 ± 3.96 [j]	Kairouan, Tunisina	
	17.93 ± 1.47 [e]	39.77 ± 4.18 [j]	Kasserine, Tunisia	

[a] mg ETA/ g DM; [b] g GAE/ kg DM; [c] mg GAE / ml E; [d] mg GAE/ L; [e] mg GAE/ g DW; [f] mg GAE /g DW; [g] mg EQ/ g DM; [h] mg EQ/ kg DM; [i] mg RE/ g DW; [j] mg CE / g DW.

ETA: tannic acid equivalents; DM: dry mass; GAE: gallic acid equivalents; E: extract; DW: dry weight; EQ: quercetin equivalents; RE: rutin equivalents; CE: catechin equivalents.

To identify polyphenols, Touil et al. (2019) used HPLC/ESI-MS on *A. herba alba* methanolic extract, which led to the characterization of 12 new compounds. The phenolic profile of methanolic extract is documented in Table V.

Table V. Phenolic compounds identified in *Artemisia herba alba* extracts.

Phenolic compounds	References
3-Caffeoylquinic acid	[15,56,67]
4-Caffeoylquinic acid	
Vicenin-2	[12,14,15]
Isoschaftoside	
Acacetin	
Feruloyquinic acid 1	
Feruloyquinic acid 2	
3,4,5-Tricaffeoylquinic acid	[15,68]
Cirsilineol	[15,69,70]
Cirsimaritin	[15,67,71]
Skullcapflavon II*	[15]
Chrysoeriol-methyl-ether*	
Vitexin*	
5,3'-Dihydroxy-7,4'-dimethoxyflavanone*	
Tomentin*	
Chrysoeriol*	
Iristectorigenin A*	
Iristectorigenin B*	
Irigenin*	
Cirsiliol*	

Skullcapflavon I*	
Tectorigenin*	
Feruloylglucoside	
5,7-Dihydroxy-3',4',5'-trimethoxyflavone	
Dicaffeoyliquinic acid 2	
Dicaffeoyliquinic acid 3	

***** New compounds Identified in this material

II.3. Phenolic compounds

II.3.1. Definition

Phenolic compounds are natural secondary metabolites synthesized exclusively by plants. Found in fruits, vegetables, whole grains and other types of foods and beverages [72,73]. They are involved in plant growth, development and defense. Phenolics exhibit a wide range of health benefits such as strong antioxidant activity which confers antibiotic, anticancer, anti-inflammatory, antiallergic, antimutagenic, and cardioprotective properties [74–76].

They mostly ascend from a common origin, specifically, the amino acids phenylalanine or tyrosine [77]. They contain at least one aromatic ring with one or more attached hydroxyl groups [78]. They are usually found as glyco-conjugated forms, and are also linked to other molecules including organic acids, amines, lipids and other phenols [79].

II.3.2. Classification

Based on their chemical structure and complexity, polyphenols are generally classified into flavonoids and non-flavonoids [75,80].

II.3.2.1. Flavonoids

Flavonoids are the most commonly found polyphenols in the human diet [79]. They are composed of fifteen carbon atoms arranged in a C_6- C_3- C_6 configuration with a low molecular weight. The structure consists of two aromatic rings A and B, joined by a 3-carbon bridge, usually in the form of a heterocyclic [74,81,82]. Flavonoids may be divided into six subclasses: flavonols, flavones, flavanones, flavanols, anthocyanins, and isoflavones [83] shown in Table VI.

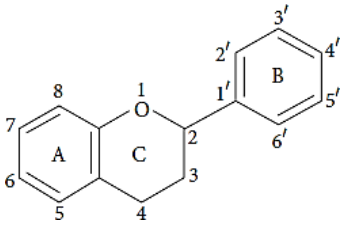
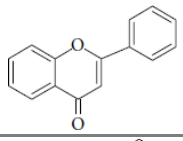
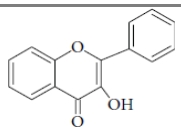
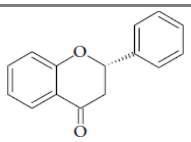
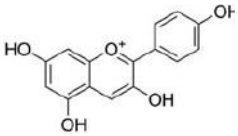
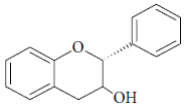
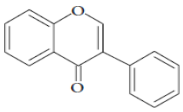


Figure 3. Basic flavonoid structure [84].

Table VI. Structure of flavonoids [84–86].

Subgroup of flavonoid	Structure Backbone	Examples	Food
Flavone		Luteolin, Apigenin, Chrysin...	Fruits, vegetables, cereals.
Flavonol		Quercetin, Kaempferol, Galangin...	Apples, cherries, berries, onions, tomatoes, broccoli and tea.
Flavonones		Hesperitin, Naringenin, eriodictyol...	Citrus fruits.
Anthocyanins		Cyanidin, delphinidin, malvidin...	Fruits.
Flavanols		Catechin, Epicatechin...	Apples, red grapes and tea.
Isoflavones		Genistein, Daidzein...	Legumes such as soybeans

II.3.2.2. Non flavonoids

The basic structure of non-flavonoids is a single aromatic ring. Non-flavonoid compounds include phenolic acids, stilbenes, and lignans [87].

II.3.2.2.1. Phenolic acids

Phenolic acids represent the main group of non-flavonoids [87]. They are characterized by a carboxyl group linked to a benzene ring [88]. The most important being C_6- C_3 derived from the hydroxycinnamic acid and C_6- C_1 compounds with a hydroxybenzoic structure [89,90]. Phenolic acids represent around one third of our dietary intake of polyphenols. They occur in all vegetables and fruits, especially in red fruits and onions [83].

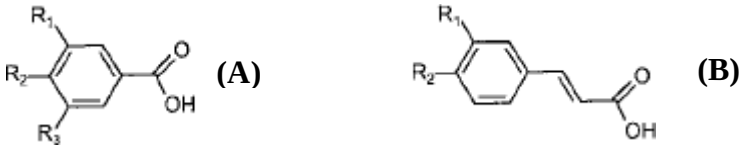


Figure 4. Phenolic acids sub-groups: Hydroxybenzoic (A) and Hydroxycinnamic acid (B) [76].

II.3.2.2.2. Stilbenes

Stilbenes consist of two phenyl groups linked by a methylene bridge [79]. They have a C_6- C_2- C_6 structure and are phytoalexins produced by plants in response to fungi and toxin attacks [91]. One of the most well-known stilbenes is resveratrol (3,5,4'- trihydroxystilbene), that is produced by several plants such as grapes, peanuts, and berries [92].

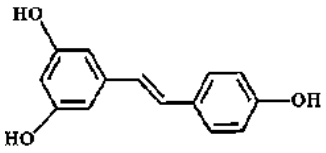


Figure 5. Stilbene chemical structure [79].

II.3.2.2.3. Lignans

Lignans are formed of two phenylpropane units [76]. Flaxseeds are the richest source of lignans [93]. When ingested, they are converted by intestinal microflora into two simple phenols: enterolactone and enterodiol [74,76].

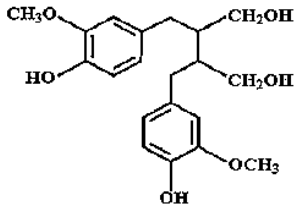


Figure 6. Lignan chemical structure [79].

II.4. Biological effects

Several experimental studies have reported the potential biological activities of different extracts of *A. herba alba*. Indeed, the aqueous extract was proven to have hypoglycemic, hypolipidemic, antioxidant, anti-nociceptive and anti-inflammatory activities [65,94]. Similarly, flavonoids from methanolic extract showed potential immuno-modulatory effects when supplemented *in vitro* in human cells [95]. Moreover, the hydromethanolic extract showed a moderate antibacterial activity against *Staphylococcus aureus*, *Bacillus thurigiensis* and *Aeromonas hydrophila* [14]; however, phenolic acids were effective against *S. aureus* [61]. In addition, hydroethanolic extract of *A. herba alba* was found to be effective against leukemia, bladder and larynx carcinoma cell lines [12]. Furthermore, a strong anticancer capacity was observed against MCF 7 breast cancer and HeLa human cervical cell lines [14]. Despite different yet interesting therapeutic profiles, we will only focus on the antioxidant, anti-inflammatory and anti-asthmatic activities of *A. herba alba* for the purposes of this thesis.

II.5. Anti-oxidant activity

II.5.1. Reactive Oxygen Spices

Reactive oxygen species (ROS) are molecules capable of independent existence, containing one or more oxygen atoms and at least one unpaired electron that occupies an atomic or molecular orbital by itself [96]. This group includes oxygen free radicals, e.g., superoxide anion radical (O_2•–), hydroxyl radical (–•OH), hydroperoxyl radical (HO_2•–), singlet oxygen ($^1O_2$), as well as free nitrogen radicals [97]. However, several ROS are regarded as non-radicals due to the absence of unpaired electrons, such as hydrogen peroxide (H_2O_2), peroxynitrite (ONOO•), hypochlorous acid (HOCl), and ozone (O_3) [96].

ROS can be generated endogenously (i.e. organelles, various enzymes...) and exogenously (i.e., cigarette smoke, ultraviolet light, pollutants, xenobiotics, etc.) [98,99]. ROS may regulate cellular homeostasis and act as prime modulators of cellular dysfunction, contributing to disease pathophysiology [100]. Exposure to exogenous and endogenous sources of ROS involved in the inflammatory process can induce oxidative stress and the oxidant/antioxidant imbalance [101].

II.5.2. Oxidative stress

Oxidative stress is defined as the increased production of free radicals and ROS and/or a decrease in antioxidant defense that leads to damage of biologic macromolecules and dysregulation of normal metabolism and physiology [98,102]. The main targets of oxidative stress are proteins, lipids, and DNA/RNA; however, modifications in these molecules may increase the chances of mutagenesis [103]. Multiple evidences show that oxidative stress may be responsible for several diseases including cancer, diabetes, and various airway respiratory disorders such as asthma [104,105].

II.5.3. Mechanisms of action

Several beneficial effects derived from phenolic compounds are mainly due to their antioxidant activity. With redox properties, they act as reducing agents, hydrogen donors, singlet oxygen quenchers and metal ions chelators [74]. As antioxidants, they oxidize into recyclable nontoxic oxidized molecules [106].

Polyphenol antioxidant activities are related to their capacity to scavenge a wide range of ROS. Indeed, the mechanisms involved in the antioxidant capacity of polyphenols include

suppression of ROS formation by either inhibition of enzymes involved in their production, or upregulation and protection of antioxidant defenses [103].

II.5.4. Antioxidant activity of *A. herba alba*

The *Artemisia herba alba* antioxidant activity is reported in the literature [66,107]. In fact, the response of antioxidants depends on many factors such as substrate, solvent affinity, substrate purity [108], reaction time, concentration, structure, and the interaction between the antioxidants in the mixture [64]. The most frequent methods used to estimate the antioxidant activity of *A. herba alba* were the scavenging activity of a free radical and the reducing power.

II.5.4.1. The scavenging activity

The scavenging activity is based on the scavenging of a free radical by *A. herba alba* extract or essential oil, then the absorbance is measured. Two free radicals were used in the experiments, DPPH (2.2 diphenyl 1 picryl hydrazyl) and ABTS (2,20-azinobis-3-ethylbenzothiazoline-6-sulphonate radical).

The scavenging activity of *A. herba alba* essential oil was found to be interesting [107,109,110] but weak in other studies [111,112]. Interestingly, hydromethanolic [12] and hydroethanolic [113,114] extracts showed high antioxidant activity. Indeed, Bourgou et al. (2016) reported that pure methanolic extract was more effective than the BHT (Butylated Hydroxytoluene) standard.

II. 5.4.2. The reducing power

The reducing power of *A. herba alba* essential oil [66,112,115], ethyl acetate, aqueous [14], and methanolic [66] extracts were assayed using ferric reducing antioxidant power (FRAP), based on the reduction of ferric iron ($Fe^{3+)}$ to ferrous iron (Fe^{2+}), then absorbance was measured [112]. The absorbance of the reaction mixture is proportional to reducing power [14].

The lowest activity was obtained in *A. herba alba* essential oil [66,112,115]. Recently, Aljaiyash et al. (2018) compared the reducing power of wild and cultivated *A. herba alba* essential oil and revealed a better performance in the cultivated one. Other results showed a moderate reducing power in methanolic [66], aqueous, and ethyl acetate [14] extracts.

Moreover, Orhane et al. (2010) tested the ferric chelating ability of acetone and ethanolic extracts and showed a chelating capacity lower than 50% against ferric ion.

The antioxidant activity variations of the essential oil may be explained by the dominance of non-phenolic compounds [111] and the absence of phenolic monoterpenes [66].

However, Zouari et al. (2010) demonstrated a high scavenging activity which may be related to the abundance of oxygenated terpenes. These differences may be related to essential oil composition which is influenced by many factors including the location, temperature, and the length of growing season [112].

The organic extracts revealed a higher antioxidant activity than essential oil and aqueous extract. This activity is mainly correlated with phenolic composition. Polyphenols and flavonoids are significantly associated with the antioxidant potency [14,58,61,116]. The antioxidant activity of phenolics is mainly due to their redox properties, which makes them act as reducing agents and hydrogen donors [12].

II. 5.5. Anti-inflammatory activity of *A. herba alba*

Inflammation is the adaptive response triggered by external noxious stimuli. Throughout its evolutionary process, the human body has developed multiple mechanisms to detect, respond to, and repair with the aim of maintaining homeostasis [117,118]. However, dysregulated inflammation has an important implication in chronic systemic damage that can result in inflammatory disorders such as cardiovascular disease, cancer, respiratory diseases or obesity [119]. At the tissue level, inflammation is characterized by redness, swelling, heat, pain, and loss of tissue function [120].

The nature of the stimulus and its location in the body determine the inflammatory response processes. A common pattern has been noticed in every inflammatory mechanism: first, cell surface pattern receptors recognize detrimental stimuli, then the inflammatory pathways are activated and the inflammatory markers are released, and finally the inflammatory cells are recruited [120].

In this context, lung inflammation diseases are linked to complex interactions among and between structural and immune cells. In cases of unresolved lung injury and chronic inflammation, frequently pulmonary conditions such as asthma are observed [120]. The implicated inflammatory immune cells in this pathogenesis are eosinophils and mast cells, but also include lymphocytes and neutrophils [17].

Several studies reported different biological activities of *A. herba alba*, however, very few investigated its anti-inflammatory activity using *in vitro* and *in vivo* methods.

II. 5.5.1. *In vitro* methods

The *in vitro* methods are based on immune cell culture, usually followed by an activation with lipopolysaccharides (LPS). To evaluate the anti-inflammatory potential of *A. herba alba* extracts, the production of nitric oxide (NO) was measured.

Abu-Darwish et al. (2015), tested the effect of *A. herba alba* essential oil on the macrophage (RAW 264.7) and microglia (BV2) cell lines. These inflammatory cells were stimulated with LPS to estimate the NO production by colorimetric reaction with the Griess reagent. This study showed that *A. herba alba* essential oil decreased the NO production in both cell lines.

In addition, methanolic extract of *Artemisia herba alba* were investigated in murine macrophages (RAW 264.7) stimulated by IFN-γ and LPS [12]. The results were expressed by the percentage of NO inhibition (NOi). The highest anti-inflammatory activities (72% and 100% NOi) were reported at 150 and 600 mg/L of extract. In addition, the mRNA expression of induced nitric oxide synthase (iNOS) was measured by quantitative real-time PCR on cell extracts and revealed a correlation with the inhibition of NO production [12].

Furthermore, flavonoids from *A.herba alba* hydroethanolic extract were tested on a culture of peripheral blood mononuclear cells (PMBCs) and neutrophil cells (NCs) from patients with Adamantiades-Behçet's disease (ABD) which is an inflammatory multisystemic disorder. These experiments highlighted that flavonoids decreased NO concentration. The same cells were treated with different concentrations of *A. herba alba* flavonoids using enzyme linked immunosorbent essays (ELISA) to investigate the effect of concentration of these flavonoids on IL-12 and IL-4 release. This showed that flavonoids stimulated the production of IL-4 and reduced the production of Il-12 in a dose-dependent manner [121].

Nitric oxide is an inflammatory marker in asthma [122], and inhibition of its production could attenuate asthma features.

II. 5.5.2. *In vivo* methods

Carrageenan-induced edema is one of the used methods to assess the anti-inflammatory activity in animal models. For example, different groups of adult rats were treated with *A. herba alba* extracts. The anti-inflammatory activity of *A. herba alba* extracts was examined by measuring the volume of inflamed rat's paws compared to controls.

In a study by Qnais et al. (2014), carrageenan was injected in the right hind foot followed by different doses of *A. herba alba* aqueous extract, astragalin and eupatilin (isolated from this plant), physiological saline solution, or indomethacin as an anti-inflammatory drug in each group. Then the inflammation intensity was quantified by measuring the paw's displayed volume using a plethysmometer at different time points.

As a result, the aqueous extract, astragalin and eupatilin showed an anti-inflammatory effect by a significant reduction of the paw's swelling which may be due to inhibition of the synthesis and/or production of inflammatory mediators. Statistically significant inhibition of edema exerted by aqueous extract was found to be a dose-dependent and astragalin and eupatilin in doses of 100 mg/kg provided anti-inflammatory effects comparable to those produced by 10 mg/kg indomethacin [94].

Another study examined the oral administration of *A. herba alba* ethanolic extract at different concentrations in rats, 1h after injection with carrageenan solution in a sub-planter area. Normal saline solution and indomethacin were used as controls and the measurement of the paw volume was done by a plethysmometer [57]. Interestingly, *A. herba alba* ethanolic extract showed an inhibition of paw edema by 46.8, 35.0 and 62.5% at doses of 400, 200 and 100 mg/kg, respectively [57].

Biomolecules of interest found in *Artemisia herba alba*

III. Molecules

Various secondary metabolites have been isolated from *A. herba alba*. Many studies related the biological activities of *A. herba alba*, specifically antioxidant [14,15,65] and anti-inflammatory [12,94] activities, to its phenolic compounds. In fact, flavonoids and phenolic acids from various plant extracts were tested in cell cultures [123,124] and animals [125,126], as *in vitro* and *in vivo* models, respectively, to investigate their effects and therapeutic potential in inflammatory diseases.

On the other hand, essential oil products containing biogenic volatile organic compounds like terpenes are associated with respiratory symptoms, sensitivity, and asthma. Indeed, some essential oils as lavender and tea tree are found to have adverse effects by forming allergens due to autoxidation [127]. Moreover, terpenes from essential oils were involved in many reactions that lead to tissue damage and further pro-inflammatory mediators [128]. No data were found on the effect of *A. herba alba* essential oil on lung diseases or asthma. Therefore, we decided to only highlight molecules from organic and aqueous plant extracts in this thesis.

The most redundant molecules, with great potential as cited in the literature, are listed below:

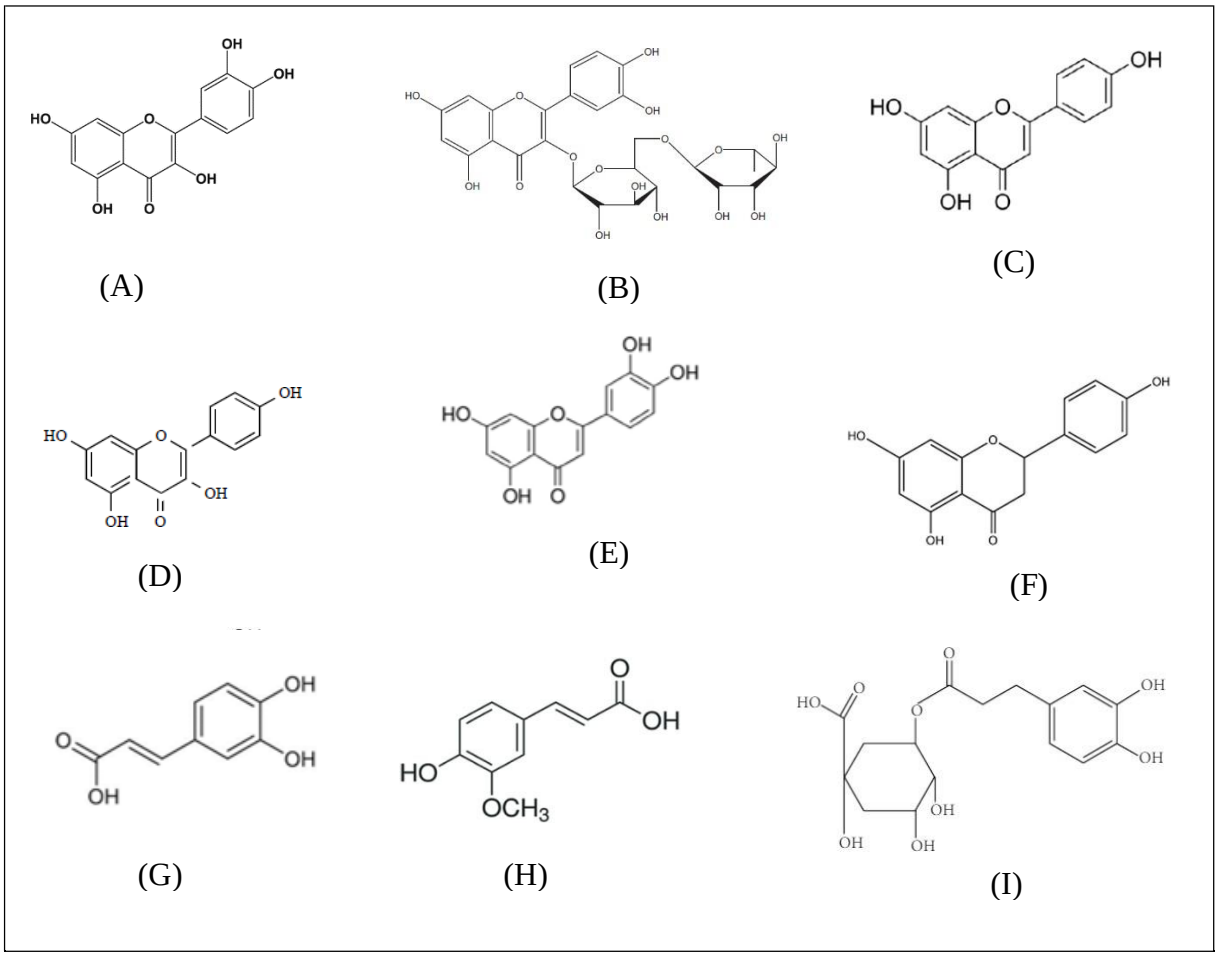


Figure. 7 Molecules of interest found in *Artemisia herba alba*: A) Quercetin, B) Rutin, C) Apigenin, D) Kaempferol, E) Luteolin, F) Naringenin, G) Caffeic acid, H) Ferulic acid, I) Chlorogenic acid.

III.1. Quercetin

Quercetin (3,3′, 4′, 5, 7- pentahydroxyflavone) is a naturally occurring flavonoid (Figure 5 (A)) that belongs to the flavonol group and is commonly found in many fruits and vegetables [129] including tea, onions, apples and red wine [130].

Quercetin was reported as one of the important compounds in *A. herba alba* methanolic extract [66]. This flavonol exhibited interesting antioxidant [84] and anti-inflammatory activities [84,131] through different mechanisms including radical scavenging, metal chelating, affectation of certain enzymes involved in the generation of inflammatory processes particularly tyrosine and serine-threonine protein kinase, etc. Moreover, quercetin showed anti- asthmatic activity in conscious guinea pigs ovalbumin (OVA)-sensitized, via inhibition of the specific airway resistance in both immediate and late-phase asthmatic responses and decreased recruitment of neutrophil, eosinophil, lymphocyte cells in BAL [125].

Furthermore, 3-O-Methylquercetin exerted an anti-inflammatory effect [123,125,126]. According to Ko et al. (2004), it induced the inhibition of iNOS DNA transcription and bronchodilation in BALB/c mice model and guinea pig OVA- sensitized trachea cells. In addition, it inhibited mast cell degranulation and histamine release [125,126].

III. 2. Rutin

Rutin (quercetin-3-O-rhamnosylglucoside) is a natural flavone (Figure 5(B)) derivative [132]. It is widely distributed in nature in various vegetables and fruits such as the passion flower, buckwheat, green asparagus, apples, and tea. Rutin is composed of quercetin and rutinose. It is also called vitamin P [133].

Rutin was isolated in the ethanolic [134] and aqueous extracts [135] of *A. herba alba*. It was reported to exhibit high antioxidant, free radical scavenging and anti-inflammatory activities [133,136]. It showed a significant inhibitory effect on rat paw edema formation [132]. Moreover, the anti-asthmatic activity of rutin in the OVA-induced BALB/c mice model showed great results by reducing the inflammatory cells, decreasing IgE levels in serum, improving airway function and reducing AHR [125], and restoring the normal lung histology by suppressing eosinophil and neutrophil infiltration [137,138].

Despite the fact that rutin and quercetin possess the same effects on the inflammatory process, rutin was shown to be less effective than quercetin [125], which may be attributed to its slow absorption due to the presence of a rutinoside in position 3 of the C ring [139,140].

III.3. Apigenin

Apigenin, (4', 5, 7-trihydroxyflavone), is a naturally occurring flavone (Figure 5(C)) that is found in abundant amounts in herbs and vegetables such as chamomile, thyme, parsley, and broccoli [141]. It has revealed a strong antioxidant activity that contributes to its anti-inflammatory properties [142].

Interestingly, some studies have reported high levels of Apigenin in ethyl acetate [61] and methanolic [66] extracts of *A. herba alba* collected in Algeria and in Tunisia, respectively.

Apigenin inhibited NO production in both LPS-activated RAW 264.7 [143] and human lung epithelial cells [124], exhibiting a strong anti-inflammatory activity. It also showed anti-asthmatic activity by decreasing inflammatory cell infiltration, AHR, and total IgE levels [144].

III.4. Kaempferol

Kaempferol (3,5,7,4'-tetrahydroxyflavone) is a yellow compound (Figure 5(D)) that is found in various plant parts, such as seeds, leaves, fruits, flowers, and vegetables. Importantly, it was found in plants used in traditional medicine [145,146]. Kaempferol and its glycosylated derivatives have been shown to be anti-inflammatory, antioxidant, and have anticancer activities [146].

Interestingly, a high level of kaempferol was found in *A. herba alba* methanolic extract from the Kef region in Tunisia [66].

Many studies have reported the antiallergic and anti-asthmatic activities of kaempferol [147–150], which include inhibiting the release of inflammatory mediators such as IL-8 [147] and histamine [150], decreasing eosinophilic infiltration in the airways [148], and inhibiting mucus secretion [149] in OVA-associated allergic asthma in BALB/c mice.

Moreover, astragalin, a 3-O-glucoside of kaempferol found in the aqueous extract of *A. herba alba*, exhibited significant antinociceptive and anti-inflammatory properties in carrageenan-induced paw edema by suppressing the synthesis and/or production of inflammatory mediators such as histamine, prostaglandins, serotonin, and cytokines (such as TNF-α), blocking the infiltration of neutrophils and production of neutrophil-derived free radicals [94]. Indeed, astragalin, was found to inhibit LPS- and H_2O_2-induced oxidative stress in airway epithelial cells [151].

In addition, kaempferol has been shown to alleviate airway inflammation and has demonstrated its potential role as a therapeutic agent for asthmatics [148].

III.5. Luteolin

Luteolin (3′,4′,5,7-tetrahydroxyflavone) is a natural flavonoid (Figure 5(E)) widely found in the plant kingdom belonging to the flavone group. Celery, broccoli, and apple skin are among the richest fruits and vegetables in luteolin [152].

Luteolin is found in high concentrations in *A. herba alba* ethyl acetate and chloroform extracts [61]. This flavone exhibited a strong antioxidant activity [61,153,154] through its scavenging ability, chelation capacity, inhibition of pro-oxidant, and by inducing antioxidant enzymes [155]. It also showed anti-inflammatory activity in mouse alveolar and peripheral macrophage cells by inhibiting inducible nitric oxide synthase expression (iNOS), NO

production, scavenging, and inhibiting ROS. Furthermore, luteolin reduced the release of LPS pro-inflammatory cytokines in macrophages [153].

Furthermore, luteolin exerted an anti-asthmatic effect on human mast cells by decreasing the release of inflammatory mediators (histamine and prostaglandin) [156]. Additionally, it showed noticeable attenuation of asthmatic features during and after sensitization in an experimental mice BALB/c model [157].

III.6. Naringenin

Naringenin (4',5,7-trihydroxyflavanone) is a natural flavanone (Figure 5(F)) predominantly found in some edible fruits like citrus, tomatoes, cocoa, and tangerines [158].

Naringenin was isolated in *A. herba alba* methanolic extract [14]. It showed an antioxidant activity by downregulating ROS production [159] and scavenging free radicals [160]. It also exhibited an anti-inflammatory activity by reducing oxidative stress, increasing antioxidant enzymes in rats [158,161], and reducing iNOS expression and gut edema in an induced colitis model in mice [162].

Additionally, it showed anti-asthmatic activity in BALB/c mice model by lowering subepithelial fibrosis, smooth muscle hypertrophy, and lung atelectasis [163], attenuating acute airway inflammation, and reducing AHR [164].

III.7. Caffeic acid

Caffeic acid (3,4-dihydroxycinnamic acid; Figure 5(G)) is a phenolic acid, frequently occurs in fruits and coffee beans [165,166]. It was found in ethyl acetate [61] and methanolic extracts [66] from *A. herba alba.*

Caffeic acid showed a broad spectrum of biological activities including an interesting antioxidant activity through its metal chelating property and radical scavenging [165–167], an anti-inflammatory capacity by suppression of pro-inflammatory cytokines [165,168,169] and anti-asthmatic activity by decreasing inflammatory cells in spleen cell culture [170] and in a BALB/c asthma model [168,170].

III.8. Ferulic acid

Ferulic acid (trans-4-hydroxy-3-methoxycinnamic acid; Figure5(H)) [171] is abundantly found in vegetables and grains, such as rice bran, nuts, tomatoes, carrots, artichokes, and sweet corn [172].

Moderate levels were found in methanolic [66] and ethyl acetate extracts of *A. herba alba* [173].

Ferulic acid has various biological activities such as antioxidant, anti-inflammatory, vasodilatory actions, metal chelation, and modulation of enzyme activity [174].

The antiallergic potential was demonstrated by suppression of OVA-specific IgE production and proinflammatory cytokine reduction in an asthmatic mouse model [171]. Similarly, Singer et al. (2017) speculated the anti-asthmatic potential of ferulic acid treatment in an OVA-induced pulmonary allergy murine model via decreasing lung and airway inflammation, eosinophil infiltration, mucus production and serum levels of OVA-specific IgE. These results were associated with lower levels of some chemokines and cytokines such as IL-4, IL-5, IL-13.

III.9. Chlorogenic acid

Chlorogenic acid (Figure 5(I)) is an ester of quinic acid with one of the cinnamic acids: caffeic, ferulic and p-coumaric acids. It is widely found in coffee, and in beverages prepared from herbs, fruits and vegetables [175]. It is also characterized as one of the important polyphenols found in Asteraceae family [176].

According to Bourgou et al. (2016), the methanolic extract of *A. herba alba* collected from the Kasserine region in Tunisia, has encountered a great proportion of chlorogenic acid. It was also found in aqueous extract from the M'sila region in Algeria [62] and in hydroethanolic extract from Morocco [177].

Chlorogenic acid found in most natural products demonstrated anti-inflammatory effects and may be a noteworthy anti-oxidative agent [178]. Additionally, in an OVA-induced asthma model in mice treated with chlorogenic acid, there was a decrease of relevant inflammatory features such as pulmonary eosinophilia, serum total, and OVA-specific IgE concentration which may reduce asthmatic symptoms as well as the incidence of asthma [179].

Conclusion

A. herba alba showed a rich phenolic profile as previously described in the literature. Total polyphenol yield varies depending on geographic location, solvent extraction, harvest time, and growth stage.

The biomolecules usually found in methanolic extract are quercetin, naringenin, caffeic acid, apigenin, ferulic acid, chlorogenic acid and kaempferol. Rutin was only found in ethanolic and aqueous extracts [134,135]. Luteolin, caffeic acid, apigenin and ferulic acid were also found in ethyl acetate extract [61]. In the chloroform extract, only luteolin was found. In the light of these results, methanol seems to extract most of the biomolecules.

Conclusion & perspectives

Conclusion & perspectives

In addition to the side effects and high cost of the current treatments for asthmatics, asthma as a chronic inflammatory lung disease is associated with elevated mortality and morbidity rates. Our research project's aim was to review and discuss the therapeutic potential of *A. herba alba* as alternative treatment in asthma.

A. herba alba is a medicinal plant used by different populations, especially North African and Middle East, in treating diabetes, bronchitis, diarrhea, heart ailments, respiratory diseases among other disorders.

A. herba alba is rich in bioactive compounds reported to have anti-inflammatory and/or anti-asthmatic effects. Indeed, important anti-inflammatory and anti-asthmatic activities were shown due to its abundance in phenolic compounds including flavonoids, thereby confirming its traditional use as an herbal medicine. Interestingly, quercetin, rutin, apigenin, kaemferol, luteolin, naringnin in addition to caffeic, ferulic, and chlorogenic acids demonstrated high anti-inflammatory activity. Methanol seemed to extract most of these biomolecules, which exhibited noteworthy antioxidant and anti-asthmatic activities.

A. herba alba may be a good candidate for complementary or alternative treatments in asthma, however, further investigations are needed to examine its effect on asthma in animal models and to determine the involved molecular mechanisms.

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