Herbal Medicine for Autoimmune Diseases

Editors: **Cennet Ozay & Gokhan Zengin**

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Herbal Medicine for Autoimmune Diseases

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FOREWORD

Autoimmunity is defined by the presence of self-reactive immune components, while autoimmune diseases result from the combination of autoimmunity and pathology. Both phenomena are significantly increasing worldwide, likely due to changes in our exposure to environmental factors. Significant changes in our diet, exposure to xenobiotics, air quality, infection rates, personal habits, stress levels, and the effects of climate change are all associated with this increase. These factors have significant consequences not only for the individuals and families affected but also for our society and healthcare expenditures. Projections suggest that autoimmune diseases may soon become the most common medical conditions, underscoring the urgency of addressing these complex health challenges.

Autoimmune diseases represent a family of around 100 disorders that share a common pathogenesis, namely an immune-mediated attack on the body's organs. Although immunosuppressive and immunomodulatory drugs represent the fundamental basis for the treatment of autoimmune diseases, there is currently no known radical treatment for these diseases. The use of medicinal plant extracts or secondary plant substances in herbal remedies is currently being investigated as a possible therapeutic approach for autoimmune diseases. Bringing together many studies on autoimmune diseases and herbal remedies in one book titled "Herbal Medicine for Autoimmune Diseases" with great dedication, this will be an excellent resource for researchers studying this topic.

The editors have strived to highlight the potential effectiveness of herbal treatments for autoimmune diseases, while bringing a broad viewpoint from various disciplines, such as pharmacy, medicine, nutrition, and basic sciences. Also, I would like to compliment the authors of all the chapters and acknowledge their efforts in publishing this comprehensive book.

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PREFACE

Autoimmune diseases are common conditions in which impaired immune activation leads to pathological immune responses directed against either cellular or organ-specific self-antigens. The exact cause of autoimmune diseases is generally unknown, but stress, genetics, and environmental factors have been suggested as possible triggers. However, the connection between these proposed factors and autoimmune diseases is very complex. They are generally undertreated and there is currently no cure for these diseases. Immunosuppressive and immunomodulatory drugs are used in the treatment of autoimmune diseases, but they cannot cure these diseases, only slow down their progression. These medications are also associated with significant adverse effects. Given that the global increase in autoimmune diseases is leading to increased individual and societal suffering as well as higher private and public healthcare costs, the development of appropriate treatments for patients with autoimmune diseases is of great importance.

Therefore, various studies have been carried out to find an effective treatment. Due to their anti-oxidant and anti-inflammatory properties, herbal medicines and their phytochemicals appear to be a promising therapy. Hence, the main purpose of this book is to draw attention to herbal medicines for autoimmune diseases. Data on the therapeutic potential of related medicinal plants for autoimmune diseases can now be accessed from a single source. The book begins with an introductory chapter that serves as a framework for understanding autoimmunity and autoimmune diseases, as well as key principles and components of the immune system. The following chapters of the book, introduce potential medicinal plants and their phytochemicals that can be used in the management of autoimmune diseases such as multiple sclerosis, type 1 diabetes, rheumatoid arthritis, celiac disease, inflammatory bowel disease, Graves' disease, Hashimoto thyroiditis, and systemic lupus erythematosus, which are among the most common autoimmune diseases in the society mentioned with evidence-based data from preclinical and clinical studies. It is known that traditional knowledge about the use of medicinal plants in therapy is an important resource for the discovery of new treatment options and drug targets. One chapter of the book focuses on phyto-nano drug delivery systems that can enhance the efficacy of medicinal plants in the treatment of rheumatoid arthritis. Another chapter provides a comprehensive overview of berry fruits related to autoimmune diseases.

As editors, we would like to express our special thanks to all the contributing authors for making their invaluable chapter contributions in a timely manner, thereby enabling us to publish this book on time. We would also like to express our heartfelt thanks to the team at Bentham Science Publishers for their invaluable help and kind support throughout the editorial process of this book.

Finally, we would like to thank our family members, all the esteemed teachers, friends, colleagues, and students for their constant encouragement, inspiration, and support during the preparation of this book. Together with our contributing authors and publishers, we hope that our efforts will meet the needs of students, academics, researchers, and professionals in the pharmaceutical industry.

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DEDICATION

We would like to dedicate this book to our beloved fathers, Nurettin and Munir, who passed away in recent years. Our fathers gave us the greatest gift a human being can give another human being: They believed in us. Thanks to them, we could try to touch people's lives through science. Their memories will inspire us every day of our lives.

They will remain forever in our hearts and our prayers.

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CHAPTER 1

Autoimmune Diseases, Immune System and Herbal Medicine

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Abstract: The immune system is a defense mechanism against infections and illnesses caused by various agents, including bacteria, viruses, and other causative factors. Any disruption in the functioning of the immune system, which is highly organized and precisely regulated, can result in the emergence of immune deficiencies, hypersensitivity reactions, or autoimmune diseases (AIDs). Under certain circumstances, the immune system generates autoantibodies that target their cells, giving rise to AIDs, including multiple sclerosis, type I diabetes, rheumatoid arthritis, inflammatory bowel disease, hashimoto thyroiditis, systemic lupus erythematosus, psoriasis, *etc*. In such cases, the immune system cannot differentiate between foreign substances and the body's own cells. Different factors, such as genetic, epigenetic, and environmental factors, trigger autoimmunity. Currently, autoimmune diseases of various origins are managed using glucocorticoids, non-steroidal anti-inflammatory drugs, immunosuppressive agents, and biological treatments. Nevertheless, a comprehensive cure for these conditions continues to remain beyond our reach. Numerous herbal natural products have been investigated as potential alternative approaches for the management of autoimmune disorders. In this introductory chapter, we summarized the essential concepts of the immune system, the formation, stages, and types of autoimmune diseases, and the role of herbal medicines in the management of AIDs.

Keywords: Autoimmune diseases, Autoimmunity, Herbal medicine, Herbal natural products, Immune system, Natural phytocompounds.

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INTRODUCTION

Immunity represents a harmonious equilibrium in which the body possesses effective biological defenses to combat infections, diseases, or unwanted biological intrusions, all while maintaining tolerance to prevent allergies and autoimmune diseases (AIDs). Immune responses result from effective interactions between innate (natural/non-specific) and acquired (adaptive/specific) immune system components. The interaction between phagocytes and micro-organisms in the immune system is a protective pathway, but if inappropriately or improperly organized, it can damage the body and contribute to the development of various long-term inflammatory conditions such as allergies, carcinomas, and AIDs [1].

There are over 80 AIDs known to date, ranging from relatively common to rare conditions. The determination of which AIDs are the most common can vary based on a variety of factors, including patient-reported data, clinical experience, hospital records, and research studies. As of the current information available, some of the more prevalent AIDs include rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus, inflammatory bowel disease, hashimoto thyroiditis, Alopecia areata, Graves' disease, celiac disease, systemic lupus erythematosus, and psoriasis, among others. However, the prevalence and ranking of AIDs may change as new research and data emerge [2].

AIDs, arising from the immune system's misalignment targeting the body itself, presents a notable and escalating unmet demand within clinical healthcare. Generally, due to their wide-ranging action rather than being tailored to specific diseases, current treatments are linked to a multitude of side effects. Hence, there is a rising need for the usage of herbal drugs that lead to suppressive effects on the immune system.

The aim of this introductory chapter is (1) to establish a fundamental understanding of the key principles and constituents of the immune system, serving as a framework for comprehending autoimmunity and autoimmune diseases, (2) to provide information about the formation, stages and types of autoimmune diseases, and (3) the role of herbal medicines in the management of autoimmune diseases.

AUTOIMMUNE DISEASES

Autoimmune diseases are a wide range of disorders characterized by chronic inflammation and tissue damage [1, 2]. Autoimmune diseases range from Psoriatic arthritis to Type 1 diabetes mellitus (T1DM), Crohn's disease, Rheumatoid arthritis (RA), Grave's disease (GD), Psoriasis, and Multiple sclerosis (MS). Most of these are incurable, but the symptoms can be managed

[3]. Recently, autoimmune diseases have emerged as a significant health concern with increasing incidence. Autoimmune diseases affect approximately 10% of the population worldwide. These diseases are associated with tremendous economic burden [4, 5]. According to Conrad and Misra [3], autoimmune diseases affect almost one in ten individuals in the UK. In 2019, an estimated 18 million people worldwide were diagnosed with Rheumatoid arthritis [6]. In 2020, the data showed that 2.8 million people were diagnosed with MS worldwide [7]. Crohn's disease has emerged as a global disease and affects over 3.5 million people [8]. There were approximately 8.4 million people worldwide with T1DM in 2021. An estimated number of people with T1DM is expected to reach 13.5-17.4 million by 2040 [9] (Table **1**) (Fig. **1**).

Table 1. Incidence of common autoimmune diseases.

Autoimmune Diseases	*Incidence*	*References*
Psoriatic arthritis (PsA)	0.5-0.8% of the general population.	[10]
Rheumatoid arthritis (RA)	0.5-1% of the global population aged between 25 and 60 years.	[11]
Ankylosing spondylitis (AS)	0.07-0.32% of the general population.	[12]
Multiple sclerosis (MS)	2.8 million people.	[7]
Crohn's disease (CD)	3.5 million people.	[8]
Grave's disease (GD)	1-1.5% of the general population.	[13, 14]
Type 1 diabetes mellitus (T1DM)	8.4 million people.	[15]
Psoriasis	1.5-3% of the general population.	[16]
Scleroderma	30-300 cases per million.	[17]

Causes of Autoimmune Diseases

Autoimmune diseases are multifactorial diseases. The development of AIDs is affected by many factors, including viral infections, genetic predisposition and environmental factors [18, 19]. A large number of autoimmune diseases are more prevalent in women than men [20, 21]. The abnormal activation of chemokine signaling pathways is implicated in the development of several autoimmune diseases including RA and SLE and systemic sclerosis [22]. Tumor necrosis factor-alpha (TNF-α) plays an important role in many AIDs, including RA, MS, PsA, CD, and AS [23].

CHAPTER 2

Role of Herbalism in Systemic Lupus Erythematosus Treatment

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Abstract: The well-known inflammatory and autoimmune condition known as systemic lupus erythematosus (SLE) causes symptoms in the kidneys, the skin, the brain, and the heart. It can also cause complications that affect several organs. The diversity in organ involvement and heterogeneous conditions of patients led to the complicated management of SLE. Increasingly, there is evidence highlighting the importance of phytochemicals in both dietary and non-dietary contexts in the management of SLE without side effects.

Herein, we discuss the role of different plant extracts with their metabolites and their modes of action against SLE updated to 2023, in addition to the incorporation of herbal formulas in the management of the SLE. The present work is an overview of different plant extracts and their secondary metabolites with significant anti-inflammatory, antioxidant, and immunomodulation in SLE. The current chapter focuses on the various targets, mechanisms, and pathways of natural products that manage SLE. Based on the current work, it can be inferred that natural products show potential as effective agents in the medical care of SLE.

Keywords: Autoimmune, Anti-inflammatory, Diet, Herbalism, Immunomodulation, Mode of action, Natural compounds, Plant extract, Systemic lupus erythematosus, Treatment.

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INTRODUCTION

Systemic lupus erythematosus (SLE) exemplifies a typical autoimmune-related multisystemic condition [1]. SLE is a persistent and recurrent autoimmune disorder characterized by inflammation that impacts various organs, such as the skin, joints, blood, and kidneys. The involvement of macrophages in the pathogenesis of this condition has been deemed significant [2]. Numerous immunological abnormalities and excessive inflammatory responses that affect numerous organs throughout the body are features of SLE [3, 4]. Manifestations vastly differ across patients, SLE can manifest with a range of symptoms, such as malar, discoid, and photosensitive skin rashes, arthralgias, and arthritis, constitutional symptoms like pain and fatigue, psychiatric disturbances, and potentially extensive internal organ disease involving renal, pulmonary, cardiac, neurologic, and/or gastrointestinal systems. Additionally, SLE is characterized by the production of autoantibodies, which can be detected by the presence of an antinuclear antibody (ANA) (Fig. **1**). Systemic lupus erythematosus is reported to have an incidence ranging from 0.3 to 31.5 instances per 100,000 people annually, and its adjusted prevalence is predicted to be close to or greater than 50 to 100 cases per 100,000 people [5].

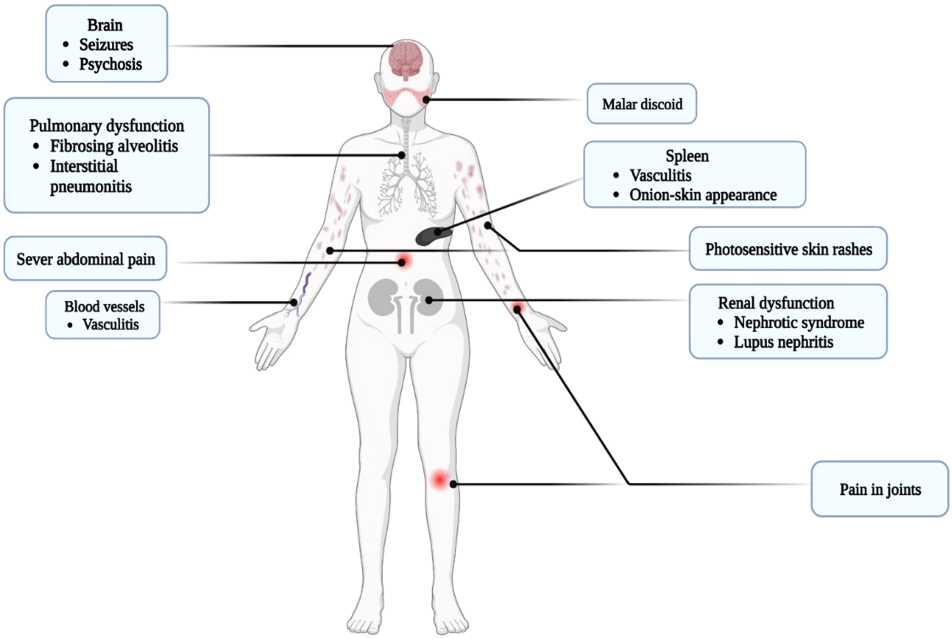

Fig. (1). Manifestations of systemic lupus erythematosus (SLE).

Treatment for SLE as a whole necessitates a comprehensive, interdisciplinary strategy that goes well beyond treating immunological dysfunction and takes into account the patient's distinct and particular demands. For dermatologic indications, strategies might range from conservative treatments like acetaminophen and non-steroidal anti-inflammatory medicines to alleviate joint pain, and the use of topical steroid creams and cautious sunscreen to more targeted immunologic therapy with varying degrees of immunosuppressive potential. Complementary and alternative medicine (CAM) is frequently used in conjunction with conventional treatment. Patients with active SLE, who often have a diminished quality of life and significant unmet needs, commonly turn to CAM as an additional approach to managing their condition [6]. CAM usage is linked to worse health status in Yucatan, Mexico individuals with SLE [7].

Increasingly, there is evidence highlighting the importance of herbalism as well as its secondary metabolites in the management of different conditions of inflammation, oxidative stress, and apoptosis [8 - 12]. Also, the presence of variable secondary metabolites belong to different classes, including volatile oils, alkaloids, flavonoids, terpenoids, and fatty acids [13 - 16] that regulate abnormal responses in the innate and adaptive immune systems, kidneys, intestines, bone system (including chondrocytes, osteoclasts, joints, and paw tissues). This suggests that plant metabolites could be a potential target for managing SLE without adverse effects [17]. Many reports have documented the utilization of diverse plant species in the management of SLE; most of them belong to families namely, Celastraceae, Lamiaceae, Apiaceae, Ranunculaceae, Oleaceae, Theaceae, Simaroubaceae, Achariaceae, Campanulaceae, Urticaceae, Oxalidaceae, Clusiaceae, Hypericaceae, Schisandraceae, Menispermaceae, Orobanchaceae, Rubiaceae, Paeoniaceae, Rutaceae, Dioscoreaceae, Alismataceae, Cornaceae, Rosaceae, Alismataceae, Lauraceae, Nelumbonaceae, Linaceae, Solanaceae, Polygonaceae, Equisetaceae and others. Fungi are also involved such as fungi from Ganodermataceae, Ophiocordycipitaceae and Polyporaceae families [18 - 20].

This aim of this chapter is to assemble and analyse the prospective applications of herbalism, including plant extracts and isolated bioactive compounds, in managing SLE. The focus is on exploring the efficacy and mechanisms of action of these natural remedies, as well as discussing the role of isolated bioactive compounds in combating the disease. It is hoped that this chapter will inspire further research by scientists towards the development of potent medications for the therapy of SLE.

CHAPTER 3

Type 1 Diabetes Mellitus and Herbal Medicines

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Abstract: The global incidence of type 1 diabetes mellitus (T1DM) is rising substantially and T1DM remains a marked economic burden despite advances in the diagnosis, prevention, and treatment of complications. T1DM, often associated with autoimmune disease, is characterized by insulin deficiency and insufficiency due to beta cell destruction. The primary treatment for T1DM is insulin therapy, limited by the risk of hypoglycemia and weight gain. Other treatments for T1DM are teplizumab and donislecel, which have recently received FDA approval. Beyond these treatment options, T1DM patients are interested in non-pharmacological interventions and are willing to use herbal products. Therefore, we reviewed the effects of herbal medicines used for T1DM, including fenugreek, ficus extracts, cinnamon, berberine, silymarin, silibinin, curcumin, resveratrol, catechins, ginseng, olive leaf, allicin, thymoquinone, and mangiferin to understand their level of evidence and associated effects, and their potential for use as antidiabetic agents in the clinic. As a result of our research, the majority of the studies were conducted on diabetic animal models. There are limited clinical studies investigating herbal medicines in T1DM. Studies show that the abovementioned herbal medicines are beneficial in T1DM by lowering glucose levels, increasing insulin levels, and exerting anti-oxidant, anti-inflammatory, and pancreas islet β-cell protective mechanisms. However, these studies are insufficient to recommend the use of existing herbs in treating T1DM on a clinical level.

Keywords: Alloxan, Autoimmune diabetes, Insulin-mimetics, Insulin-dependent diabetes mellitus, Streptozotocin, Type 1 diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a severe and chronic disease characterized by insufficient insulin production or utilization, resulting in elevated levels of circulating blood glucose [1]. Prolonged insulin deficiency and sustained hyperglycemia can lead to serious complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease. The prevalence of diabetes mellitus is escalating as a

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global health challenge, with the number of people affected increasing every year. According to the 10th edition of the International Diabetes Federation (IDF) Diabetes Atlas, the global prevalence of diabetes is estimated to reach 537 million people in 2021, a number that is projected to increase to 783 million by 2045 [2]. The Atlas suggests that diabetes affects men and women equally, with a higher prevalence observed in people aged 75-79 years. The economic burden of diabetes-related conditions is estimated to have reached $966 billion in 2021, with a projected increase to $1,054 billion by 2045 [2].

Diabetes mellitus is classified into four subgroups: Type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), specific types of diabetes, and gestational diabetes mellitus [3]. T1DM is characterized by insulin deficiency and insufficiency, resulting from β-cell destruction, often associated with autoimmune disease. Conversely, T2DM is often non-autoimmune and characterized by reduced insulin secretion and insulin resistance [3]. Contrary to the misconception that T1DM only affects children, T1DM can also occur in adulthood [4]. T2DM is not age restricted but is more prevalent in adults over the age of 40. T2DM is associated with overweight conditions, insulin resistance, and relative insulin insufficiency. Patients with T2DM are managed with lifestyle interventions and glucose-lowering medications [5]. The primary treatment for T1DM is insulin therapy with continuous blood glucose monitoring. Nonetheless, the risk of hypoglycemia and weight gain are limitations of insulin therapy. In recent years, the FDA has approved a monoclonal antibody called teplizumab [6] and a cellular therapy called donislecel for treating patients with T1DM [7]. In addition to these therapeutic options, there is a growing trend among patients with T1DM to explore non-pharmacological interventions. Alongside regular physical activity and a healthy diet, patients are also willing to use herbal products.

This chapter aims to evaluate the effects of herbs and herbal metabolites on the pathophysiology and symptoms of T1DM through preclinical and clinical studies. The herbs and herbal metabolites most frequently studied for their effects on T1DM, including fenugreek, ficus extracts, cinnamon, berberine, silymarin, silibinin, curcumin, resveratrol, catechins, ginseng, olive leaf, allicin thymoquinone, and mangiferin are reviewed comprehensively in this chapter.

TYPE 1 DIABETES MELLITUS

Epidemiology

T1DM affects all age cohorts; however, data on the epidemiology of T1DM in adults are limited [8]. The incidence of diabetes among children and adolescents is increasing, with projections from the 10th IDF Atlas indicating an estimated number of over 1.2 million affected children and adolescents by 2021 [9].

Given the lack of comprehensive global epidemiological data on the prevalence and incidence of T1DM, a meta-analysis of 193 studies was conducted [10]. The global incidence of T1DM is estimated to be 15 per 100,000 individuals, while its prevalence is 9.5% [10]. In 2017, a study estimated the number of global incidences as 234,710 and prevalence as 9,004,610 for T1DM cases in all age groups [11]. High-income countries contributed to 49% of the global incidence of T1DM and 52% of its prevalence [11]. Furthermore, a study conducted in 2018 revealed that individuals aged 31-60 years accounted for 42% of T1DM cases, representing 4% of all diabetes patients diagnosed after the age of 30 [5].

Diagnosis

The diagnosis of diabetes is established through several criteria, as outlined in the "Standards of Care in Diabetes" published by the American Diabetes Association in 2023 [3]. These include a fasting blood glucose (FBG) concentration of ≥ 126 mg/dL, an oral glucose tolerance test at blood glucose concentration of ≥ 200 mg/dL, or a hemoglobin A1c (HbA1c) level of ≥ 6.5%. In addition, many patients are diagnosed based on a random blood glucose concentration of ≥ 200 mg/dL, accompanied by classic symptoms such as dysglycemia, polyuria, polydipsia, and weight loss [12]. T1DM is diagnosed by hyperglycemia, ketosis, rapid weight loss, short-term symptoms, an early onset, lower body mass index, and autoimmune disease history.

Most cases of diabetes among young individuals are attributed to T1DM, which is easily diagnosed. In people over 30, however, T1DM can be challenging to distinguish from T2DM [5]. Measurement of circulating C-peptide levels, indicating endogenous insulin secretion and detection of autoantibodies against islet antigens can help differentiate T1DM from T2DM. However, it is noteworthy that these biomarkers are not routinely tested.

Clinical Manifestations

Patients diagnosed with T1DM progress through three distinct stages [13]. In the first stage, patients have two or more islet autoantibodies. Subsequently, in the second stage, patients develop glucose intolerance and dysglycemia. Ultimately, the third and final stage is characterized by the manifestation of clinical symptoms characteristic of the disease (Fig. **1**). The clinical presentation of both T1DM and T2DM is remarkably similar, with patients presenting with symptoms including polyuria, polydipsia, fatigue, dehydration, vision impairment, susceptibility to infections, and weight loss [14]. In the context of T1DM, these symptoms tend to be more severe and occur more rapidly, although the progression of immune-mediated damage is slow [14]. A critical complication associated with T1DM is diabetic ketoacidosis, a potentially life-threatening condition [15]. Individuals

CHAPTER 4

Traditional Medicine and Modern Drug Delivery Systems: Promising Roles of Phyto-Nanotechnology in Rheumatoid Arthritis Treatment

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Abstract: Phyto-nanotechnology presents a promising avenue for revolutionizing rheumatoid arthritis (RA) treatment. By integrating plant-derived compounds with nanotechnology, this approach addresses the limitations of conventional RA therapies. Nanoformulations of phytochemicals, such as curcumin, resveratrol, and quercetin, enable targeted drug delivery to inflamed joints, optimizing therapeutic efficacy while minimizing systemic side effects. Enhanced bioavailability, attributed to the encapsulation of phytochemicals within nanoparticles, facilitates improved pharmacokinetics and delivery across biological barriers. The immunomodulatory and anti-inflammatory properties of phytochemicals are harnessed more effectively through nanoparticle-mediated sustained release, offering the potential to suppress inflammatory processes and mitigate joint damage. Furthermore, the cartilage-protective and regenerative capabilities of certain plant-derived compounds can be optimized with nanotechnology, promoting joint health. The versatility of phyto-nanotechnology allows for combination therapies, synergizing the benefits of multiple compounds and conventional drugs within nanoparticles. While these advancements hold substantial promise, further research is imperative to refine nanoparticle formulations, assess safety, and validate efficacy through preclinical and clinical studies, ultimately paving the way for transformative RA treatments in clinical practice. In this chapter, phyto-nano drug delivery systems that can increase the effectiveness of medicinal plants in RA treatment are focused on.

Keywords: Green synthesis, Herbal medicine, Modern drug delivery systems, Nanoparticles, Nanocarriers, Phyto-nanotechnology, Rheumatoid arthritis, Traditional medicine.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive inflammation of the joints and damage to many organs, including the heart, kidneys, lungs, digestive tract, eyes, skin, and nervous system [1, 2]. While only a few of the joints are affected at the beginning of the disease, symptoms in other organs, particularly bone and cartilage, are encountered in the later stages of RA. While around 350 million people worldwide experience one type of arthritis, RA has the highest incidence [3]. Apart from RA, the types with the highest incidence among more than a hundred different types of arthritis are osteoarthritis, inflammatory arthritis, and psoriatic arthritis. Inflammation, synovial swelling, monocyte infiltration, joint stiffness, pannus development, and deterioration of articular cartilage are the general features of all types of arthritis. The specific cause and permanent treatment of arthritis are still under investigation. However, it is entirely known that many risk factors such as environmental variables, genetic variables, and lifestyle also trigger the pathogenesis of RA [4, 5]. Various bacterial and viral infections, gout, smoking, red meat and coffee consumption, air pollution, decreased antioxidant and vitamin D consumption are thought to play a role in the exacerbation of RA in vulnerable individuals. Symptoms can be treated with medication, but no successful treatment approach has been found for its etiology [6]. If the patient's condition becomes severe enough to cause loss of function, it can be restored by surgical intervention. Although the most commonly used drugs for treatment are anti-inflammatories, their notable side effects such as heart attack and bleeding in the gastrointestinal tract limit the use of these active pharmaceutical ingredients for most individuals [7]. Also, the administration of biological agents, corticosteroids, and disease-modifying anti-rheumatic drugs does not promote complete recovery [8]. Due to the limitations encountered in conventional treatments such as serious side effects, allergic reactions, and hematological disorders, adjunctive therapies, including herbal medicines, are being studied for the treatment of RA. Although there are many herbal phytocomponents effective in the treatment of RA, they lack the desired physical, chemical, and pharmacokinetic properties. It is inevitable to develop new nano drug delivery systems loaded with phytocomponents that are stable and have increased therapeutic efficacy [9, 10].

In this chapter, the etiology and pathophysiology RA, RA treatment approaches, RA treatment with plants, preparation and characterization techniques of phyto-nano drug delivery systems and improving the properties of herbal medicines effective in RA with nano drug delivery systems will be discussed.

Aetiology of RA

RA is the most common chronic inflammatory polyarticular autoimmune disease in the world. In addition, women suffer from RA 2-3 times more than men [1, 11]. It is characterized by arthralgia due to chronic synovitis which leads to cartilage and bone defects [12]. Early clinical symptoms of rheumatoid arthritis include fatigue, flu-like feeling, swollen and tender joints, and morning stiffness. In the advanced stage, pleural effusions, lung nodules and interstitial lung disease, lymphomas, vasculitis of small or medium-sized arteries, keratoconjunctivitis, atherosclerosis, hematological abnormalities, joint misalignment, immobility, bone erosion, cartilage destruction, and rheumatic nodules occur [1].

RA is a multifactorial disease and the severity and course of the disease depend on both genetic and environmental factors [13]. The diagnosis of RA is made by evaluating and detecting the patient's symptoms, physician examination results, evaluation of risk factors, family history, joint evaluation with ultrasound sonography, and laboratory markers such as elevated C-reactive protein (CRP) and erythrocyte sedimentation rate levels in serum. Although there is no definitively accepted biomolecular hypothesis regarding the pathophysiology of RA, it has been proven that innate and acquired immune reactions play a role in its pathological mechanism [12]. As hypothesized for other autoimmune diseases, the early onset of RA occurs through two separate situations. The first one is the patient's genetic predisposition resulting in the generation of autoreactive T and B cells, and the second one is a triggering condition such as viral and bacterial infections or tissue damage. Smoking, obesity, exposure to UV light, sex hormones, drugs, changes in gut, mouth and lung microbiomes, periodontal disease (periodontitis) and infections are risk factors for the development of RA [14]. More than 100 loci associated with RA have been identified through genomic studies. Moreover, epigenetic modifications are also associated with disease etiology. Factors such as infection and smoking lead to the development of the disease. Smoking induces the formation of free radicals, causes increased cell death, increases the level of monocytes and macrophages in the alveoli, and triggers synovial inflammation. It also causes higher expression of fibrinogen, CRP, interleukin (IL)-1, IL-6 and IL-8. Increased alcohol consumption is associated with a lower risk of RA, while red meat is associated with increased risk and disease severity. Dietary habits such as the Mediterranean diet and intermittent fasting have been proven to reduce RA activity score and inflammation [13, 15].

Autoimmune tissue destruction in RA manifests as synovitis, an inflammation of the joint capsule (Fig. **1**). Excessive activation of fibroblast-like synoviocytes (FLSs) is the central event of RA synovial hyperplasia [16]. This state is initiated

CHAPTER 5

The Effects of Herbal Medicines on the Management of Inflammatory Bowel Disease

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Abstract: Inflammatory bowel disease (IBD) that affects a large population worldwide, is a gastrointestinal disorder that includes Crohn's disease and ulcerative colitis. The genetic factors, immunological, and microbial factors play critical roles in the pathogenesis of IBD. However, there is still no pharmacological therapy providing the definitive treatment of the disease. Gastrointestinal symptoms of IBD significantly reduce the patient's quality of life and IBD patients often tend to use herbal medicines as an alternative and complementary therapy for improving the symptoms. Among herbal medicines used for IBS, *Andrographis paniculata, Boswellia serrata,* and *Aloe vera* are prominent plant species, and catechins and curcumin are the commonly investigated phytochemicals. Here, we summarized the main factors in the pathogenesis of IBD, the current treatment strategies, and commonly used natural compounds and herbs with evidence-based data. The findings pointed out that further clinical trials having a higher sample size are required prior to the recommended use of these herbal medicines in therapy.

Keywords: *Andrographis paniculata*, *Aloe vera*, *Boswellia serrata*, Catechins, Crohn's disease, Curcumin, Herbal medicine, Inflammatory Bowel Disease, Ulcerative colitis.

INTRODUCTION

Inflammatory bowel disease (IBD), which is divided into two types ulcerative colitis (UC) and Crohn's disease (CD), is one of the chronic inflammatory diseases of the gastrointestinal tract that is common especially in adolescence and young adulthood [1]. The onset of IBD is dependent on the effects of genetic and environmental parameters on the immune system [2].

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The symptoms of IBD generally present early in life, and approximately 25% of IBD patients are diagnosed before the age of twenty years [3]. Even though the incidence rate of IBD has started to decline in Western countries since 1990, the incidence rate continues to increase rapidly in newly industrialized countries [4, 5]. While the European countries with the highest prevalence of IBS are reported to be Norway and Germany, the disease is more common in Canada, and USA [5]. Inflammatory bowel disease directly or indirectly affects the patients' quality of life, mental health, work productivity and overall health [6 - 8]. The diagnosis of IBD, its treatment and follow-up of the patients bring a great economic burden to the national health systems of the countries. The estimated annual treatment costs for IBS patients in the United States alone, are more than USD 6.8 billion [6, 9]. Therefore, it is necessary to understand the pathogenesis of this disease and develop new evidence-based diagnosis and treatment strategies for IBD disease.

PATHOGENESIS OF IBD

The reason why and how IBS occurs is not yet fully understood, but it was known that the dysregulated mucosal immune response against commensal gut microbiota of the host is responsible for the pathogenesis of the diseases. Host genetic factors and enviromental conditions have been identified as the main reasons for this dysregulation in recent studies [1, 2, 10]. Inflammatory bowel disease is classified into two predominant groups, ulcerative colitis and Crohn's Disease, which have similar symptoms. A healthy colon consists of a loose outer layer suitable for bacterial growth, a firmer and sterile inner layer and a continuous mucus coating. There is a marked increase in bacteria associated with the adherent mucus layer of the colon when IBD occurs, particularly in CD [11 - 13]. Some of these similar symptoms of CD and UC are diarrhea, weight loss, abdominal pain, and rectal bleeding. The main characteristic feature of CD and UC is inflammation in the gastrointestinal tract and its gradual exacerbation [2, 14, 15]. On the other hand, there are certain variations between the symptoms of patients suffering from CD and UC.

Crohn's disease is more common in patients at the ages of 15-35 and directly affects the mouth, the stomach, the esophagus, the anus and the intestinal mucosa in the body. Differently, ulcerative colitis is mostly confined to the colon and affects parts of the large intestine, including the rectum [16]. Ulcerative colitis mostly causes damage to the internal parts of the body and isassociated with osteoporosis and colon cancer. Crohn's disease, which affects the entire intestine, mostly cause skin diseases and biliary stones in the later stages of the disease [17]. The four main components of IBD pathogenesis characterized by a chronic inflammation in gut may be listed as genetic, environmental, microbial and immunological factors [11].

Genetic Factors

Thanks to the technological developments in recent years, new important informationhas been obtained regarding the interaction between the pathogenesis of IBD and the genetic characteristics of the host [11, 18]. By using genome-wide association studies (GWAS), which identify single nucleotide polymorphisms, 200 IBD-associated risk alleles have been identified until nowadays [19]. The findings of recent studies on the genetic factors associated with IBD, provided noteworthy clues about the underlying mechanism of the disease [11]. A total of 163 IBD-associated gene loci were detected, of which 30 were CD-specific, 23 were specific for UC, and 110 were associated with both diseases [11, 20]. NOD2 (nucleotide-binding oligomerization domain containing 2 domains) was the first gene discovered to be associated with CD, in 2001 [21]. The protein that performs encoding by NOD2 was described as an intracellular receptor, which recognizes the muramyl dipeptide (MDP) in the peptidoglycan layer of the bacterial cell membrane [22]. Autophagy contributes to the removal of intracellular microbes by the degradation of cytosolic contents and organelles [10]. The autophagy-associated genes (ATG16L1 and IRGM) relate with the risk of CD. CD-associated polymorphisms and various mutations in these genes cause defects in antibacterial autophagy [23, 24].

One of the most important genetic findings related to IBD is the determination of the relation between the IL23R gene and the proinflammatory cytokines encoded by this gene. IL-23 is a receptor peptide playing a role in Th17 cell generation. It is well known that Th17 cells and interleukin IL-23, a pro-inflammatory cytokine, have a detrimental effect on CD and UC progression [25 - 27]. These risk-associated gene loci show heterogenicity between populations; NOD2 and IL23R variants are present in the majority of European patients, but rare in East Asian ancestry patients. Additionally, some individuals having IBD-associated gene loci, may not even develop the symptoms of the disease [28]. Various environmental factors and the interactions between the gut microbiota and host immune system are critical for the pathogenesis of IBD, in addition to genetic parameters [4].

Environmental Factors

External environmental factors have direct or indirect effects on IBD as in almost every disease. Smoking, diet and nutrition, drug usage, air pollution, demographic properties, and stress conditions are prominent environmental prompters associated with the development of IBD [29]. High-stress levels have been paid attention to as a predisposing factor the pathogenesis of both CD and UC for many years [30, 31]. It has been reported that individuals with low stress levels

CHAPTER 6

Multiple Sclerosis (MS) and its Treatment with Natural Products

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Abstract: Multiple sclerosis (MS) is an autoimmune disease that causes myelination defects and axonal impairment in the central nervous (CNS) system, causing inhibition of electrical transmission. The disease's typical symptoms include stiffness, persistent discomfort, exhaustion, motor and mobility problems, and cognitive deficits. Although immunosuppressive and immune-modulating medications have been the fundamental basis of MS treatment, there is currently no known treatment for the disease. Herbal-originated therapies are now being considered a possible therapeutic option for MS by using medicinal plant extracts or phytochemicals. Numerous research works have emphasized the medicinal herbs' anti-inflammatory and antioxidant properties, which make them a natural treatment for MS. According to the literature, several plants, such as hemp, turmeric, ginkgo, St. John's wort, black cumin, ginseng, and ginger have been reported to have various therapeutic effects in MS patients. Otherwise, the most promising substances that have been suggested to treat MS symptoms include curcumin, resveratrol, cannabinoids, apigenin, omega 3, and vitamin D. In this chapter, we compiled medicinal plants, and phytochemicals that have potential effects on MS. It is suggested that clinical trials were conducted on MS patients with medicinal plants, which were prominent *in vivo* findings. We also advise further research in this field to identify the precise active ingredients present in these extracts for the best composition necessary for the intended therapeutic effect.

Keywords: Herbal remedy, Multiple sclerosis (MS), Natural product, Neurodegenerative diseases.

INTRODUCTION

Multiple sclerosis (MS) is a central nervous system (CNS) problem related to autoreactive T cells and inflammation. It is characterized by the immune system mistakenly attacking the protective covering of nerve fibers called myelin. This leads to inflammation, demyelination (loss of myelin), and disruption of nerve signals [1].

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The symptoms of MS can vary widely and may include fatigue, muscle weakness, coordination and balance problems, numbness or tingling, cognitive impairment, and visual disturbances. The course of the disease can also vary, with some individuals experiencing relapses and remissions (RMS). In contrast, others may have a progressive decline in function without remission (primary progressive MS-PPMS) [2].

The exact reason for MS is not fully understood, but it is believed to involve a combination of genetic and environmental factors. There is currently no cure for MS, but various treatment options are available to manage symptoms, slow down disease progression, and improve the quality of life. These may include disease-modifying therapies, symptom management medications, physical and occupational therapy, and lifestyle modifications. Ongoing research in the field of MS aims to better understand the underlying mechanisms of the disease, identify new therapeutic targets, and develop more effective treatments. Advances in imaging techniques, such as magnetic resonance imaging (MRI), have provided valuable insights into the progression and pathology of MS. Moreover, patient advocacy groups and organizations play a crucial role in raising awareness, providing support, and advocating for better access to care and research funding for individuals with MS. Individuals with MS need to work closely with healthcare professionals to develop a personalized treatment plan and to actively manage their condition through regular monitoring, lifestyle modifications, and adherence to prescribed medications [3].

Natural products, especially medicinal plants, are the new leading therapeutic targets. Studies conducted to date have revealed that herbs play a complementary role in the treatment of MS disease by relieving symptoms or preventing the progression of the disease. Recently, in newly published articles, it has been seen that drug discovery studies based on phytochemical compounds responsible for the effect and different formulations and different techniques have gained importance [4].

Pathophysiology of MS

The pathophysiology of MS involves a complex interplay of immune system dysfunction, inflammation, demyelination, and neurodegeneration [5]. While the exact cause of MS remains unknown, several key mechanisms contribute to the development and progression of the disease.

Autoimmune Response

MS is considered an autoimmune disease, meaning the immune system mistakenly attacks the body's tissues. In MS, immune cells, particularly T cells,

become activated and cross the blood-brain barrier into the CNS. This immune system malfunction leads to chronic inflammation within the CNS [6].

Inflammation and Blood-Brain Barrier Dysfunction

Inflammatory immune cells, such as T cells and macrophages, release cytokines and other pro-inflammatory molecules within the CNS. This inflammatory response causes damage to the blood-brain barrier, which normally protects the brain and spinal cord from harmful substances. The compromised blood-brain barrier allows immune cells to infiltrate the CNS, leading to further inflammation and tissue damage [7].

Demyelination

Myelin, the protective covering around nerve fibers, is a primary target in MS. Inflammatory processes in the CNS cause immune cells to attack and damage the myelin sheath. Demyelination disrupts the conduction of nerve impulses, resulting in impaired nerve signaling and the characteristic symptoms of MS [8].

Reactive Gliosis and Neurodegeneration

In response to demyelination and inflammation, supportive cells in the CNS called glial cells [astrocytes and microglia] become activated. This activation, known as reactive gliosis, leads to the release of inflammatory molecules and contributes to further damage to myelin and nerve fibers. Over time, neurodegeneration can occur, leading to an irreversible loss of neuronal tissue [9].

Remyelination and Repair

In some cases, the CNS can initiate a process called remyelination, in which oligodendrocytes [cells responsible for myelin production] attempt to repair damaged myelin. However, the effectiveness of remyelination can vary among individuals and may become less efficient as the disease progresses [10].

The interplay between immune dysregulation, inflammation, demyelination, and neurodegeneration results in the clinical manifestations and progression of MS. The heterogeneity of MS, with various disease courses and clinical phenotypes, further reflects the complex pathophysiology of the condition.

Understanding these underlying mechanisms is crucial for developing targeted therapies that modulate the immune response, reduce inflammation, promote remyelination, and protect against neurodegeneration. Ongoing research aims to unravel the precise factors that trigger MS and develop more effective treatments to halt or slow down disease progression.

CHAPTER 7

Celiac Disease and Gut Microbiota: Herbal Treatment and Gluten-Free Diet

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Abstract: Celiac disease (CD) manifests as a targeted autoimmune response that adversely affects the small intestine, primarily affecting individuals with a particular genetic predisposition. Diagnosis centers on identifying this gluten-sensitive enteropathy, which can be ameliorated through the implementation of a gluten-free diet (GFD), correlating with mucosal healing and symptom alleviation. The human microbiota, a vast symbiotic community within the gastrointestinal tract, profoundly impacts human health. Advances in genome sequencing have elucidated the intricate relationship between gut microbiota and autoimmune diseases, including CD, emphasizing the significant role of dietary patterns in shaping the gut microbiota. The influence of GFD on microbiota composition, the only clinically validated treatment for CD, leads to a nutritional shift and potential macronutrient imbalance. Emerging research also highlights the therapeutic potential of various herbs with antioxidant, anti-inflammatory, antimicrobial, gastroprotective, and immunomodulatory properties as complementary approaches to manage CD. This chapter synthesizes the complex interactions between genetics, diet, gut microbiota, and potential herbal interventions in CD, paving the way for more comprehensive understanding and management strategies.

Keywords: Autoimmune diseases, Antioxidant, Antimicrobial, Anti-inflammatory, Celiac disease, Gluten sensitivity, Gluten-free diet, Gut microbiota, Herbal treatment.

INTRODUCTION

Celiac disease (CD) is a complex autoimmune disorder characterized by an immune-mediated enteropathy that primarily inflicts damage upon the small intestine [1, 2]. This pathology is not arbitrary in its manifestation but is rather confined to individuals with a specific genetic predisposition, indicating the

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pivotal role of genetics in the onset of celiac disease [3]. These individuals demonstrate a detrimental reaction to the ingestion of gluten, a protein complex found in various grains.

The diagnosis of celiac disease hinges upon the identification of gluten-sensitive enteropathy, a damaging inflammation and structural deterioration of the small intestinal mucosa, culminating in malabsorption and diverse clinical symptoms [4]. This inflammation, triggered by an immune response specifically directed towards gluten, is notable for its amelioration through the implementation of a gluten-free diet (GFD), implying a direct correlation between gluten intake and intestinal damage [5]. Consequently, the exclusion of gluten leads to mucosal healing, alleviation of symptoms, and a reduced risk of associated complications, reaffirming the essential role of a GFD in the management of this autoimmune disorder [6].

Overview of Celiac Disease

CD is a multifaceted autoimmune disorder that exhibits variable global prevalence with estimates ranging from 0.3% to 1% [4]. Detailed regional analysis reveals a 1% prevalence in Europe and the United States, translating to a substantial affected population, considering the sizable demographics of these regions [7]. The CD also pervades the Middle East, North Africa, and India, although diagnostic limitations potentially lead to underdiagnosis or delayed diagnosis [8].

CD's prevalence shows a correlation with dietary habits; higher in countries where wheat, rich in gluten, is a dietary mainstay [9]. Conversely, in countries like China and Japan, where rice is a staple, CD incidence is low [10]. In Western Europe, CD prevalence exhibits age-related variations, with increasing incidence in adults and adolescents over 65 years of age [11].

A gender-related prevalence pattern also emerges, with women being more susceptible to CD than men, possibly pointing towards hormonal or genetic factors contributing to disease susceptibility [12, 13]. Genetic factors also play a vital role, evidenced by higher disease frequency among monozygotic twins and first-degree relatives, reinforcing genetic predisposition [14, 15].

Celiac patients and their first-degree relatives exhibit an elevated risk of other autoimmune diseases, suggesting a complex interplay of genetic and immune-related factors beyond CD [16]. Gluten absorption triggers a cascade of immune responses primarily involving T lymphocyte activation and the release of cytokines and surface antigens [17]. The intestinal epithelium's integrity, critical for gut health, deteriorates in CD, resulting in elevated gliadin levels, a key component of gluten implicated in CD [18]. Inflammatory response and immune

reactions in CD prominently involve Immunoglobulin A (IgA) and a 33-mer peptide contained within gliadin [19].

Chronic inflammation in CD causes the destruction of intestinal villi, leading to malabsorption symptoms [15]. Clinical findings span a broad spectrum, dictated by disease duration, intestinal damage extent, patient age, and specific symptoms [20]. Given the significant number of undiagnosed patients vis-a-vis potential prevalence, the "Iceberg Model Theory" proposes a much higher number of undiagnosed CD patients in the community [21].

CD's complexity necessitates its categorization into five forms—classical, atypical, silent, or asymptomatic, latent, and refractory—each characterized by unique symptoms and disease progression, demanding a personalized approach to diagnosis and treatment [22 - 24].

Celiac Disease and Gut Microbiota

The human microbiota, a symbiotic community of approximately 10-100 trillion microbial cells, primarily resides within the gastrointestinal tract (GIS), skin, genitourinary system (GUS), and respiratory system [25]. The microbiome, encompassing the genes of these microbes, profoundly impacts human health and disease [26]. These co-inhabitants, estimated to be around 1014, are largely bacteria, supplemented by viruses and fungi [27]. The GIS is particularly hospitable due to its abundant nutritional supply, accounting for over 70% of the body's microorganisms [27]. Determining the number and diversity of intestinal bacteria is challenging; however, advances in high-throughput genome sequencing have yielded significant insights, suggesting the GIS hosts over 35,000 bacterial species [28, 29].

The GIS microbiota encompass aerobic, anaerobic, and facultative anaerobic bacteria. However, they predominantly consist of anaerobic bacteria, including Firmicutes, Bacteroides, Proteobacteria, and Actinobacteria [28]. A human GIS tract may host between 500-1000 distinct gut bacteria types, with Firmicutes and Bacteroidetes comprising over 60% and 20% of the microbiota, respectively [30]. Other substantial anaerobic bacteria include Fusobacteria, Verrucomicrobia, Spirochaet, Lentisphaerae, and Cyanobacteria [31]. Notably, obligate anaerobes are more prevalent than facultative anaerobes. The intestinal microbiota exhibits dynamic shifts over time, primarily influenced by diet, diseases, antibiotic use, and environmental changes [32, 33]. A study indicated that approximately 95% of the virome content in a healthy adult remained stable over a year, and attributed to dietary habits [34].

CHAPTER 8

Beneficial Effects of Berry Fruits on Autoimmune Diseases

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Abstract: The prevalence of autoimmune diseases in developed societies suggests the use of natural products for prevention and treatment. At the beginning of preventive approaches, the idea of regularly consuming herbal products that can have positive effects on autoimmune diseases and making them a part of the diet is common. Beneficial phytochemicals can be reached by consuming these herbal products directly and/or the products obtained from them. In addition, numerous studies have demonstrated that berries offer the potential to protect against autoimmune diseases if they are consumed regularly with their phytochemicals, especially phenols, anthocyanins, vitamins, and specific minor components. There are also studies on the effects of these phytochemicals on autoimmune diseases. It is stated that the regular consumption of berry fruits increases the quality of life, and the protective effect it provides is much easier and less costly than the treatment of autoimmune diseases. This chapter is aimed at revealing the potential of berry fruits to protect from autoimmune diseases, reduce the negative effects of the disease, and/or support treatment. Although studies on the beneficial effects of berries have increased in recent years, they are still behind other fruits.

Keywords: Autoimmune diseases, Anthocyanins, Berry fruits, Diet, Herbal products, Phytochemicals, Phenols, Quality of life.

INTRODUCTION

Well-known berries are strawberry, raspberry, blueberry, blackberry, gooseberry, redcurrant, currant, and cranberry. Boysenberry, bilberry, jostaberry, cloudberry, loganberry, and lingonberry are more rarely known berry fruits. Berry fruits represent an important fresh product variety in Europe in terms of production volume and economic profitability [1, 2].

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Berry berries have a special taste and unique texture. In addition, berry fruits offer a very different experience than other fruits with their striking and bright colours, delicate textures, and different shapes. In this way, they win the appreciation of consumers. Berry fruits are a group of fruits that have attracted intense interest not only for their sensory qualities but also for the beneficial components they have [3].

Growing conditions such as climate, soil structure, irrigation, number of sunny days, variety, and maturity level directly affect the phytochemical content of berry fruits [4, 5]. Berries contain many phytochemicals, fibers, vitamins, and minerals. Berries also have a high concentration of polyphenols, so it is possible to use them for treating various diseases pharmacologically by acting on oxidative stress and inflammation [6]. In studies, it has been reported that berry fruits can be a source of functional components that can be used in the food and pharmaceutical industries due to their unique phytochemical composition [7, 8]. Studies on not only fruit but also berry seeds have shown that they have high health potential. For this reason, examining the functional properties of berry seeds and determining their effects on health have been among the topics of interest in recent years. In addition, studies report that berry seeds can have beneficial effects on autoimmune diseases. Studies on the by-products formed after the processing of berry fruits indicate that extracts that can be effective in the prevention of autoimmune diseases can be made with the tip in the raw material [9, 10]. Consumption of berries or berry products with high phytochemical content is expected to provide an advantage for protection from autoimmune diseases. It should not be forgotten that the variety, amount, and frequency of their consumption in the diet are very effective in the health benefits that will emerge [11, 12].

It is reported that unhealthy living conditions such as less physical activity during the day, unbalanced diet, stressful lifestyle, insufficient sleep, and air pollution weaken the immune system and weaken people's defence against diseases. It has been stated that this situation not only weakens the immune system but also causes problems with the immune system [13]. It is reported that autoimmune diseases also fall into this group. Autoimmune diseases are conditions in which the immune system mistakenly damages healthy cells in the body. Your immune system works to protect the body from diseases and infections. The immune system can distinguish between foreign cells and body cells and detect foreign cells as disease agents. But in case of an autoimmune disease, the immune system may perceive parts of your body, such as the joints or skin, as foreign and unfortunately begin to attack these healthy cells or tissues [14]. The reported number of autoimmune diseases is increasing every year. Some of those are celiac diseases, type 1 diabetes, psoriasis, rheumatoid arthritis, inflammatory bowel

disease, multiple sclerosis, Guillain, chronic inflammatory demyelinating polyneuropathy, Graves' disease, Hashimoto's thyroiditis, myasthenia gravis, scleroderma, and vasculitis [15, 16].

In order to be protected from diseases in unhealthy living conditions, the search for plants offered by nature to people attracts the attention of scientists. With this point of view, it has been reported that pharmaceutical raw materials and food supplements have been developed, and successful results have been obtained with previous studies. This chapter's purpose is to assemble and analyze the current studies on the beneficial effects of berry fruits on autoimmune diseases. Also, it aims at providing a collective perspective for consumers and scientists.

EFFECT OF BERRIES ON AUTOIMMUNE DISEASES

Both autoimmune diseases and the characteristics of berry fruits are not widely known. Increasing studies on this subject may be beneficial for raising awareness. This section of the chapter provides a review of studies investigating the effects of some berries on autoimmune diseases.

Effect of Berries on Vasculitis

Berry consumption has been associated with a reduction in all-cause mortality [17]. Epidemiological studies and meta-analyses have reported the positive effect of polyphenols and polyphenol-rich foods on vascular function [18, 19]. Since all berry fruits are rich in polyphenols, it suggests that their regular consumption may be beneficial for the prevention of vascular diseases. It has also been reported that anthocyanins protect against cardiovascular and neurodegenerative diseases [20]. Berry berries are already characterised by their rich anthocyanin content. Therefore, it is accepted that both phenol and anthocyanin contents may be effective in preventing vascular diseases and have positive effects on vascular functions [19, 21]. It has been stated that protective effects may be seen on vascular function depending on the regular consumption of berry fruits in the diet, the frequency, amount, and type of consumption [19, 22].

A study investigating the effect of a single serving of blueberries (250 g) in elderly subjects (≥ 60 years) evaluated the effects of bioactive substances on markers of oxidative stress, inflammation, and vascular function following blueberry ingestion. In the study, it was reported that blueberries slowed vascular dysfunction and the development of cardiovascular diseases and showed potential beneficial effects on vascular function [23]. Post-harvest processing, such as pressing, pasteurisation, and conventional and vacuum drying, can significantly affect the polyphenol (including anthocyanin) and vitamin content of berries, and

CHAPTER 9

The Role of Herbal Therapy in the Treatment of Graves' Disease and Hashimoto Thyroiditis

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Abstract: Currently, Hashimoto's thyroiditis (HT) and Graves' disease (GD) are the foremost conditions that people think of when discussing autoimmune thyroid disorders. While radioactive iodine (RAI) treatment, anti-thyroid drugs, and surgical resection are currently at the forefront for GD; thyroid replacement therapy is used for HT. Many studies are being performed to develop new treatment methods for Graves and Hashimoto thyroiditis patients who do not respond to traditional treatments. While herbal treatments are being tried for GD, studies are being carried out on changing nutritional habits or additional food supplements for HT. While there are currently many studies on traditional Chinese medicine in the literature for GD, nutrients for HT are considered complementary treatments using their anti-inflammatory and antioxidant properties. In patients with HT, the need for levothyroxine increases, especially due to possible interactions of gliadin with thyroid antigens, the presence of lactose components in levothyroxine preparations, and damage to the intestinal villi in those with lactose intolerance. Therefore, the course of the disease may be better in HT patients with additional dietary recommendations.

Keywords: Autoimmune thyroid diseases, Chinese medicine, Hashimoto's thyroiditis, Graves' disease, Herbal therapy, Hyperthyroidism, Hypothyroidism, Thyroglobulin, Thyrotoxicosis.

INTRODUCTION

The prevalence of autoimmune diseases (AIDs) is gradually increasing worldwide. Autoimmune diseases are seen in approximately 5% of the general population in developed countries and their cause is multifactorial and is not fully known. The first diseases that come to mind when it comes to autoimmune thyroid diseases (ATD) are Graves' Disease (GD) and Hashimoto thyroiditis (HT). Clinically, HT usually manifests with hypothyroidism and GD with thyrotoxicosis [1].

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Graves' disease (GD) is an autoimmune disease defined by diffuse thyroid enlargement of the thyroid gland and elevated blood thyroid hormone levels. Patients suffer from symptoms of thyrotoxicosis including excessive sweating, irritability, palpitations, weakness, fatigue, heat intolerance, and insomnia. Anti-thyroid drugs are currently used as the first step in treatment against GD. Thyroidectomy or ablation with radioactive iodine (RAI) causes permanent hypothyroidism and necessitates life-long thyroid hormone replacement therapy [7].

Also called chronic lymphocytic thyroiditis, Hashimoto thyroiditis (HT) is currently regarded as the most frequent AID. HT is characterized by the existence of circulating autoantibodies against thyroglobulin (TG), thyroid peroxidase (TPO) and lymphocytes infiltrating the thyroid tissue. Although hyperthyroidism and euthyroidism phases are observed in HT, most patients eventually develop hypothyroidism. Early diagnosis and intervention are particularly important as high thyroid autoantibody levels cause lower quality of life in euthyroid HT patients. It involves the substitution of thyroid hormones to address hypothyroidism associated with HT [2]. This chapter aims to evaluate the effects of herbs and herbal metabolites on the management of Hashimoto's thyroiditis and Graves' disease.

AUTOIMMUNE THYROID DISEASES

Worldwide, there is a gradual increase in the prevalence of autoimmune diseases. The etiology of autoimmune diseases is multifaceted and remains incompletely understood. However, it is thought that T-lymphocytes escaping from central and peripheral tolerance mechanisms trigger autoimmunity. The organ most affected by these diseases is the thyroid gland. The first diseases that come to mind when it comes to autoimmune thyroid diseases (ATD) are Hashimoto thyroiditis (HT) and Graves' Disease (GD). Clinically, HT usually manifests with hypothyroidism, and GD with thyrotoxicosis. These disorders can emerge in genetically susceptible individuals with the addition of environmental factors [1]. Other autoimmune diseases such as vitiligo, rheumatoid arthritis, myasthenia gravis, coeliac disease, and primary adrenal insufficiency may accompany ATDs [2].

Although HT is most commonly seen between 45 and 65 years of age, it may also be seen in children. Its prevalence in adults is reported to be 5%. The prevalence of autoimmune thyroid diseases in school-age children is reportedly 2.5% [2].

The Pathophysiology of Graves' Disease

Graves' disease (GD) is an autoimmune disease characterized by diffuse enlargement of the thyroid gland and elevated blood thyroid hormone levels. It is

most commonly seen in women of 20-40 years of age. Patients suffer from symptoms of thyrotoxicosis including excessive sweating, irritability, palpitations, weakness, fatigue, heat intolerance, and insomnia. Blood TSH level is low, T3 and/or T4 levels are elevated. In addition, increased vascularization and parenchymal heterogeneity of the thyroid gland, and the presence of TSH Receptor Antibody (TRAB) are sufficient to make the diagnosis [3].

In GD, there is an abnormal activation of the immune system and a loss of immune tolerance against TSHR [4]. In addition, hydrophilic muco-polysaccharides proinflammatory cytokines released as a result of the effect of TRAB on TSHR on the surface of fibroblasts cause local edema, congestion, and exophthalmos in the eye [5].

Recent research has indicated that the insulin-like growth factor-1 receptor (IGF-1R) plays a crucial role as both a significant factor and autoantigen in the development of Graves' ophthalmopathy (GO) [6, 7] (Fig. **1**).

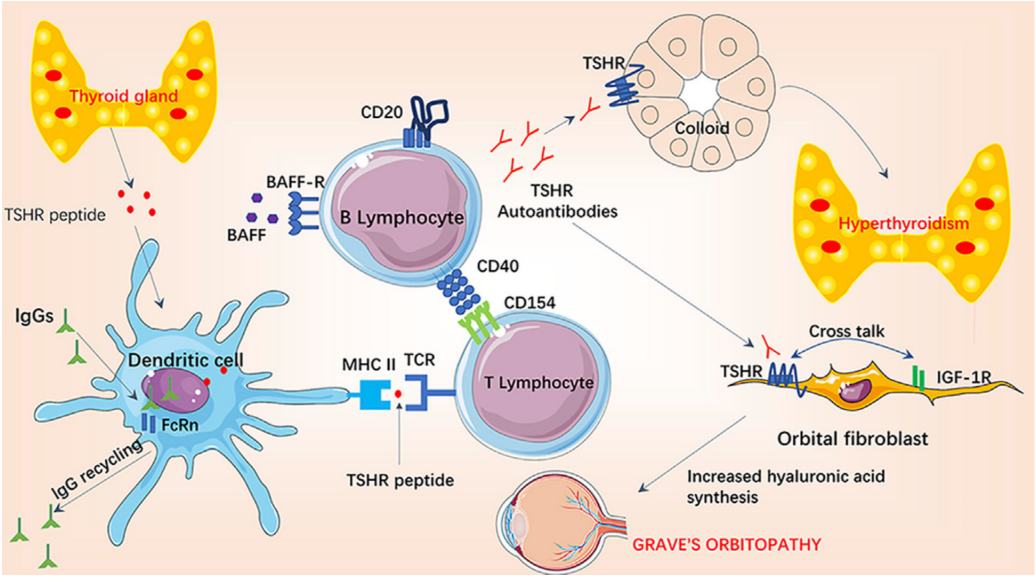

Fig. (1). Pathogenesis of Graves Hyperthyroidism and Orbitopathy [7].

Large amounts of TRAB are released from B lymphocytes as a result of humoral immune response activation. TRAB, which is released from B lymphocytes, is divided into two groups, namely inductor TRAB and inhibitor TRAB [8]. Circulating TRAB acts like a TSH agonist and binds to TSHR to stimulate thyroid cells to proliferate and get hypertrophied. As a result, the expression of the thyroglobulin, thyroid peroxidase, and sodium-ion cotransporter genes is

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