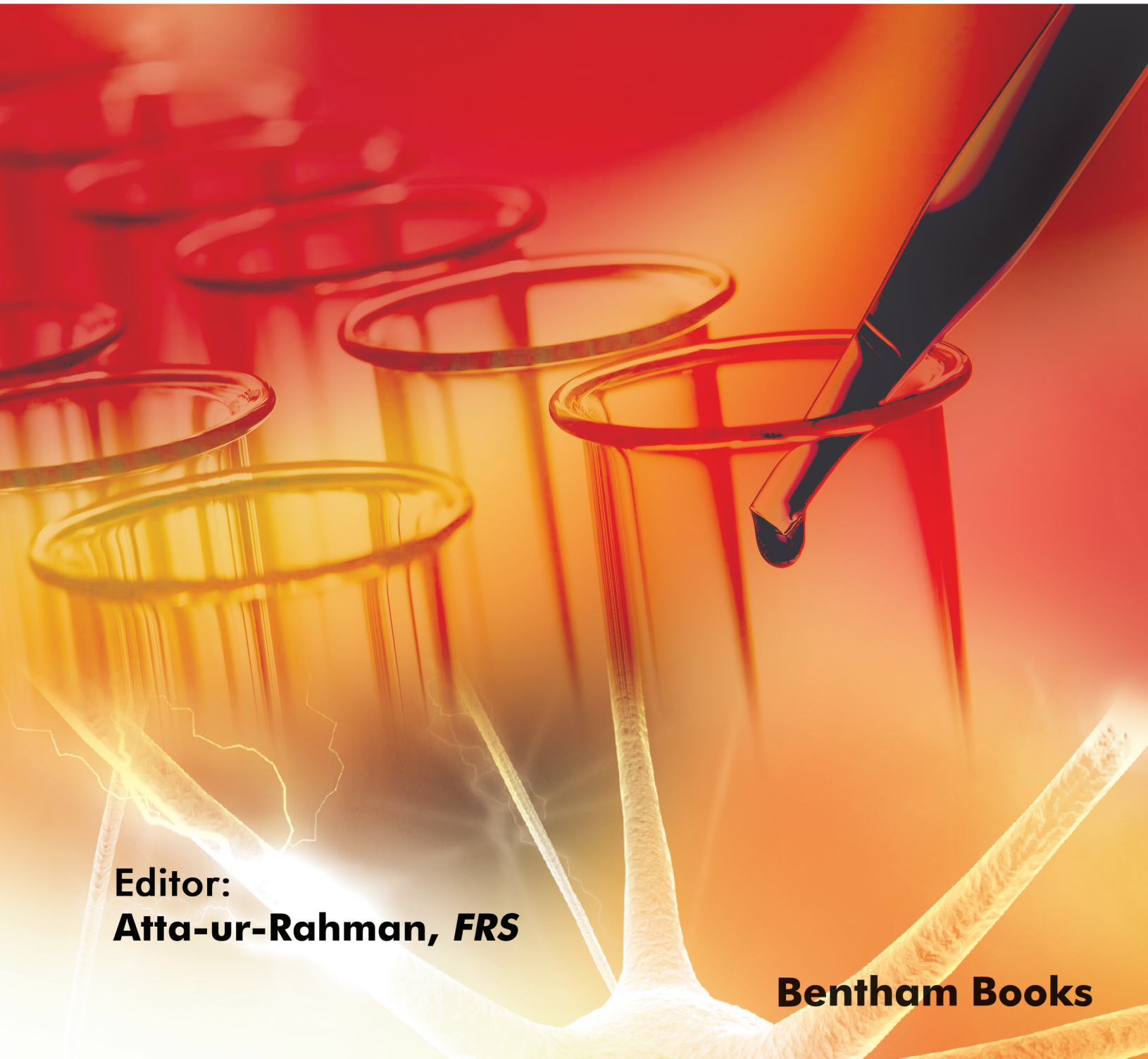
Frontiers in Clinical Drug Research

Anti Allergy Agents



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Frontiers in Clinical Drug Research – Anti Allergy Agents

(Volume 5)

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PREFACE

Frontiers in Clinical Drug Research - Anti Allergy Agents (Volume 5) comprises five comprehensive chapters on various treatment strategies for allergic conditions.

In chapter 1, Ozkan and Bakar Ates have doscussed the multi-faceted roles of resistin in cellular events as well as its contribution to allergic and inflammatory diseases. Khan *et al*., in chapter 2 of the book have focused on asthma in adults, its evaluation, prevalence, and clinical management. In the next chaptet, Ameta *et al*., discuss the role of nitrogen-containing heterocycles as anti-allergy agents. Boskabady *et al*., in chapter 4, present the experimental and clinical studies on the effects of Nigella sativa and its constituents on allergic and immunologic disorders. In the last chapter, Rezabakhsh and Soleimanpour summarize the new achievements and novel findings of recent clinical advances related to the desensitization approaches following aspirin consumption in patients with coronary artery diseases (CADs).

I hope that this volume will be of great interest to the scientific community and will play a vital role in the development of more effective therapeutic agents to combat various pulmonary ailments.

I would like to thank all the authors for their contributions and the excellent team of Bentham Science Publishers, particularly Mr. Mahmood Alam (Editorial Director) and Ms. Asma Ahmed (Senior Manager Publications), for their support and hard work.

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CHAPTER 1

Resistin: An Irresistible Therapeutic Target for Inflammatory Diseases, Allergy-Related Disorders, and Cancer

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Abstract: Resistin is a cytokine that has gained popularity over the last decade for its roles in allergic and inflammatory reactions. It is a cysteine-rich protein secreted mostly by macrophages in humans and adipocytes in mice. It was first identified as a small molecule that mediates insulin resistance in rodents. Following the discovery of resistin, many researchers have started investigating its activity in a wide range of pathological conditions where inflammation is present. Findings from these studies have revealed that resistin serves a major function in almost all inflammatory diseases. Elevated serum resistin levels have been associated with allergic contact dermatitis, atherosclerosis, osteoarthritis, obesity, neurological and cognitive disorders, and cancer. Therefore, it is critically important to understand the exact role of resistin in these pathological conditions to develop an effective therapeutic approach. So far, four receptors are known to interact with resistin. Two of these receptors, toll-like receptor 4 (TLR4) and adenylyl cyclase-associated protein 1 (CAP1), are present on the membrane of human macrophages. The other two receptors, receptor tyrosine kinase-like orphan receptor 1 (ROR1) and decorin (DCN), are found in mice. Even though it is possible that ROR1 exists in humans, too, there is still an open question regarding other receptors that interact with resistin in humans. However, accumulated data suggest that resistin is involved in multiple signaling pathways *via* binding to TLR4 and CAP1. This chapter aims to elaborate on the multi-faceted roles of resistin in cellular events as well as its contribution to allergic and inflammatory diseases with a focus on cancer formation based on the current and most recent findings.

Keywords: Adipokines, Allergy, Cancer, CAP1, Cytokines, Diabetes, IL-6, Inflammation, Resistin, TLR4, TNF-α.

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INTRODUCTION

In 2001, a group of researchers discovered a unique peptide while investigating adipocyte-derived factors that cause insulin resistance. They named this unique compound 'resistin' because it was highly expressed in obese mice with insulin resistance, and its downregulation improved insulin sensitivity [1]. Following the identification of resistin, the same research group did further analyses to find its homologs based on its unique structure and discovered a family of resistin-like molecules (RELMs) in both humans and rodents. Each identified member of this family (resistin, RELMα, RELMβ) was found in different tissues with possible different functions [2]. Interestingly, a different research group discovered the same family of proteins simultaneously while screening for molecules associated with allergic inflammation in mice with ovalbumin-induced asthma, and they named these novel compounds 'found in inflammatory zone' or FIZZ in short [3].

In the decade following the discovery of resistin, numerous studies were conducted in order to illuminate its roles and functions in the pathogenesis of various inflammatory disorders. Data obtained so far have demonstrated a potential benefit in targeting resistin in metabolic diseases in which immune cells are most active. This chapter aims to present current findings regarding the role of resistin in inflammatory and allergic disorders as well as its association with cancer development.

RESISTIN

Structure and Function

Resistin is a 12.5 kDa polypeptide that consists of 108 amino acids in humans and 114 in mice. It was the first identified member of the RELM family. The other members, RELMα, RELMβ, and RELMγ, are found in different tissues with diverse functions. Among these, only resistin and RELMβ exist in humans [4].

The general structure of resistin, as well as the other RELM proteins, consists of 3 main domains: a cleavable N-terminal signal sequence, a variable middle section, and a cysteine-rich conserved C-terminal region (Fig. **1**) [2, 5]. The C-terminal, which constitutes almost half of the entire molecule, is the signature sequence that makes RELM members unique peptides and is responsible for stabilizing the structure as well as binding to receptors [2, 6]. It has been reported that resistin and RELMβ contain an additional cysteine residue in N-terminal, which is necessary for multimerization. Due to this extra cysteine, resistin can have a trimer and a hexamer form by disulfide bonding, both of which can be found in serum [7]. The diversity of RELM proteins can be attributed to different coding genes (RETN) present in different species. For instance, mice have four different

RETN genes (Retn, Retn1a, Retn1b, Retn1g), while humans have two (Retn and Retn1b) [4]. Furthermore, single nucleotide polymorphisms of RETN have been reported in humans and are associated with varying impacts on metabolic disorders such as obesity and diabetes [8].

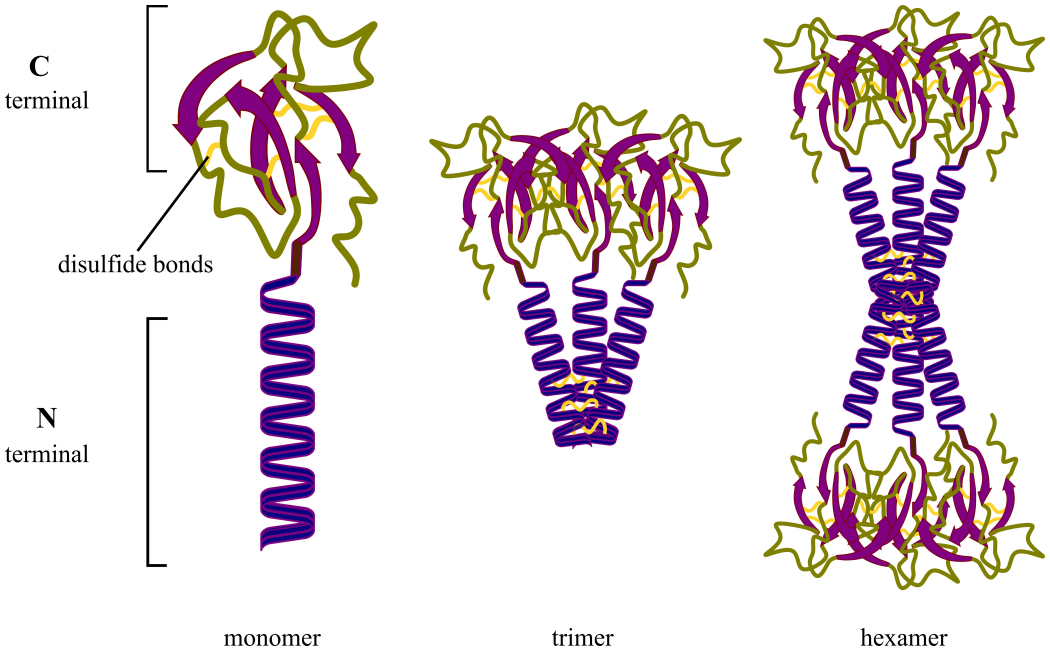

Fig.(1). A representation of the structure of resistin in monomer, trimer, and hexamer forms.

Current data on the function of RELM proteins are very limited. However, resistin has received much attention and has been well-studied in recent years due to its close relationship with inflammation and diverse roles in various pathologies. So far, 4 receptors have been reported to interact with resistin: toll-like receptor 4 (TLR4), adenylyl cyclase-associated protein 1 (CAP1), receptor tyrosine kinase-like orphan receptor 1 (ROR1), and decorin (DCN). In humans, mainly TLR4 and CAP1 receptors are expressed, while the other two are predominantly found in mice [4]. These receptors and their downstream signaling pathways have been explored in numerous studies and are still being investigated for their potential to develop new treatment strategies. The binding of resistin to TLR4 stimulates TNF receptor-associated factor 6 (TRAF6) *via* the MyD88-dependent signaling pathway, leading to the phosphorylation and activation of p38mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) signaling pathways. Resistin can also activate p38-MAPK and NF-κB *via* binding to CAP1, which then upregulates cyclic AMP (cAMP) concentration and protein kinase A (PKA)

CHAPTER 2

Asthma in Adults: Evaluation, Prevalence, and its Clinical Management

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Abstract: Asthma is among the world's most common severe lung disorders, affecting one-third of the world's population with incidence ranging from 4.9% to 12.7%. Around 3.5 million people die annually due to the worse health effects of asthma. Men (6.2%) have been seen to be less prevalent than women (10.4%) internationally. As a product of inflammation and super sensitivity, asthma is a multifactorial condition with symptoms such as cough, shortness of breath, wheezing, and chest pain. There are a number of agents that may be responsible for the development of asthma.This includes air pollution, obesity, bacteria, viruses, fungi, flu germs, dust, pollen, tobacco, smoking, exercise, depression, anxiety, allergic agents, physical and emotional stress. Depending on the susceptibility of the individual, asthma showed mild to serious results. For a deeper understanding of disease pathogenicity, mechanistic mechanisms should concentrate on a number of aspects like metabolic abnormalities, molecular genetics, inflammatory asthma complexity, *etc*. Commensal micro biota is one of the main factors that cures disease and has a major role in balancing the immune system in the gut and lung. In addition to the foregoing, potential indicators include serum IgE, a number of bloodstream eosinophil or levels of sputum eosinophil, FeNO (fractional exhaled nitric oxide), and serum periostin are presently employed in the asthma diagnosis. The two key therapies available on the basis of disease severity for patients are oral corticosteroids and bronchodilators. However, steroid-based therapy has certain side effects, such as elevated BP, adrenal suppression, and bone weakening. Due to this, we should target non-steroid medications, including anti-cholinergic medication (Tiotropium) and biological therapy. For serious asthma patients, various new medications (such as Anti-IL-4, Anti-IL-5, Anti-IL-13, and Anti-IgE therapy) have been used and found effectiveTo select the right medication and system for a better

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treatment plan, asthma patient requires proper review such as guidance, constancy, advice, drug alert, refill warning, notification warning, *etc*.

Keywords: Allergy, Anti-Cholinergic, Asthma, Biomarkers, Bronchodilators, Corticosteroids, Immunesystem, Inflammation, Micro biota, Wheezing.

INTRODUCTION

Allergic diseases are widespread, can have a major effect on a patient's physical and mental health ultimately affecting an individual's standard of living. Recent epidemiological studies show that the prevalence of such diseases is still increasing and they discover novel signs and symptoms for the progression of disorder (atopic/allergic) in youngsters [1, 2]. It is found in both well-established [3] and emerging [4] countries, bolstering the notion that asthma is partly an allergenic condition. Asthma is a severe lung disorder that is marked by bronchial hyper-responsiveness, reversible airflow restriction, and symptoms such as wheezing, chest tightness, and cough [5]. These symptoms are frequently episodic in nature and can differ in severity due to changes in stimuli, including allergens, airway pathogens, or respiratory illnesses such as allergic rhinitis and sinusitis [6]. Upper airway symptoms should be elicited because they may reflect different presentations of similar allergy aetiology.

Asthma accounts for about 1.1% of all disability adjusted life years (DALYs) loss globally [7]. According to the latest statistics, 623 million individuals suffer from asthma related symptoms, with 250,000 individuals who die every year as a result of this disease [8]. Asthma is projected to have the highest economic losses among chronic disease patients due to high healthcare use. Many studies have indicated that poor asthma regulation, individual vulnerability, fungal inflammation, pathogen consumption, ambient tobacco smoke (ETS) susceptibility, and exposure to air pollution from ozone (O_3), sulphur dioxide (SO_2), nitrogen dioxide (NO_2), and particle matter (PM) cause or aggravate asthma [9]. New treatments such as omalizumab for asthma and urticaria have been tested and approved in recent years, which have now become real-life experiences for patients and clinicians, are providing long-term data.

EPIDEMIOLOGY

Asthma is significantly more prevalent in females (10.4%) who had much higher rates of asthma related to males (6.2%) [10]. The prevalence varies significantly from 4.9% to 12.7% geographically [11]. Asthma is traditionally considered to be a disease that starts in the youth. Despite the fact that asthma has been most commonly diagnosed in children, this could develop significantly at whatever

time of life. According to national data, the incidence of asthma first appears in people over the age of 65, which have a 7% prevalence of asthma in comparison to overall asthma cases. Precocious history, initial chest infections, rhinitis, tobacco, and overweight have all been associated with adult-onset asthma [12].

WHAT IS AN ALLERGY?

Your immune system is in charge of protecting yourself against germs and viruses. Meanwhile, when you do have allergies, a part of our defense system is overworked. This can target innocuous things inside your nasal, chest, eyeballs, and under your skin like cat dander or pollen. When the body is exposed to an allergen, it (body) produces molecules known as IgE antibodies. Substances such as histamine are also released, which cause swelling and inflammation. When your body attempts to eliminate the allergen, a sign including a bad cold, eye irritation, and coughing can occur.

FORM OF ASTHMA

There are two forms of asthma that usually affect adults. The first form of asthma is allergic asthma/ Early-onset asthma which is closely linked to allergens. Early-onset asthma is asthma that begins during puberty and is typically followed by allergic rhinitis and/or atopic dermatitis. The second form of asthma is intrinsic (eosinophilic) asthma/ Adult-onset or late-onset asthma which frequently develops in adulthood and is unrelated to allergens [13]. Increased levels of certain types of cytokines and eosinophil granulocytes in both forms of asthma, as well as structural cell abnormalities, are found.

CONTROL AND SEVERITY OF ASTHMA

Asthma control is the main objective of treatment, and to fulfil this objective, a lot of weight is given to the clinical setting. For the assessment of disease management, various questionnaire forms have now been approved [14 - 17]. The Asthma Therapeutic Assessment Questionnaire (http://www.asthmacontrol-check.com/asthmacontrol/asthmacontrolcheck/consumer/index.jsp) [18], the Asthma Management Questionnaire (http://aafa.org/pdfs/SWP percent 20final% 20questionnaire.pdf) [19], and an Asthma Control Test (http://www.asthma control.com) [20] give verified asthma regulate “scores” which could be useful to categorise asthma in three groups: well controlled, not well controlled, and extremely poorly controlled [21].

According to disease management standards, determining the pathogenicity is necessary to begin treatment and maintain it in a step-by-step way [22]. Misinterpretation of severities can result in either misuse or excessive use of anti-

CHAPTER 3

Nitrogen-containing Heterocycles as Anti-allergy Agents

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Abstract: Nitrogen-containing heterocycles exhibit a diverse range of biological activities and are widely explored and utilized by the pharmaceutical industry for drug discovery. There are a lot of synthesized N-Containing heterocyclic compounds that showed antiallergic/antihistamine activities. A series of imidazole derivatives (Such as cimetidine), benzimidazole derivatives (Such as Astemizole, Bilastine, Emedastine, Mizolastine, and Clemizole), and 2-methylpropanamide and benzamide derivatives of carboxyterfenadine are synthesized and evaluated as H_1 antihistamine activity. Quinazolinone derivatives, pteridinones related compounds, and piperidine derivatives (such as Fexofenadine) also have strong antihistamine activity with a low sedative effect. Antihistaminic activity of the synthesized compounds was studied on the histamine-induced contractions of guinea-pig ileum tissues.

Keywords: Anti-allergic, Antihistaminic, Drugs, Heterocycles, Nitrogen.

INTRODUCTION

Histamine is a physiologically active β-imidazolylethylamine derivative found in many tissues, including mast cells, basophils, lymphocytes, neurons, and gastric enterochromaffin-like cells [1 - 4]. Histamine is a major mediator of the allergic and inflammatory process and also has significant roles in regulating gastric acid secretion, neurotransmission, and immune modulation [5]. It is synthesized from the amino acid histidine in a decarboxylation reaction with the enzyme histidine decarboxylase [6, 7]. Histamine exerts its actions by combining with specific cellular receptors located on cells. Histamine receptors belong to the family of G-protein coupled receptors (GPCRs). The subtypes of histamine receptors are H_1, H_2, H_3, and H_4 [8 - 15].

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H_1 receptor is found on endothelial cells, smooth muscle, heart, adrenal medulla, and CNS [16]. It causes bronchoconstriction, vasodilation, separation of endothelial cells (responsible for hives), local tissue redness and swelling, *etc*. H_2 receptor is located on gastric parietal cell, vascular smooth muscles, and CNS. It regulates gastric acid secretion and inhibits IgE-dependent degranulation. H_3 receptor distributed in central and peripheral nerve endings of the presynaptic membrane inhibit histamine synthesis and release. H_4 receptor is highly expressed in bone marrow, spleen, small intestine, and WBC. It plays a role in chemotaxis [5, 16 - 23].

Allergy is defined as an overreaction of the immune system to external harmless substances (allergens). The common allergens are pollen, dust, animal dander, mites, chemicals, drugs, insect venom, and various foods. The common allergic reactions include skin redness and swelling, itching, rash, patches, allergic rhinitis, laryngeal edema, systemic anaphylaxis, bronchial asthma, atopic dermatitis, and other symptoms [24 - 30].

A drug that reduces or blocks the effects of chemical mediators (in particular Histamine) of mast cells is called antihistamine (H_1 receptor antagonists)/anti-allergic drugs. Currently, the H_1 receptor antagonists are used in clinical practice as anti-allergic drugs. The H1 antagonists are mainly classified into three types:

i. **First-generation H_1 receptor antagonists**- these are the classical drugs such as piperazine derivatives (cyclizine & meclizine), propylamine derivatives (chlorpheniramine), and ethylenediamine derivatives (tripelennamine & methapyrilene), *etc*. The main adverse effect of 1st generation antagonist is sedation and cross the blood-brain barrier.
ii. **Second-generation H_1 receptor antagonists**- these are largely free from sedation and do not cross the blood-brain barrier. For example- fexofenadine, loratadine, desloratadine, levocetirizine, cetirizine, azelastine, *etc*.
iii. **Third generation (newer) H_1 antagonist** s- these are active metabolite derivatives or active optical isomers of second-generation drugs. They are safe and have minimum side effects [31 - 34].

Most of the drugs belong to the class of heterocyclic compounds. Heterocyclic compounds played a vital role in medicinal chemistry. Among heterocyclic compounds, the nitrogen-containing heterocycles exhibit a diverse range of biological activities and are widely explored and utilized by the pharmaceutical industry for drug discovery.

Several synthesized five and six-membered N-containing heterocyclic compounds have shown anti-allergic/anti-histamine activities. The structures of many

marketed drugs that are recently used as anti-histamine drugs are bilastine, astemizole, mizolastine, emedastine, clemizole (benzimidazole derivatives), cimetidine (imidazole derivatives), cetirizine and fexofenadine (piperidine derivatives), *etc*. All these molecules contain different N-heterocyclic moieties (Fig. **1**) [31, 33, 35 - 39].

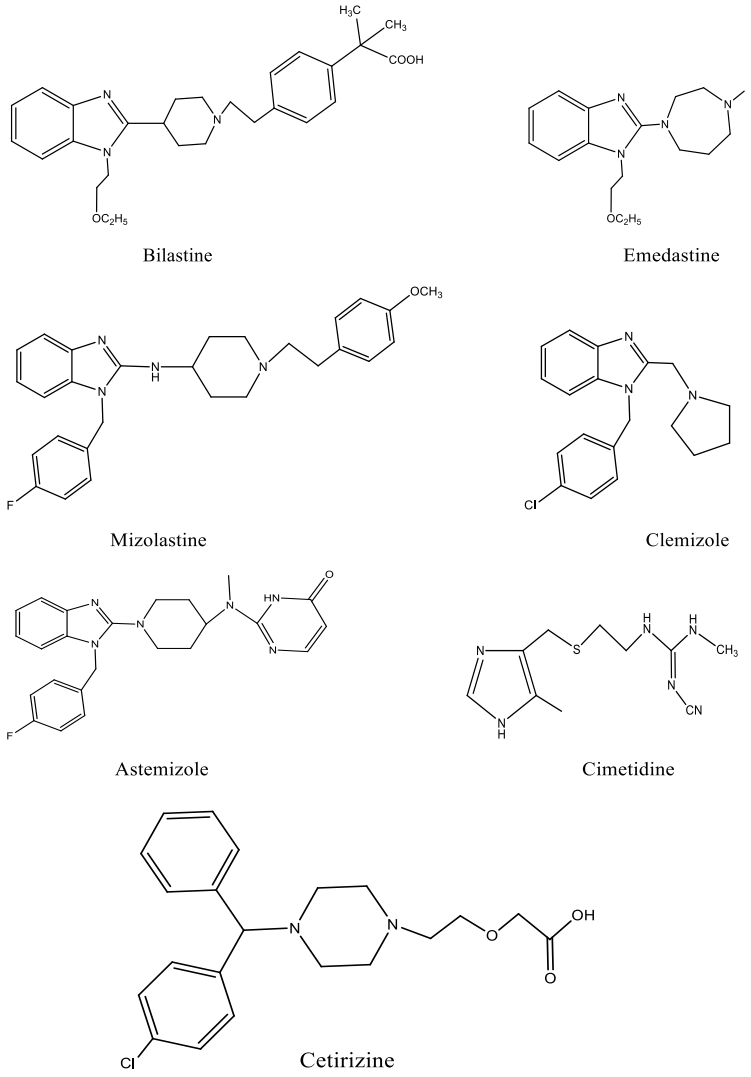

Fig. (1). Structure of some antihistamine drugs available in the market.

This chapter mainly focuses on the research progress, design, and synthesis of various new N-containing compounds as anti-allergic drugs.

CHAPTER 4

Experimental and Clinical Studies on the Effects of *Nigella Sativa* and its Constituents on Allergic and Immunological Disorders

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Abstract: Various pharmacological effects were shown for *Nigella sativa* (*N. sativa*), including anti-inflammatory, antioxidant, and immunomodulatory properties. The plant also has been used in traditional medicine for the treatment of various diseases. In this chapter, the effects of *N. sativa* and its constituents in allergic and immunologic disorders based on the experimental and clinical studies are provided. Articles published on the effect of *N. sativa* and its constituents on allergic and immunologic disorders in the experimental and clinical studies were searched until July 2020. For this purpose, keywords including; *Nigella sativa*, black seed, thymoquinone, alpha-hederin, carvacrol, allergic disorders, and immunology disorders were searched in different databases such as PubMed, Science Direct, Scopus, and Google Scholar. Experimental studies showed various immunologic effects of *N. sativa* extracts and their constituents, including their effects on Th1/Th2/ balance. Treating patients with *N. sativa* seed, alleviate symptoms of allergic rhinitis and decrease the body temperature in allergic patients which is due to immunomodulatory properties of the plant. Treatment of Vitiligo patients with *N. sativa* also reduced the Vitiligo Area Scoring Index (VASI). Various studies showed that *N. sativa* and its constituents showed significant effects on allergic and immunologic disorders. Therefore, *N. sativa* and its constituents could be good candidate drugs for treating allergic and immunologic disorders.

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Keywords: Alpha-hederin, Allergic disorders, Carvacrol, Clinical studies, Experimental studies, *Nigella sativa*, Immunologic disorders, Thymoquinone.

INTRODUCTION

Nigella sativa (N. sativa), known as 'Black Seed,' is an annual flowering plant in the family Ranunculaceae, native to a large region of Southern Europe, North Africa, and Southwest Asia [1]. It grows to 20-90 cm tall and has divided green leaves, delicate, pale blue, and white flowers. Its seeds are named as 'Black Seed' or 'Black Cumin' in English, 'Habba Al-Sauda' or 'Habba Al-Barakah' in Arabic, 'Kalonji' in Urdu, 'Siyah Daneh' in Persian, and 'Corek Out' in the Turkish language. The scientific name is a derivative of Latin 'niger', meaning 'black [2].

Chemical analysis of the plant seeds has demonstrated that oils, proteins, carbohydrates, fibers, ashes, moisturizers, *etc*., are the plant's general compound [3]. Non-oily and non-caloric components of the plant consist of phyto-alkaloids, including pyrazol (nigellicine and nigellidine), isoquinoline (nigellicimine and nigellicimine-N-oxide) as well as a flavonoid (Comferol), diglucoside and digalactoside, alpha-hederin, saponins, vitamins (riboflavin, pyridoxine, niacin, thiamin, folic acid and vitamin E and minerals (sodium, potassium, calcium, magnesium, copper, iron, and phosphorus) [4, 5]. The oil component of *N. sativa* mostly consisted of inoleic, palmitic, oleic, dihomolinoleic, and eicodadienoic acids [5 - 7]. The most essential pharmacologically active compounds in the plant's essential oil are thymoquinone (TQ), thymohydroquinone, dithymoquinone, p-cymene carvacrol, 4-terpineol, t-anethol, sesquiterpene longifolene α -pinene, and thymol [8].

In the acute and chronic toxicity studies using animal models, *N. sativa* and its oil are commonly considered safe, particularly when given orally [2, 9, 10].

N. sativa is an extensively used medicinal plant throughout the world. Traditionally, *N. sativa* is used in the treatment of various diseases such as cough, bronchitis, asthma, chest congestion, chronic headache, migraine, dizziness, infertility, paralysis, rheumatism, back pain, hemiplegia, fever, dysmenorrhea, obesity, diabetes, hypertension, infection and inflammation, flatulence, dyspepsia, and diarrhea [3, 8, 11]. In traditional medicine, this plant's administration, combined with honey, also improved respiratory diseases such as chest congestion, asthma, and bronchospasm [12]. *N. sativa* and its ingredient showed a variety of pharmacological activities such as a diuretic [8], antidiabetic [13], antihypertensive [14], anti-inflammatory [15], antioxidant [16], immunomodulatory [17], hepatoprotective [18], renal protective [19], gastroprotective [20], and bronchodilator properties [21, 22]. Black seeds were also used against various disease including allergy, bronchial asthma, respiratory distress, and lung

infection [23]. Therefore, in this chapter, an updated overview of the experimental and clinical studies on the effects of *N. sativa* and its constituents on allergic and immunologic disorders is provided.

METHOD

Different databases, including PubMed, Science Direct, Scopus, and Google Scholar were searched for finding articles published on the effect of *N. sativa* and its constituents on allergic and immunologic disorders in the experimental and clinical studies until July 2020. Keywords, including; *Nigella sativa*, black seed, thymoquinone, alpha-hederin, carvacrol, allergic disorders, and immunology disorders were used.

THE EFFECT OF *N. SATIVA* ON ALLERGIC AND IMMUNOLOGIC DISORDERS, EXPERIMENTAL STUDIES

The Effect of *N. Sativa* and its Constituents on Animal Models of Allergic Rhinitis and Asthma

The effect of *N. sativa* in different immune and inflammatory parameters was evaluated in various models of allergic asthma. In ovalbumin (OVA)-sensitized guinea pigs, the hydro-ethanolic extract of *N. sativa* (0.125 and 0.25 mg/ml) reduced tracheal responsiveness to methacholine and WBC counts in boronchoalevolar lavage fluid (BALF) [24].

Sensitized mice treated with *N. sativa* in food showed a significant decrease in the number of eosinophils, and a potential inhibitory effect on the mRNA expression level of Th2-driven immune response cytokines and mucin in the BALF, resulting in decreased production of the interleukin and mucin in allergic asthma [25].

Administration of *N. sativa* oil (5 ml/kg) in conalbumin-sensitized mice reduced the peripheral blood eosinophil count, IgG1 and IgG2a levels, cytokine profiles, and inflammatory cells in the lung tissue [26, 27].

In a model of OVA-induced bronchial asthma in mice, oral treatment with *N. sativa* oil (1 and 4 ml/kg) showed a significant decrease in the tracheal responsiveness (TR), total white blood cell (WBC) count, macrophages and eosinophils, the BALF levels of IL-4, IL-5 and IL-13, the serum levels of total IgE, OVA-specific IgE and IgG1, and a significant increase in the BALF level of IFN-γ and the serum level of OVA-specific IgG2a, indicating a restoration of local Th1/Th2 balance [28].

CHAPTER 5

Aspirin Desensitization/Challenge in Patients with Cardiovascular Diseases: Current Trends and Advances

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Abstract: Aspirin, known as acetylsalicylic acid (ASA), is one of the most commonly used medications. Available as over-the-counter medicine, ASA is prescribed as a nonsteroidal anti-inflammatory and anti-platelet drug and has the potential to decrease pain and fever. ASA is also considered as a first-line drug for the treatment of some cardiovascular diseases such as coronary artery diseases (CAD) and myocardial infarction (MI). Subsequently, it has been demonstrated to reduce the morbidity and mortality rate of these diseases. Besides the beneficial effects, ASA has the potential to provoke some allergic reactions, particularly in patients with CAD. According to previous reports, in 1.5-2.6% of the subjects with CVD treated with ASA, aspirin-exacerbated respiratory disease or chronic idiopathic urticaria were observed. In this book chapter, we aimed to summarize all-new achievements and novel findings of recent clinical advances related to the desensitization approaches following aspirin consumption in patients with CADs

Keywords: Acetylsalicylic Acid, Allergic Reactions, Anti-Platelet Effects, Anti-thrombotic effect, Aspirin (ASA), Aspirin Challenge, Aspirin Desensitization, Aspirin-Induced Exacerbated Respiratory Disease (AERD), Cardiovascular Disease (CVD), Clinical Advances, Clinical Trials, Coronary Artery Diseases (CAD), Cyclooxygenase (COX), Hypersensitivity, Leukotriene, Non-steroidal Anti-Inflammatory Drugs (NSAIDs), Prostaglandins, Rapid Desensitization, Sensitivity, Slow Desensitization.

HISTORY OF ASPIRIN

Aspirin is one of the most commonly used and popular pharmaceutical agents of the last 100 years. It is a synthetic derivative of salicylic acid, and as a natural

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product, found in willow tree bark, grains, and some fruits [1]. The name of aspirin was originally derived from the plant source of salicylic acid, and the synthesis process involved: the letter *A* originated from *acetyl chloride,* and the *spirin* originated from the genus name of *Spiraea ulmaria* plant, which is a rich source of salicin [2]. In Table **1**, the ancient history and the uses of salicylate acid (ASA) containing plants are shown:

Table 1. The ancient history of aspirin.

Scientist/ Civilization	Year	Plant/Agent	Outcomes	Ref.
Sumerians, Assyrians and the Egyptians	4000 BC	The leaves of the willow tree	Analgesic and antipyretic effects	[3]
Ebers Papyrus	1300 to1500 BC	Willow plant and myrtle	Inflammatory, antipyretic, and analgesic effects	[4]
Celsus, Pliny and Hippocrates	460 to 377 BC	Chewing brewed tea made of willow bark	Antipyretic and analgesic effects	[5,6]
Dioscorides	100 CE	Willow bark	Treatment of colic, gout and earache	[7]

Abbreviation: BC: Before Christ, CE: Christian Era.

Once the beneficial effects of salicylate (salicylic acid) were explored, scientists intended to isolate it from the bark in the early-19th century. In Table **2**, the modern history of aspirin is summarized:

Table 2. The modern history of aspirin.

Scientist/Country	Year	Plant/Agent	Outcomes	Ref.
R. Edward Stone	1763	Willow-bark	Treatment of Ague (a fever from malaria)	[8]
F. Fontana and B. Rigatelli	1824	Willow-bark	The extraction of bioactive components	[9]
J. Buchner	1828	Willow-bark	Salicin isolation	[10]
H. Leroux	1829	Willow-bark	Analgesic effects	[10]
R. Piria	1838	Aspirin	Synthesizing salicylic acid in a crystal form	[10]
Charles .F. Gerhardt	1853	Aspirin	Exposing the acetyl chloride with sodium salicylate, Synthesizing acetylsalicylic acid	[7]
H. Kolbe	1859	Aspirin	Discovering the salicylic acid chemical structure, Side effects observation *e.g.* gastrointestinal irritation	[11]

(Table 2) cont.....

Scientist/Country	Year	Plant/Agent	Outcomes	Ref.
F. Heyden	1874	A synthetic form of salicylic acid	Industrial production	[12]
T. MacLagan	1876	Salicin consumption	Planned the first clinical trial for acute rheumatism treatment published in *The Lancet* journal	[13]
F. Hoffmann	1897	Salicylic acid chemical structure modification	Synthesize a derivative of salicylates without any side effect	[13]
F. Bayer	1899	Aspirin	Tradename Registration	[6]
U.S.	1900	Aspirin	Drug Patented	[14]
U.S.	1904	Aspirin	Stamped tablet production	[15]

THE HISTORY OF CARDIOVASCULAR EFFECT

Previous findings regarding the antithrombotic property of aspirin between the 1950s and 1960s proposed that aspirin could be an effective agent for the prevention of possible cardiovascular events [16]. Herein, we outlined the historical issues in this setting:

Table 3. The clinical trial studies on the protective role of aspirin against CVDs.

Author/ Organization	Year	Study Type	Outcomes	Ref.
P. Elwood	1974	Randomized controlled trial, single dose of aspirin (300 mg daily), 1,239 patients with MI	Significant reduction in total mortality of 12% and 25% after 6 and 12 months, respectively.	[17]
R. Peto	1980	Meta-analysis on over 10,000 patients with MI	Aspirin potentially decreased the risk of re-infarction by 21% in patients.	[18]
ISIS-2 Collaborative Group	1988	17,187 patients with re-infarction (162 mg aspirin daily for 1 month)	RRR in patients diminished, up to 23% in aspirin and the mortality rate dropped to 9.4%	[19,20]
FDA	1985	_	Aspirin was approved for secondary prevention of acute MI	[14]
AHA, ACC	2019	Modification of clinical practice guidelines	Routine administration of aspirin in subjects aged over the 70	[21]

Abbreviation: ACC: American College of Cardiology; AHA: American Heart Association, FDA: Food and Drug Administration; ISIS-2: Second International Study of Infarct Survival, MI: Myocardial Infarction; RRR: Relative Risk Reduction.

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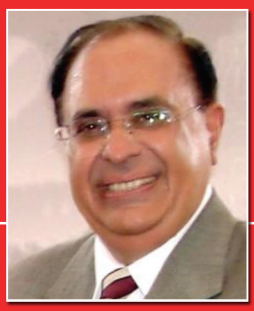

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Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.