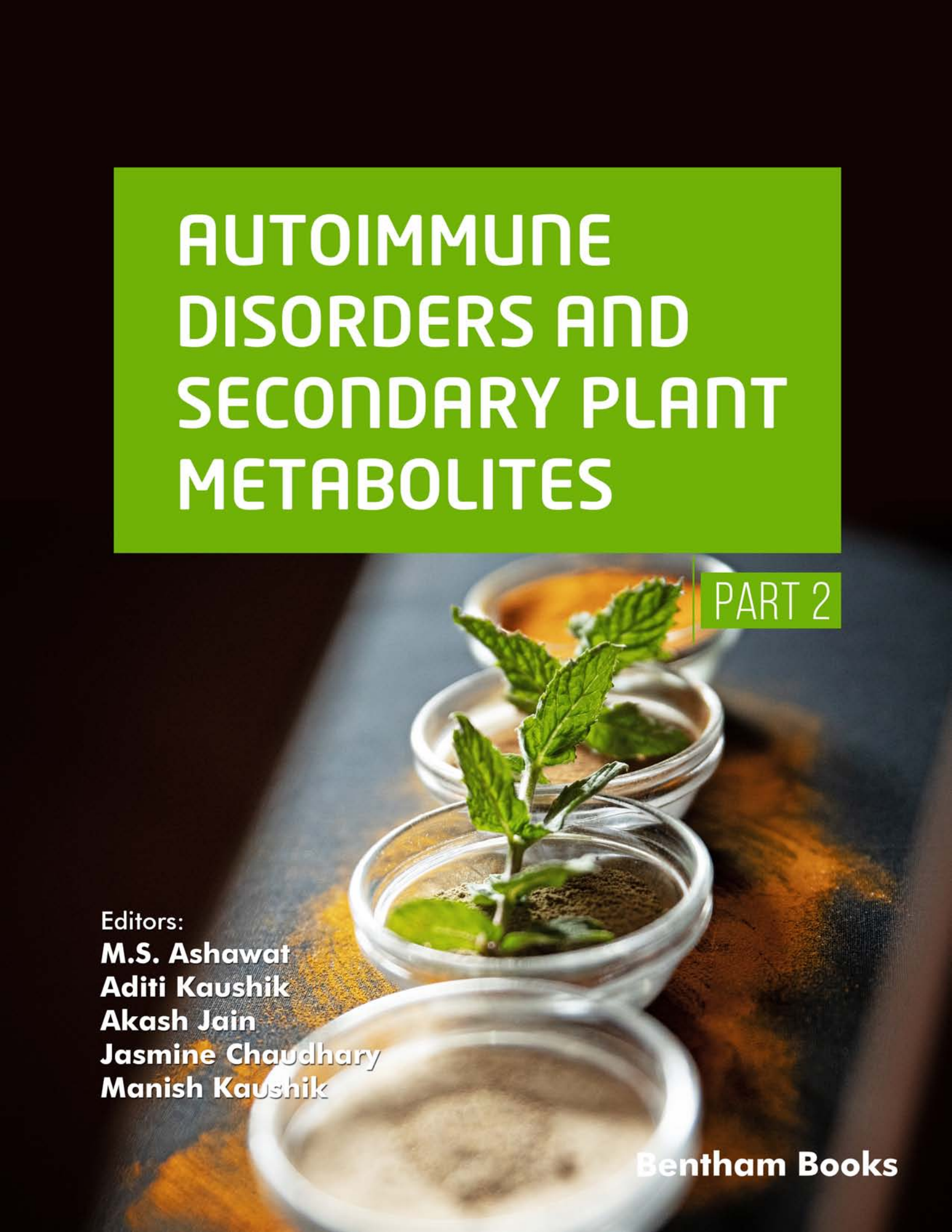
AUTOIMMUNE DISORDERS AND SECONDARY PLANT METABOLITES

PART 2



Editors:
M.S. Ashawat
Aditi Kaushik
Akash Jain
Jasmine Chaudhary
Manish Kaushik

Bentham Books

Autoimmune Disorders and Secondary Plant Metabolites

(Part 2)

Edited by

M.S. Ashawat
Department of Pharmaceutics
Laureate Institute of Pharmacy
Kangra, Himachal Pradesh, India

Aditi Kaushik
Department of Pharmaceutical Chemistry
Laureate Institute of Pharmacy
Kangra, Himachal Pradesh, India

Akash Jain
Department of Pharmacology
M.M. College of Pharmacy, M.M. (Deemed to be University)
Mullana, Ambala, Haryana, India

Jasmine Chaudhary
Department of Pharmaceutical Chemistry
M.M. College of Pharmacy, M.M. (Deemed to be University)
Mullana, Ambala, Haryana, India

&

Manish Kaushik
Department of Pharmacology
SBS College of Pharmacy
Kangra, Himachal Pradesh, India

Autoimmune Disorders and Secondary Plant Metabolites *(Part 2)*

Editors: M.S. Ashawat, Aditi Kaushik, Akash Jain, Jasmine Chaudhary and Manish Kaushik

ISBN (Online): 979-8-89881-279-9

ISBN (Print): 979-8-89881-280-5

ISBN (Paperback): 979-8-89881-281-2

Published by Bentham Science Publishers Pte. Ltd. Singapore, in collaboration with Eureka Conferences, USA.

First published in 2025.

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.
No. 9 Raffles Place
Office No. 26-01
Singapore 048619
Singapore
Email: subscriptions@benthamscience.net

CONTENTS

FOREWORD

The contents of the book "Autoimmune disorders and Secondary Plant Metabolites" have been read in detail by me and it contains highly useful information on the important functions of the secondary plant metabolites in the management of various autoimmune disorders. The editors of this book are the experts who have been working in the field of Pharmaceuticals for years and are known in the subjects of their specializations. Their focused and multidisciplinary approach aims to introduce the basic insights of the book and emphasizes the comprehensive use of the secondary plant metabolites.

All the chapters have been authored by a group of dedicated academicians and scientists who actively engaged in the field of the design and development of novel pharmaceuticals in the management of different autoimmune disorders. As a medical expert for more than 20 years, I foresee that this book will be of great value not only to postgraduates, teachers and research scholars in the field of Pharmaceuticals, but also to the industrial and scientific communities. This work contains substantial data for emphasizing herbal therapeutics as one the newer approach for the design and development of novel pharmacophore and their derivatives in the management of various autoimmune disorders.

In this post-COVID era, phytotherapy would be effectively utilized for the treatment of various diseases more effectively. The overall detail of the subject by the various authors in the different chapters of this book would go a long way in throwing new light on the area of autoimmune disorders.

I sincerely hope this venture is a great success, as it reflects the devotion, dedication and hard work of the team of editors. I am confident that this book will be very useful and gain enough attention from research scholars and academicians working in the field of medical and pharmaceuticals.

May the spirit of discovering better future remedies and optimizing phytopharmaceuticals provide superior medication to the benefit of humanity.

Nor Farid Bin Mohd Noor
Faculty of Medicine
Universiti Sultan Zainal Abidin (UniSZA)
Medical Campus, Jalan Sultan Mahmud
20400 Kuala Terengganu, Terengganu
Malaysia

PREFACE

The human immune system is a multi-faceted network of functionally diverse cells expressing a broad array of receptors that collectively function to respond to infection, eliminate precancerous cells, and maintain metabolic health. The breakdown of this delicately poised immune response is typically life-limiting; however, even subtle changes in its ability to distinguish an invading pathogen from the host can give rise to a spectrum of autoimmune diseases. Indeed, autoimmune diseases affect approximately 5%–8% of the world population and cause tremendous suffering to patients while also representing a major global socioeconomic issue. Although detailed molecular, immunological, genetic, and clinical studies have provided an increasingly sophisticated understanding of the mechanisms that underpin some autoimmune diseases, the drivers of human autoimmune diseases, including environmental triggers and the ensuing pathogenesis, remain poorly understood. In general, current immune-modulatory drugs used in the treatment of autoimmune diseases are broadly acting, non-disease specific, and, consequently, associated with side effects such as infection and malignant disease. Furthermore, it is clear that the majority of patients are not responding optimally to these therapies. Thus, there is a pressing need for the development of new drugs or repositioning of drugs based on a molecular and clinical understanding of the specific autoimmune diseases in individual patients in combination with high-throughput analysis of integrated datasets. Such personalized medicines may go hand in hand with the inclusion of new diagnostics, leading to a better disease understanding and more patient-centric clinical trials that also consider ethnic diversity and patient-reported outcome measures. Prevention should also be part of future early intervention. This book's perspective will highlight the different types of current therapies and showcase how future basic studies, new technologies, and clinical trials could dynamically and reciprocally inform each other, leading to a better understanding of disease mechanisms and, hence, more refined treatments.

Treatment of autoimmune diseases has drastically changed over the last 20 years with development and routine clinical use of synthetic or biologic drugs that block various pathways and components of the immune system, such as cytokines, cell adhesion molecules, and co-stimulatory molecules, or delete entire immune cell populations.

The novelty intensifies in this book's content, reflecting growing interest in exploring herbal alternatives as complementary or alternative therapies for autoimmune diseases. While these herbal options show promise, it is essential to consult with a healthcare professional before incorporating them into your treatment plan. Individual responses may vary, and personalized approaches are crucial for managing autoimmune disorders effectively. Always prioritize safety and work closely with your healthcare provider to find the best combination of therapies for your specific condition. The different plant’s secondary metabolites play a significant role in modern therapy, including the treatment of autoimmune disorders. Insides of book where the attempt is made to focus on the Plants secondary metabolites, have gained prominence due to their relative safety and multifunctionality. Phytoconstituents offer better pharmacokinetic profiles and reduced adverse effects compared to synthetic drugs. Hundreds of phytoconstitutents have shown promising results in biochemical and cell line studies. Certain phytoconstitutents have been studied for their potential in managing autoimmune disorders. In summary, plant secondary metabolites offer a diverse array of therapeutic possibilities, making them valuable allies in the quest for better health. Thus, the research in the field of autoimmune disorders and secondary metabolites increased the hope of the scientific community. This book is focused on the role of various secondary plant metabolites in the management of different autoimmune disorders. The contents are divided into two sections wherein the first section focuses on the basics of autoimmunity as well as the

interrelationship between autoimmune disorders, medicinal plants and drug discovery. The second section of this book strikes, therefore, a great balance at the described role of the secondary plant metabolites in different autoimmune disorders.

M.S. Ashawat
Department of Pharmaceutics
Laureate Institute of Pharmacy
Kangra, Himachal Pradesh, India

Aditi Kaushik
Department of Pharmaceutical Chemistry
Laureate Institute of Pharmacy
Kangra, Himachal Pradesh, India

Akash Jain
Department of Pharmacology
M.M. College of Pharmacy, M.M. (Deemed to be University)
Mullana, Ambala, Haryana, India

Jasmine Chaudhary
Department of Pharmaceutical Chemistry
M.M. College of Pharmacy, M.M. (Deemed to be University)
Mullana, Ambala, Haryana, India

&

Manish Kaushik
Department of Pharmacology
SBS College of Pharmacy
Kangra, Himachal Pradesh, India

List of Contributors

Akshita Arora	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab 142001, India
Amandeep Singh	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab 142001, India
Aman Upaganlawar	Department of Pharmacology, SNJBs Shriman Sureshdada Jain College of Pharmacy, Neminagar, Chandwad, Nashik 423101, Maharashtra, India
Astha	Department of Pharmaceutical Chemistry, Laureate Institute of Pharmacy, Kangra 176031, Himachal Pradesh, India
Aditi Kaushik	Department of Pharmaceutical Chemistry, Laureate Institute of Pharmacy, Kangra 176031, Himachal Pradesh, India
Ajay Kumar	Department of Pharmaceutics, Laureate Institute of Pharmacy, Kangra 176031, Himachal Pradesh, India
Arun Kumar	Faculty of Pharmacy, Integral University, Dasauli, Kursi Road, Lucknow, Uttar Pradesh 226026, India
Amrit Kaur	Department of Pharmacy Practice, University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali 140413, Punjab, India
Amit Kumar Srivastava	Department of Biosciences and Bioengineering, Indian Institute of Technology Roorkee, Roorkee, Uttarakhand, India
Anjali Chandel	Department of Pharmacology, Laureate Institute of Pharmacy, Kathog, India
Chinmay Deshmukh	School of Health Sciences and Technology, Dr Vishwanath Karad, MIT World Peace University, Pune 411038, India
Dilpreet Singh	Department of Pharmaceutics, University Institute of Pharma Sciences, Chandigarh University, Gharuan 140413, Punjab, India
Gaurav Joshi	Department of Pharmacology, Laureate Institute of Pharmacy, Kathog, Jawalamukhi, Kangra, Himachal Pradesh, India
Himanshu Gandhi	Department of Pharmaceutics, School of Pharmaceutical Sciences, Shoolini University, Solan, Himachal Pradesh, India
Isha Thakur	Department of Pharmacy Practice, University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali 140413, Punjab, India
Kuldeep Singh	Faculty of Pharmacy, Integral University, Dasauli, Kursi Road, Lucknow, Uttar Pradesh 226026, India
MS Ashawat	Department of Pharmaceutics, Laureate Institute of Pharmacy, Kangra 176031, Himachal Pradesh, India
Mohd Maaz Khan	Faculty of Pharmacy, Integral University, Dasauli, Kursi Road, Lucknow, Uttar Pradesh 226026, India
Mandeep Kumar Gupta	Department of Pharmaceutical Chemistry, Moradabad Educational Trust Group of Institutions, Faculty of Pharmacy, Moradabad, Uttar Pradesh, India
Nilesh Mahajan	Dadasaheb Balpande College of Pharmacy, Besa, Nagpur, Maharashtra, India

Nitin Pandey	Faculty of Pharmacy, Integral University, Dasauli, Kursi Road, Lucknow, Uttar Pradesh 226026, India
Nishant Goutam	Department of Pharmacology, Laureate Institute of Pharmacy, Kathog, Jawalamukhi, Kangra, Himachal Pradesh, India
Pragya Sharma	Department of Pharmaceutical Chemistry, Amity Institute of Pharmacy, Amity University, Jaipur, Rajasthan, India
Rajnish Srivastava	Department of Pharmacology, Chitkara University School of Pharmacy, Chitkara University, Baddi, Himachal Pradesh, India
Rupali Rana	Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, Punjab, India
Simranjeet Kaur	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab 142001, India
Satish Polshettiwar	School of Health Sciences and Technology, Dr Vishwanath Karad, MIT World Peace University, Pune 411038, India
Shraddha Kulkarni	School of Chemical Engineering and Bioengineering, Dr Vishwanath Karad, MIT World Peace University, Pune 411038, India
Shom Prakash Kushwaha	Faculty of Pharmacy, Integral University, Dasauli, Kursi Road, Lucknow, Uttar Pradesh 226026, India
Samar Vihal	School of Pharmaceutical Sciences, KC Institute of Pharmaceutical Sciences, Pandoga, Una, Himachal Pradesh, India
Shagun Thakur	Department of Pharmacology, Laureate Institute of Pharmacy, Kathog, India
Tuhin James Paul	Department of Pharmacy Practice, ISF College of Pharmacy, Moga, Punjab 142001, India
U.S Mahadeva Rao	Faculty of Medicine, University Sultan Zainal Abidin, Malaysia
Varun Singh	Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, Punjab, India
Vandana Bhatia	Department of Pharmacology, Laureate Institute of Pharmacy, Kathog, India
Yogita Ozarde	Department of Pharmaceutics, SNJBs Shriman Sureshdada Jain College of Pharmacy, Neminagar, Chandwad, Nashik 423101, Maharashtra, India
Yavnika Minhas	Department of Pharmacology, Laureate Institute of Pharmacy, Kathog, India

CHAPTER 1

Plant Secondary Metabolites: Therapeutic Potential and Pharmacological Properties in Psoriasis

Simranjeet Kaur[1,#], Akshita Arora[1,#], Tuhin James Paul[2,#], Dilpreet Singh[3,#] and **Amandeep Singh[1,*]**

[1] *Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab 142001, India*

[2] *Department of Pharmacy Practice, ISF College of Pharmacy, Moga, Punjab 142001, India*

[3] *Department of Pharmaceutics, University Institute of Pharma Sciences, Chandigarh University, Gharuan 140413, Punjab, India*

Abstract: Psoriasis, an autoimmune skin condition characterized by inflammation and excessive cell growth, necessitates ongoing treatment due to its recurrent nature. Conventional therapies often involve synthetic drugs, which are associated with some severe side effects. Recent research highlights the potential of herbal medicines as safer and more effective alternatives. This chapter explores the potential of natural remedies like *Dysidea avara, Tripterygium wilfordii, curcuma longa, Strobilanthes Cusia, Capsicum annum., Polygonum cuspidatum, Ligusticum chuanxiong,* and *Thymus vulgaris*, which offer promising and safe alternatives for psoriasis management. The phytoconstituents obtained from these herbal plants exhibit anti-inflammatory, immunomodulatory, and anti-oxidant properties that could help modulate the immune response and reduce skin inflammation. This chapter focuses on the utilization of medicines in psoriasis treatment, highlighting their enhanced therapeutic profiles and reduced toxicity.

Keywords: Anti-psoriatic activity, Mode of action, Phytoconstituents, Plant secondary metabolites, Psoriasis, Skin inflammation.

INTRODUCTION

Psoriasis

Psoriasis is a chronic autoimmune skin disorder characterized by the abnormal proliferation of epidermal cells at specific sites, leading to the formation of thick,

* **Corresponding author Amandeep Singh:** Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab 142001; E-mail: ad4singh@gmail.com

# These authors have equal contribution

M.S. Ashawat, Aditi Kaushik, Akash Jain, Jasmine Chaudhary & Manish Kaushik (Eds.)

white, itchy plaques. Various factors, including environmental triggers, genetics, immune dysfunction, and lifestyle choices, contribute to the onset and progression of the disease [1]. Psoriasis significantly increases the risk of comorbidities such as cardiovascular disease, diabetes, gastrointestinal disorders, liver disease, depression, and anxiety. Though it often begins with mild, localized inflammation, it can rapidly progress into a more severe condition. Psoriasis affects approximately 2-3% of the global population, with peak incidence occurring between the ages of 20-30 and 50-60. Family history plays a critical role in its development, with a higher likelihood of occurrence in individuals with a genetic predisposition [2, 3].

Psoriasis is clinically classified into several subtypes: inverse psoriasis, guttate psoriasis, pustular psoriasis, erythrodermic psoriasis, and the most common type, chronic plaque psoriasis (psoriasis vulgaris), which accounts for 80-90% of cases. Psoriasis vulgaris is characterized by well-defined, erythematous plaques covered with silvery scales [4]. Inverse psoriasis, or flexural psoriasis, affects areas where the skin folds, such as the armpits, groin, and under the breasts, and presents as slightly erosive, erythematous plaques [5]. Guttate psoriasis typically occurs in children or adolescents and is often triggered by a group-A streptococcal infection, such as tonsillitis. It manifests as small, red, scaly plaques [6]. Pustular psoriasis is distinguished by the presence of multiple sterile pustules, which can be either localized or generalized [7]. Erythrodermic psoriasis is a severe and acute form of the disease, involving more than 90% of the body's surface, which becomes red and inflamed. This form can develop from any psoriasis and requires urgent medical intervention [8].

Pathophysiology of Psoriasis

Psoriasis is a chronic inflammatory skin disorder caused by an overactive immune response involving T-cells, keratinocytes, and dendritic cells. Its pathogenesis is triggered by environmental factors like infections or skin injuries, which activate immune cells, particularly dendritic cells [9]. These cells present antigens to T-cells, leading to the release of pro-inflammatory cytokines that drive excessive keratinocyte proliferation and abnormal differentiation. This process results in the formation of the characteristic thick, scaly plaques [10] as shown in Fig. (**1**). The ongoing interaction between immune cells and keratinocytes creates a feedback loop that sustains inflammation and perpetuates the disease.

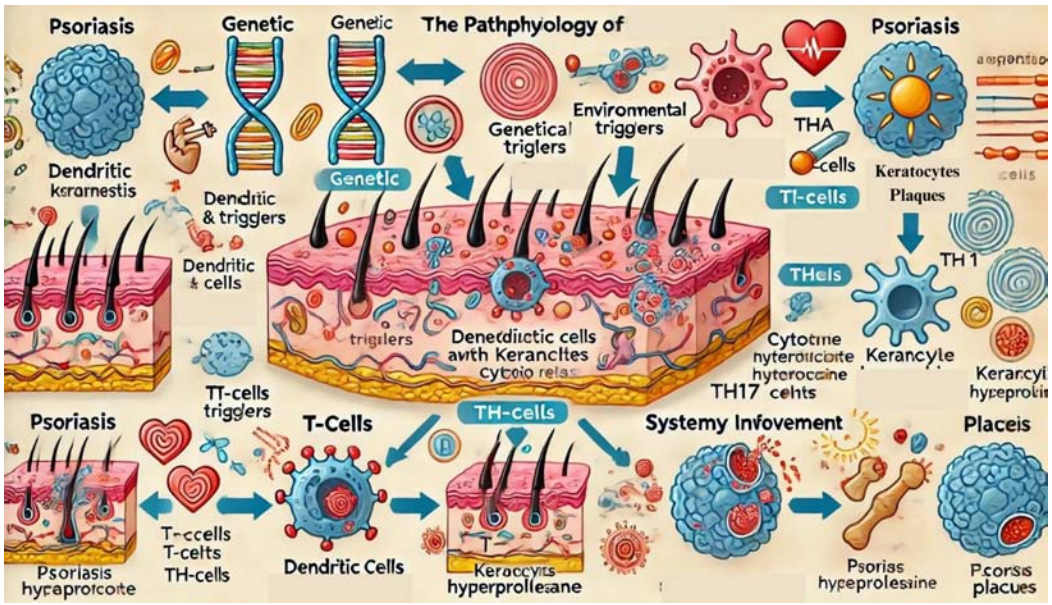


Fig. (1). Pathogenesis of psoriasis.

Cells Involved in the Pathogenesis

Keratinocytes

Keratinocytes, a major component of the epidermis, form the skin's mechanical barrier while also playing a crucial role in initiating, maintaining, and regulating the immune response. Although they are not classical antigen-presenting cells, they can process and present antigens to T-cells. Normally, keratinocytes in the basal layer mature into spiny and granular layers, eventually losing their nuclei to form the stratum corneum, which is regularly renewed. In response to environmental stimuli, keratinocytes release cytokines and Antimicrobial Peptides (AMPs), which bind to nucleic acids like DNA or RNA to form antigenic complexes. These complexes activate dendritic cells, which deliver antigens to T-cells. Activated T-cells then release cytokines (such as IL-23, IL-17, IL-22, and IFN-γ) that promote abnormal keratinocyte differentiation and proliferation, leading to incomplete keratinization. This creates a positive feedback loop between keratinocytes and the immune system, driving the development of psoriasis [11, 12].

CHAPTER 2

The Role of Flavonoids in Inflammatory Bowel Disease

Satish Polshettiwar[1,*], Shraddha Kulkarni[2], Aman Upaganlawar[3], Yogita Ozarde[4], Nilesh Mahajan[5] and **Chinmay Deshmukh[1]**

[1] School of Health Sciences and Technology, Dr Vishwanath Karad, MIT World Peace University, Pune 411038, India

[2] School of Chemical Engineering and Bioengineering, Dr Vishwanath Karad, MIT World Peace University, Pune 411038, India

[3] Department of Pharmacology, SNJBs Shriman Sureshdada Jain College of Pharmacy, Neminagar, Chandwad, Nashik 423101, Maharashtra, India

[4] Department of Pharmaceutics, SNJBs Shriman Sureshdada Jain College of Pharmacy, Neminagar, Chandwad, Nashik 423101, Maharashtra, India

[5] Dadasaheb Balpande College of Pharmacy, Besa, Nagpur, Maharashtra, India

Abstract: Inflammatory Bowel Disease (IBD), encompassing ulcerative colitis and Crohn's disease is a chronic condition involving inflammation of the Gastrointestinal Tract (GIT) characterized by periods of remission and exacerbation. The pathogenesis of IBD involves a complex influence of genetic, environmental, microbial, and immunological factors. Conventional treatments, including corticosteroids, immunosuppressants, and biologics, often have significant side effects and do not provide a cure, highlighting the need for alternative therapeutic approaches. Flavonoids, a diverse group of poly-phenolic compounds found in vegetables, fruits, and certain beverages, have garnered significant attention due to their anti-inflammatory, antioxidant, and immunomodulatory properties. The present chapter explores the considerable role of flavonoids in the management and treatment of IBD, involving their mechanisms of action, therapeutic benefits, and evidence from preclinical and clinical studies. Key mechanisms by which flavonoids exert their beneficial effects include modulation of inflammatory pathways, inhibition of pro-inflammatory cytokines, suppression of oxidative stress, and regulation of gut microbiota composition. Preclinical studies using animal models of IBD have demonstrated that flavonoids can mitigate inflammation, decrease disease severity, and improve histopathological outcomes. Clinical trials, although limited, have provided preliminary evidence supporting the efficacy of flavonoid supplementation in reducing clinical manifestations and inflammatory markers in IBD patients. Despite the

[*] **Corresponding author Satish Polshettiwar:** School of Health Sciences and Technology, Dr Vishwanath Karad, MIT World Peace University, Pune 411038, India; Tel: 8796022838;
E-mail: satish.polshettiwar@mitwpu.edu.in

M.S. Ashawat, Aditi Kaushik, Akash Jain, Jasmine Chaudhary & Manish Kaushik (Eds.)

encouraging data, challenges remain regarding the bioavailability, dosage, and long-term safety of flavonoid supplementation. Future research should focus on optimizing delivery methods, elucidating the synergistic effects of flavonoid combinations, and conducting large-scale, well-designed clinical trials to establish standardized guidelines for their use in IBD management. This chapter emphasizes the important role of Epigallocatechin Gallate (EGCG), quercetin, curcumin, and resveratrol in reducing intestinal inflammation and promoting mucosal healing.

In conclusion, flavonoids represent a promising adjunctive therapy for IBD. Their multifaceted anti-inflammatory and immunomodulatory actions have the potential to improve patient outcomes. Integrating flavonoids into conventional treatment regimens could offer a more holistic approach to managing this debilitating condition.

Keywords: Curcumin, Epigallocatechin gallate, Flavonoids, Immunomodulatory actions, Inflammatory Bowel Disease, Preclinical studies, Quercetin.

INTRODUCTION

The human digestive system often referred to as the Gastrointestinal Tract (GIT) that is having the most important biological roles such as absorption, digestion, and assimilation of important and essential nutrients, vitamins, and minerals. In addition, one of the most important functions of GIT is protection against the impact of pathogens. In various diseases of GIT, pathogens are involved. Various ailments of the digestive tract are known clinically and among them all, one is Inflammatory bowel disease, commonly called IBD [1]. IBD is a collection of all inflammatory conditions that involve mild to severe swelling of the gastrointestinal tract often involving the bowel. The continuous and prolonged swelling of this tract may damage the delicate structures in the bowel, hampering the functions of the pipe. There are two broad categories of this inflammatory condition, one of which is Crohn's disease, often abbreviated clinically as CD and the other is Ulcerative colitis *i.e.,* UC. Both diseases typically have the same signs and symptoms. IBD has some clinical manifestations such as diarrhoea, GIT bleeding, pain in the stomach, intestinal obstruction, ulcer, perforation, and even sometimes cancer. The CD is an autoimmune disease that can harm any portion of the alimentary canal, but the distal part of the small intestine and colon is commonly involved. UC is also a long-lasting inflammatory condition where swelling occurs mostly in the rectum and the colon [2]. More specifically, there is confluent mucosal inflammation in the colon which is observed at the verge of the anal and continued proximally for the variable length and severity. It is regarded as proctitis, which is the swelling of the lining of the rectum, left-sided colitis in which inflammation extends up through the descending or sigmoid part of the colon, or pancolitis, where inflammation affects the entire length of the colon. UC has symptoms such as diarrhoea with blood and abdominal pain. CU has common characteristics with the presence of transmural granulomatous inflammation

anywhere in the tract, but mostly near the ileocecal valve and terminal ileum or colon. About 75% of the patients have these problems in the small bowel and 90% of patients have diseases in the terminal ileum [3].

Prevalence and Incidence

Different geographical areas have different incidences of IBD. Sweden, the United Kingdom, the United States, and Norway have the highest rates. In the US, the incidence of UC is 11 per 100,000 and that of CD is 7 per 100,000. Countries in South Africa, Australia and Southern Europe, have lower incidence rates: for UC, 2 to 6.3 per 100,000, and for CD, 0.9 to 3.1 per 100,000 [4]. IBD is rare in South America and Asia. For example, incidence rates of 0.5 and 0.08 per 100,000 of UC and CD, respectively (Fig. **1**). The IBD has mortality in the first year of disease diagnosis and when it becomes chronic, patients die due to colon cancer. The standardized mortality ratios were 1.51 and 1.37, respectively, for CD and UC in a Swedish population study. The onset of UC peaks in the age group of 15-30 years. Between the age groups of 60 and 80, a second peak may be observed. The males and females are equally affected, but the incidence varies due to several factors. The male-to-female ratio for CD is 1.1 to 1.8 and for UC is 1:1. IBD is also different in severity and frequency based on genes, race, and gender. Different Jewish population has different impacts and frequencies of IBD [6]. Similarly, Ashkenazi Jews have a prevalence of IBD two to three times more than Sephardic, Oriental Jews, or Israeli-born [5]. The prevalence progressively decreases in African-American, non-Jewish Caucasian, Asian populations, and Hispanic people. Considering urbanization and industrialization, rural areas such as villages have less chance of developing IBD and urban regions have a higher chance of developing IBD. Similarly, the high economic classes have a higher chance of IBD than lower economic classes. This is probably due to adulterated fruits, vegetables, cereals, and lentils that are consumed in urban areas or due to various unhealthy eating habits in cities. Similarly, IBD is commonly observed in obese people. Chair syndrome is the most suspected cause of IBD. In Asia, the number of IBD cases is increasing, but not at the same rate as in Europe. As per the latest findings, Punjab and Haryana had some documented cases of IBD. In 2003, the task force for the study and prevalence of IBD was constituted, which has collected information from various gastrologists across the nation. It is observed that CD was much higher in the South than in the East, as compared with other regions of India. The information was collected from a real hospital-based OPD through a questionnaire [7, 8]

In IBD patients, smokers have different effects. The risk of patients who are addicted to smoking is 40% higher than that of non-smokers. In contrast, the CD is observed to double in smokers than in non-smokers. Oral contraceptives are

CHAPTER 3

Management of Addison's Diseases by Secondary Plant Metabolism.

Astha[1], MS Ashawat[2,*], U.S Mahadeva Rao[3], Aditi Kaushik[1] and **Ajay Kumar[2]**

[1] *Department of Pharmaceutical Chemistry, Laureate Institute of Pharmacy, Kangra 176031, Himachal Pradesh, India*

[2] *Department of Pharmaceutics, Laureate Institute of Pharmacy, Kangra 176031, Himachal Pradesh, India*

[3] *Faculty of Medicine, University Sultan Zainal Abidin, Malaysia*

Abstract: Adrenal insufficiency causes Addison's disease, a chronic endocrine disease that needs to be managed by hormone replacement therapy for the rest of one's life. Alternative and complementary methods for reducing symptoms and improving patient quality of life have been studied recently. Using secondary plant metabolites, bioactive substances are generated by plants that can alter a variety of physiological processes. Alkaloids, flavonoids, terpenoids, and phenolic compounds are examples of secondary plant metabolites that display a variety of pharmacological activities, including immunomodulatory, antioxidant, and anti-inflammatory properties. The various symptoms of Addison's disease, which include immunological dysfunction, persistent fatigue, and muscle weakness, may be better managed with these qualities. Multiple pathways contribute to the therapeutic potential of secondary plant metabolites in the management of Addison's disease. Flavonoids, which are anti-inflammatory substances, can help reduce systemic inflammation, a common issue in patients with Addison's disease. By reducing oxidative stress, antioxidants such as phenolic acids can protect adrenal tissue from further damage. Moreover, considering that Addison's patients have reduced cortisol production, adaptogenic herbs containing terpenoids help to support the body's stress response. Certain plant extracts, such as those from *Glycyrrhiza glabra* (Licorice) and *Withania somnifera* (Ashwagandha), have been shown in studies to have the ability to modify adrenal function and promote hormone synthesis. For example, glycyrrhizin, found in *Glycyrrhiza glabra*, can act as a corticosteroid substitute and help alleviate specific symptoms of adrenal insufficiency. *Withania somnifera* is recognized for its adaptogenic properties, which have been demonstrated to enhance the body's ability to withstand stress and may benefit the overall health of patients with Addison's disease. Including secondary plant metabolites in the treatment of Addison's disease provides an alternative strategy that may reduce reliance on synthetic corticosteroids and minimize related adverse effects. To determine the effectiveness, ideal doses, and safety profiles of these substances in the

[*] **Corresponding author Mahendra Singh Ashawat:** Department of Pharmaceutics, Laureate Institute of Pharmacy, Kangra 176031, Himachal Pradesh, India; E-mail: msaresearchg@gmail.com

M.S. Ashawat, Aditi Kaushik, Akash Jain, Jasmine Chaudhary & Manish Kaushik (Eds.)

context of Addison's disease, further clinical trials are needed. This Chapter advocates for integrative approaches that utilize the medicinal capabilities of substances produced from plants by highlighting the potential of secondary plant metabolites as an adjunct therapy in the management of Addison's disease. Patients with this challenging endocrine condition may experience improved patient outcomes and a higher quality of life by leveraging secondary plant metabolism. An overview of the possible management of Addison's disease by secondary plant metabolites is given in this abstract, with a focus on the pharmacological characteristics of these compounds and the need for additional study to confirm their therapeutic utility.

Keywords: Addison's diseases, Alkaloids, Anti-inflammatory, Anti-oxidants, Immunomodulatory, Phenolic Compounds.

INTRODUCTION

Overview of Addison's Diseases

Primary adrenal insufficiency, also known as Addison's disease, is a rare endocrine disorder characterized by the inadequate production of essential hormones by the adrenal glands, particularly cortisol and aldosterone. All ages and genders are susceptible to this illness, despite its relative rarity.

The tiny glands, known as adrenal glands, are located atop each kidney and are essential for the production of hormones that regulate a range of body processes [1]. Of these hormones, aldosterone helps balance sodium and potassium levels in the blood, which is essential for maintaining blood pressure and healthy muscle and nerve function. Cortisol, on the other hand, helps control stress, regulate blood pressure, and maintain metabolism. Dr. Thomas Addison, a British physician who initially described Addison's disease in 1855, is the reason behind the disease's name [2]. The understanding of endocrine problems was greatly advanced by Dr. Addison's identification of the main symptoms of the condition and its correlation with damage to the adrenal glands. The outer layer of the adrenal glands, known as the adrenal cortex, is harmed in Addison's disease. This damage is frequently brought on by an autoimmune response, in which the body's immune system unintentionally targets the adrenal tissue. Addison's disease is thought to affect only 1 in 100,000 persons, making it a very uncommon condition [3]. Although it can manifest at any age, adults between the ages of 30 and 50 are the most frequently diagnosed. The effects are the same for males and women. Additional reasons may include bleeding into the adrenal glands, some malignancies, infections, including tuberculosis, and hereditary factors. The symptoms of the illness are caused by the glands' reduced ability to produce sufficient cortisol and aldosterone due to this damage [4]. Hormone replacement therapy is the mainstay of traditional care, which aims to replace the missing

hormones. The potential of secondary plant metabolites as supplemental medicines has been brought to light by recent studies. These bioactive substances, present in various plants, possess pharmacological properties that can help manage Addison's disease by reducing oxidative stress, enhancing adrenal function, and mitigating inflammation. Typically, nonspecific symptoms of Addison's disease appear gradually and insidiously, which might cause a delay in diagnosis. It may take some time for the symptoms to get worse, which makes early diagnosis challenging. Frequently, the patient's severe adrenal crisis, characterized by hypotension, hyponatremia, hyperkalemia, and hypoglycemia, is the reason for the diagnosis [5]. Low cortisol and aldosterone levels, elevated renin levels, and blunt cortisol response to ACTH stimulation are used to establish the diagnosis. Addison's crisis is a serious endocrine emergency that requires prompt recognition and treatment. Hormonal replacement therapy must be administered for the rest of a patient's life to stabilize Addison disease patients [6]. The goal of maintenance therapy is to supply an equivalent to sustain a normal level of glucocorticoids and mineralocorticoids. Typically, nonspecific symptoms of Addison's disease appear gradually and insidiously, which might cause a delay in diagnosis. It may take some time for the symptoms to get worse, which makes early diagnosis challenging. A high level of clinical examination is maintained to prevent misdiagnosis [7]. Frequently, the patient's severe adrenal crisis, characterized by hypotension, hyponatremia, hyperkalemia, and hypoglycemia, is the reason for the diagnosis. A stressful illness or other triggers, such as an infection, trauma, surgery, vomiting, or diarrhea, may cause this. A significant amount of stress or illness can reveal a shortage of cortisol and mineralocorticoids [8].

Current Treatment Landscape and Challenges

The hormones cortisol and aldosterone, which are absent in Addison's disease, are substituted with synthetic forms. Drugs such as hydrocortisone and fludrocortisone are used to replace cortisol and aldosterone, respectively. Since Addison's disease is a chronic condition, lifelong medication is required [9]. The dosage of these medications varies from person to person. To prevent an acute adrenal crisis, your doctor may increase the dosage if you experience an illness, undergo surgery, suffer trauma, or face another stressful situation. If you are taking fludrocortisone, your doctor may recommend increasing your salt intake, especially in hot and humid weather or after intense physical activity. The symptoms of Addison's disease usually develop gradually, as damage to the adrenal glands typically occurs over an extended period [10]. The symptoms differ among individuals, and some are represented in Table **1**. Individuals with Addison's disease who are assigned female at birth may also experience irregular menstruation (periods), hair loss, and diminished sexual drive [11]. In certain

CHAPTER 4

Recent Advances in Managing Myasthenia Gravis Through Secondary Plant Metabolites

Mohd Maaz Khan[1], Nitin Pandey[1], Arun Kumar[1,*], Kuldeep Singh[1] and **Shom Prakash Kushwaha[1]**

[1] *Faculty of Pharmacy, Integral University, Dasauli, Kursi Road, Lucknow, Uttar Pradesh, 226026, India*

Abstract: Myasthenia Gravis (MG) is an autoimmune neuromuscular disorder characterized by fluctuating muscle weakness and fatigue. Acetylcholinesterase inhibitors, thymectomy, and immunosuppressive treatments are the mainstays of traditional MG care. However, these therapies frequently have serious drawbacks and adverse effects. Secondary Plant Metabolites (SPMs) have been shown to hold promise as alternative or supplementary therapies for Myocardial Infarction (MI) in recent developments in the field of phytotherapy. Flavonoids, alkaloids, terpenoids, and phenolic compounds are examples of SPMs. These chemicals have antioxidant, immunomodulatory, and anti-inflammatory qualities that may be advantageous to MG patients. The most recent studies on different SPMs and their modes of action with MG are examined in this chapter. Research has demonstrated that substances like quercetin, resveratrol, and curcumin can improve neuromuscular transmission, lower oxidative stress, and regulate immunological responses, all of which may help to lessen MG symptoms. Furthermore, preclinical and clinical studies have started to confirm the safety and effectiveness of these metabolites, opening the door for novel treatment approaches. Including SPMs in the MG treatment plan may improve patient outcomes, decrease dependency on prescription drugs, and minimize adverse effects. This chapter aims to provide a comprehensive overview of the current state of knowledge and future directions in the use of secondary plant metabolites for regulating *myasthenia gravis*, with an emphasis on their participation in innovative and comprehensive therapy techniques.

Keywords: Immune modulation, Innovative therapies, Myasthenia Gravis, Neuromuscular transmission, Phytotherapy, Plant metabolites.

INTRODUCTION

Myasthenia gravis is a condition characterized by voluntary muscular weakness and fatigue that worsens with repeated use and improves with rest. About half of

* **Corresponding author Arun Kumar:** Faculty of Pharmacy, Integral University, Dasauli, Kursi Road, Lucknow, Uttar Pradesh, 226026, India; E-mail: arun@iul.ac.in

M.S. Ashawat, Aditi Kaushik, Akash Jain, Jasmine Chaudhary & Manish Kaushik (Eds.)

the patients initially experience ocular muscle weakness, which is the frequent presentation of the illness. Over time, 15% of patients have weakness limited to the muscles of the eyelids and extraocular areas, whereas 85% of patients develop generalized muscle weakness. The condition primarily affects the symmetric proximal muscle groups in the limbs. Severe respiratory muscle weakness may indicate a myasthenic crisis and require artificial ventilatory support. Bimodal age distribution indicates that the disorder is more common in women in their second and third decades of life than in men in their sixth and seventh decades. The disease often manifests at age 26, and overall, women are more likely to be affected than men. Myasthenia gravis can have a variable clinical course, with symptoms that can appear gradually or suddenly. Acute exacerbations or spontaneous remissions are possible for patients. A physical examination that doesn't interfere with sensation, reflexes, or coordination only finds motor problems. A modified version of Osserman staging is used to classify the severity of the disease:

- Grade I: Ocular disease only
- Grade II: Mild to moderate generalized disease
- Grade III: Severe generalized disease
- Grade IV: Crisis

Routine thyroid function testing is necessary since 5% of myasthenia gravis patients experience thyroid impairment. Myasthenic symptoms can be aggravated or misdiagnosed as thyroid disorders, such as hypothyroidism or hyperthyroidism. A chest CT scan or MRI is the most effective method for detecting thymomas, which are seen in about 12% of patients. Furthermore, lupus erythematosus, thyroiditis, and rheumatoid arthritis are among the autoimmune conditions that have been connected to myasthenia gravis [1].

PATHOGENESIS

Understanding typical neuromuscular junction function is essential to comprehending the pathophysiology of myasthenia gravis. Acetylcholine (ACh) is a neurotransmitter that is normally released from the motor nerve terminal of the NMJ in tiny vesicles called quanta. The ACh-containing quanta attach to ACh Receptors (AChRs) on the folded muscle endplate membrane after diffusing across the synaptic cleft. The motor unit endplate depolarizes and the muscle contracts when a stimulated motor neuron releases a particular quantity of ACh quanta and enough of those quanta bind to the muscle endplate area. Acetylcholine receptors (AChRs) are proteins on muscle cells that are wrongly attacked by the immune system in the majority of Myasthenia Gravis (MG) cases.

This attack is carried out by certain antibodies, primarily IgG1 and IgG3. These antibodies can:

1. Damage the AChRs by activating a defense system in the body called the complement system, which creates a harmful complex known as the Membrane Attack Complex (MAC).
2. Block acetylcholine (ACh), a chemical messenger, from binding to the AChRs.

There are fewer AChRs available on the surface of muscle cells as a result of these attacks. This implies that during nerve impulses, fewer ACh molecules can attach to the muscle cell, resulting in less efficient muscular activation. Consequently, muscles weaken, particularly after prolonged activity, and this weakness manifests as fast muscular fatigue, a typical MG symptom [2]. Thymus alterations, such as an increase in T-cells and thymus cells, are common in MG patients with AChR antibodies, indicating that the thymus may be the source of the dangerous antibodies. Patients with severe MG often improve after thymectomy or removal of the thymus. Treatments for MG are designed to minimize adverse effects while controlling the disease, achieving remission, or reducing symptoms. Pyridostigmine, an acetylcholinesterase inhibitor, is the first-line treatment for MG, according to Italian recommendations. Immunosuppressive drugs are also used if this is insufficient to control symptoms. Because steroids quickly and effectively modify the immune system, they are frequently administered as the initial line of treatment [3].

LIMITATIONS OF CURRENT MG TREATMENTS

Acetylcholinesterase Inhibitors

In the treatment of Myasthenia Gravis (MG), a chronic autoimmune disease marked by variable muscular weakness and fatigability, Acetylcholinesterase (AChE) inhibitors are a key player. Through a well-established mechanism, these pharmacological drugs improve neuromuscular transmission by reversibly inhibiting the enzyme acetylcholinesterase, which catalyzes the hydrolysis of Acetylcholine (ACh). AChE inhibitors enhance the concentration of ACh at the Neuromuscular Junction (NMJ) by blocking its breakdown, which makes it easier for ACh to bind to postsynaptic receptors. This mode of action relieves symptoms by momentarily reducing the typical muscle weakness that MG patients experience. Despite their effectiveness, the clinical use of AChE inhibitors is marred by a spectrum of side effects, primarily stemming from the ubiquitous nature of cholinergic receptors in the human body. These adverse effects can be broadly categorized based on the type of cholinergic receptor involved: muscarinic or nicotinic [4].

CHAPTER 5

Exploration of Potential Secondary Plant Metabolites for the Treatment of Alopecia Areata

Nishant Goutam[1], Gaurav Joshi[2,*], Amrit Kaur[2] and **Isha Thakur[2]**

[1] *Department of Pharmacology, Laureate Institute of Pharmacy, Kathog, Jawalamukhi, Kangra, Himachal Pradesh, India*

[2] *Department of Pharmacy Practice, University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali 140413, Punjab, India*

Abstract: An autoimmune response is the core cause of alopecia areata, which is a disorder that causes hair loss and is influenced by a variety of different variables. It is hypothesized that genetic predisposition and lifestyle-related environmental stressors, such as physical and emotional stress, contribute to the development of the disorder. Although the specific immunological processes are not yet entirely known, many people consider that these elements play a role in the disease's progression. Current medications may be utilized for therapy, yet these treatments lack curative efficacy, and their employment is restricted due to probable harmful effects, particularly in particular extreme scenarios. Consequently, scientific investigation is undertaken to stress the development and production of new medicinal substances that are both safe and free of undesired repercussions. Secondary metabolites are a vast spectrum of natural compounds found in plants and microbes that have diverse bioactivities. The present demand for plant drug discovery research shows the huge, undiscovered pharmacological potential of secondary metabolites created by plants. Throughout history, a vast variety of plant secondary products have been gathered from ancient civilizations to effectively cure different maladies, owing to their original pharmacological characteristics. This chapter addresses the history, treatment choices, and anticipated applications of plant secondary metabolites in the construction of a curative medicine for alopecia areata.

Keywords: Alopecia areata, Flavonoids, Hair follicle dynamics, Immunomodulatory effects, Secondary plant metabolites, Terpenoids.

[*] **Corresponding author Gaurav Joshi:** Department of Pharmacy Practice, University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali, Punjab, India; Tel: +91-9449794177,
E-mail: drugs.joshi92.gj@gmail.com

M.S. Ashawat, Aditi Kaushik, Akash Jain, Jasmine Chaudhary & Manish Kaushik (Eds.)

INTRODUCTION

Background on Alopecia Areata

Alopecia is a reversible and common type of hair loss that occurs mostly in every generation. The reason behind the occurrence of the diseases is still unknown [1]. It is not necessarily found only on the scalp, but can be seen on any hair-bearing surface of the body [2]. It affects the hair follicles, resulting in nonscarring hair loss. In a study, it was observed that it is seen more in females than in males, it may occur at any age, and in any person of any hair color (3). The exact cause remains unclear, although it is believed to involve, at least in part, the loss of immune privilege in hair follicles, activation ofinflammatory pathways, and autoimmune-driven destruction of hair follicles [4]. T-helper [T_h] 1 has been known as the driver of the disease, whereas some recent studies show that the activation of the immune mediators, such as the Th2 pathway, IL-23, and IL-32, are contributors to AA's pathogenesis [5].

Current Treatment Options and Limitations

The treatment is mainly grounded on the age and the degree of scalp involvement in a patient [6].

Janus Kinase [JAK] inhibitors are used and are found to be effective in some cases of AA [5]. Ritlecitinib, a selective JAK3/TEC kinase inhibitor, shows inhibitory actions against the functions of the signaling molecules and immune cells that cause hair loss in people. A dose of 50mg and 30 mg daily for 24 weeks results in regrowth of hair in some cases [7].

Some topical therapy, which may include topical glucocorticosteroids, Minoxidil, and immunotherapy treatments, can be used in some limited cases. Some currently ongoing treatments for the diseases are glucocorticosteroids, Methotrexate, ciclosporin, azathioprine, dapsone, mycophenolate, mofetil, tacrolimus, and sulfasalazine [8].

Importance of Secondary Plant Metabolites

Secondary Plant Metabolites [SPM] are a significant part of plants as a defense system against pathogens and the environment [9]. Secondary Metabolites [SM] are important indicators for evaluating the quality of medicinal materials [10]. SMs are gaining interest in the pharmaceutical, dye, and food industries . An alternate mechanism, complicated by the biosynthesis of secondary metabolites, leads to mutual products such as phenols, flavonoids, and terpenes [11].

Overview of Secondary Metabolites in Plants

SPM carries out various functions. They contribute to many basic and pathogen-inducible phytochemicals to plant essential immunity [12]. These metabolites are compounds that are not essential for the organism to live, but they play an important role in the functioning of the organism. They belong to different metabolite families that may be highly inducible in response to stress [13]. The extraordinary biological activities of the plant SM may result in its wide use as an ingredient in medicine and some culinary and therapeutic uses. Plants may always be in contact with changing conditions of light, water, temperature, pH, and insect pest infestations, which may vastly affect the growth of SM [14].

Relevance to Human Health and Therapeutic Potential

Many secondary metabolites exhibit antioxidant, antidiabetic, anthelminthic, anticoagulant, and lipid-lowering properties, and some plants may exhibit anticytotoxic properties and may also help in the prevention of angiogenesis and tumor disorders [15]. Over time, the change in the molecular structure of these compounds is enlightening their anticancer activity and selectivity and their absorption, distribution, metabolism, and excretion volume while reducing the risk of toxicity, side effects, adverse reactions, and adverse effects [16, 17]. Plants are a vital source for discovering medical compounds for the expansion of drugs, and the main source from where the therapeutic agents are derived are secondary metabolites present in the plants [18]. The secondary metabolites have been renamed as phytoconstituents, the relative safety of the drug in terms of reducing adverse effects, multipronged mechanism of action, and improved pharmacokinetic profiles in comparison with many synthetic drugs make phytoconstituents a better and improved therapeutic agent [19].

PATHOPHYSIOLOGY OF AA

Recent pieces of evidence have shown that the failure of the HF immune privilege after causing events, that are signified by viral infections, results in an autoimmune response in which autoreactive cytotoxic CD8+NKG2D+T cells mainly target exposed HF autoantigens (Fig. **1**) [20].

Whereas the complete and exact pathogenesis is still not known, it is considered an autoimmune condition, in which the immune system unknowingly attacks the hair follicle, resulting in hair loss [21].

It is considered that certain cytokines and other immune system molecules play a part in the pathogenesis of alopecia areata, such as causing an inflammatory action and damaging the hair follicles, which subsequently lead to hair loss [22].

CHAPTER 6

The Genetics of Flavonoids in Vitiligo: Exploration of Molecular Mechanisms and Implications.

Rajnish Srivastava[1,*], Mandeep Kumar Gupta[2] and **Amit Kumar Srivastava[3]**

[1] *Department of Pharmacology, Chitkara University School of Pharmacy, Chitkara University, Baddi 174103, Himachal Pradesh, India*

[2] *Department of Pharmaceutical Chemistry, Moradabad Educational Trust Group of Institutions Faculty of Pharmacy, Moradabad 244001 Uttar Pradesh, India*

[3] *Department of Biosciences and Bioengineering, Indian Institute of Technology Roorkee, Uttarakhand, India*

Abstract: Vitiligo is a complex, multifactorial disorder that causes skin depigmentation due to melanocyte loss. Its cause is unknown, but oxidative stress, immune system dysregulation, and genetics are suspected. Vitiligo is primarily caused by oxidative stress-induced damage to melanocytes. Flavonoids can affect oxidative stress and inflammation genes, but genetic studies linking them to vitiligo are scarce. Vitiligo often involves melanocyte autoantibodies. Flavonoids affect the activity of T cells, dendritic cells, and macrophages, thereby modulating the immune system. It boosts regulatory T cell (T_{reg}) function, which maintains immune tolerance and prevents autoimmune attacks. Researchers have found several susceptibility loci for vitiligo, including genes involved in immune regulation and melanocyte function. It activates the Nuclear factor erythroid 2-related factor 2 (Nrf_2), which boosts the antioxidant response and protects melanocytes. It protects against oxidative stress by upregulating Heme Oxygenase-1 (HO-1) expression, which reduces melanocyte oxidative damage. Gene expression can be affected by DNA methylation and histone acetylation, which in turn have an effect on it. These flavonoids can alter the genetic landscape to modify vitiligo-causing genes, with therapeutic implications. The biological functions of flavonoids have led to their research on vitiligo treatment. The molecular genetics of flavonoids in vitiligo were highlighted in this chapter because they could also serve as antioxidants against oxidative stress and inflammation. Flavonoids may impact melanocyte survival and immunological pathways in vitiligo, but further research is needed to understand their genetic mechanisms and therapeutic efficacy. This chapter of the book additionally focuses on the necessity of genetic and scientific studies to design flavonoid-based treatments for vitiligo.

[*] **Corresponding author Rajnish Srivastava:** Department of Pharmacology, Chitkara University School of Pharmacy, Chitkara University, Baddi 174103, Himachal Pradesh, India; E-mail: phrajnish14091989@gmail.com

M.S. Ashawat, Aditi Kaushik, Akash Jain, Jasmine Chaudhary & Manish Kaushik (Eds.)

Keywords: Aromatic hydrocarbon Receptor (AhR) pathway, Autoimmune, Depigmentation, Dna methylation, Drug-gene interaction database, Flavonoids, Heme oxygenase-1, Heme oxygenase-1, Jak/stat pathway, Melanocyte.

INTRODUCTION

Vitiligo is a chronic dermatological condition characterized by depigmentation of some parts of the skin, resulting in the formation of white patches [1]. This occurs when melanocytes, the cells responsible for producing melanin, deteriorate or stop functioning. The etiology of vitiligo remains unknown; however, it is hypothesized to be associated with immunological responses, genetic factors, and environmental triggers. The primary indication is the presence of white or colorless patches, which are particularly prominent on sun-exposed areas of the skin such as the face, hands, arms, and feet. Occasionally, it also impacts the interior of the mouth, nose, and eyes [2, 3]. The diagnostic process includes a physical examination, a wood lamp examination, a skin biopsy, and blood tests [4]. The following categories of vitiligo exist [5]:

a. **Generalized Vitiligo**: The most prominent type, in which various body parts develop depigmented patches.
b. **Segmental Vitiligo**: Only impacts one side or body area, often progressing for a few years and then stopping.
c. **Focal Vitiligo**: Limited to one or a few areas of the body.
d. **Trichome Vitiligo**: Characterized by a white or colorless center, with a lighter hypopigmented area, and then standard skin color.
e. **Universal Vitiligo**: A rare form where nearly all the skin loses its pigment.

Global burden of Vitiligo

Depigmentation is the hallmark of vitiligo, a common dermatological condition that affects 0.5–2% of people worldwide, including adults and children [6, 7]. The incidence of vitiligo is commonly reported to vary from 0.09 to 8%, particularly in India [8]. Both males and females, including adults and children, are equally impacted by the condition. However, it is more common for women and girls to seek therapy, probably due to the more significant societal consequences they face compared to men and boys [9, 10].

Importance of Flavonoids in Skin Health and Vitiligo

Flavonoids are a class of bioactive substances derived from plants, recognized for their potent anti-inflammatory and antioxidant properties. They can be found in a variety of foods and beverages [11, 12]. These chemicals are essential for

maintaining healthy skin and have been extensively researched for their potential advantages in treating disorders such as vitiligo [13, 14] Table **1**.

Table 1. Application of flavonoids in dermatology.

Flavonoid Group	Active Chemical Moiety	Application in Dermatology
Flavones, isoflavones, Chalcones	Baicalein, Apigenin, Genistein, Luteolin, Licoflavone A, Chrysin, Nobiletin, Neobavaisoflavone. Isoliquiritigenin, Licochalcone C, Licochalcone A	Vitiligo [15] Psoriasis [16 - 19] Acne vulgaris [20, 21], Skin cancer [22 - 26]
Flavonols	Fisetin, Quercetin, Myricetin, Rutin, Kaempferol, Kaempferide, Rhamnetin	Vitiligo [27] Psoriasis [28] Acne vulgaris [29, 30], Atopic dermatitis [31] Skin cancer [32, 33]
Flavanones	Naringenin, Naringin, Liquiritigenin	Atopic dermatitis [34, 35] Skin cancer [36]
Flavanonols	Astilbin	Psoriasis [37]
Flavanols	Catechins, Epigallocatechin, Hesperidin	Skin cancer [38]
Anthocyanidins	Delphinidin, Chrysanthemin	Psoriasis [39, 40] Skin cancer [41]
Neoflavonoids	Coutareagenin, Calophyllolide, Nivetin, Dalbergin, Dalbergichromene	Atopic dermatitis [42, 43]

In this comprehensive exploration, the objective is to examine the genetic origins and molecular mechanisms by which flavonoids may be used to treat and manage vitiligo. Through an in-depth study of the genetic basis of flavonoid metabolism in individuals with vitiligo, our goal is to not only explain how these compounds affect the activity of melanocytes but also to uncover prospective targets for drug therapy. Furthermore, our investigation encompasses the field of epidemiology, where we analyze the influence of dietary flavonoids on the possibility of developing vitiligo. This enables us to make a link between genetic predisposition and environmental factors. By employing an integrative approach, we aim to provide practical insights into the specific treatment and preventive measures tailored to the genetic profile and lifestyle habits of individuals with vitiligo. Ultimately, we hope that this chapter will serve as a foundation for further research, encouraging advancements in dermatology and unlocking opportunities for novel approaches to develop flavonoid-based treatments for vitiligo.

PATHOPHYSIOLOGY OF VITILIGO

The pathophysiology of vitiligo is characterized by a complex interaction between genetic, immunological, and environmental factors. The phenomenon

CHAPTER 7

Secondary Plant Metabolites and their Role in Celiac Disease Management.

Himanshu Gandhi[1], Rupali Rana[2], Pragya Sharma[3], Varun Singh[2] and **Samar Vihal[4,*]**

[1] *Department of Pharmaceutics, School of Pharmaceutical Sciences, Shoolini University, Solan 173212, Himachal Pradesh, India*

[2] *Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, Punjab, India*

[3] *Department of Pharmaceutical Chemistry, Amity Institute of Pharmacy, Amity University, Jaipur 302001, Rajasthan, India*

[4] *School of Pharmaceutical Sciences, KC Institute of Pharmaceutical Sciences, Pandoga, Una, Himachal Pradesh, India*

Abstract: Autoimmune diseases are intricate and result from multiple factors, including genetic predispositions, epigenetic modifications, environmental exposures, and psychological influences, all of which contribute to their onset and progression. Celiac disease is a chronic autoimmune condition affecting the small intestine, initiated by gluten intake in genetically susceptible individuals and affecting around 1.4% of the global population. In addition to the complexity of the symptoms of this disease, the treatments have been completely palliative. Currently, the primary treatment for celiac disease is maintaining a strict, lifelong gluten-free diet. However, maintaining a completely gluten-free diet is very challenging, leading to a strong interest in finding alternative strategies to lower gluten levels or mitigate its harmful effects. Several studies have indicated that natural phytochemicals have promising strategies for combating autoimmune diseases. Plant-based secondary metabolites, such as flavonoids, phenolic acids, and terpenoids, are typically abundant in bioactive compounds and have shown efficacy against autoimmune diseases that affect the intestine, particularly bowel diseases. This study specifically highlights the role of secondary metabolites derived from medicinal plants in regulating inflammatory autoimmune diseases of the intestine, with a particular focus on celiac disease. It includes the latest literature on the impact of naturally occurring secondary metabolites in the management of Celiac disease.

Keywords: Autoimmune disease, Celiac disease, Flavonoids, Gluten, Phenolic compounds, Secondary metabolites.

[*] **Corresponding author Samar Vihal:** School of Pharmaceutical Sciences KC Institute of Pharmaceutical Sciences, Pandoga, Una, Himachal Pradesh, India; Tel: +917807276234; E-mail: samarvihal07@gmail.com

M.S. Ashawat, Aditi Kaushik, Akash Jain, Jasmine Chaudhary & Manish Kaushik (Eds.)

INTRODUCTION

Celiac Disease (CD) is an autoimmune condition activated by gluten intake in individuals with a genetic predisposition, marked by distinct serological and histological characteristics [1]. Gluten is a group of alcohol-soluble proteins found in various cereals such as wheat, rye, barley, spelt, and kamut [2]. CD is extensively studied among autoimmune disorders due to its well-defined triggers: gluten ingestion, specific genetic markers (HLA-DQ2 or -DQ8), and the production of circulating autoantibodies. In most cases, maintaining a strict gluten-free diet significantly reduces symptoms and helps heal the autoimmune-related intestinal damage in celiac disease [3]. Recent studies have revealed a higher global prevalence of CD than previously thought [4]. The global incidence of CD is estimated to be around 1%, with variations observed across different ages, genders, and geographic regions [3, 5, 6]. Initially, it was believed to be prevalent only in European countries. According to a 2003 study by Fasano, the prevalence of celiac disease in the United States was found to be 4.54% among first-degree relatives of affected individuals, compared to 0.75% in the general population [7 - 9]. Over time, understanding of celiac disease has progressed significantly. Initially considered primarily a paediatric condition, it is now recognized that gluten intolerance can develop at any age. Consequently, CD can be diagnosed in adults and elderly patients [10]. During that period, diagnosis generally relied on recognizing patients with common gastrointestinal symptoms and classic signs of malabsorption, confirmed through small intestinal biopsy [11]. Most cases of CD are diagnosed later in life, with an average diagnosis age of 45 years and a diagnostic delay of 10-12 years due to atypical symptoms. The National Institutes of Health estimates that 3 million Americans have CD, with over 95% undiagnosed. Physicians should be aware that CD can present at any age, in both sexes and with diverse clinical symptoms [9, 12]. The development of highly sensitive and specific serological markers, including antigliadin, antiendomysium, and anti-transglutaminase antibodies, has enabled clinicians to assess the frequency of CD more accurately. These markers also facilitated the identification of patients with mild, atypical, or asymptomatic forms of the disease [13].

The primary treatment for celiac disease is a strict, lifelong gluten-free diet. Despite the fact that this approach works for many individuals, persistent or recurring issues are frequently observed in clinical practice [14]. However, a gluten-free diet has been linked to nutritional deficiencies, including iron, vitamin B12, vitamin D, calcium, folic acid, and various minerals [15]. Promising approaches to treating celiac disease focus on detoxifying gluten, the primary trigger. These strategies include the use of synthetic polymeric binders to reduce gliadin digestibility, microbial transglutaminase to stop TG2 deamidation, gluten-

specific proteases to break down immunogenic peptides, and genetically modified low-gliadin wheat. None of these treatments is currently on the market, despite encouraging results from clinical trials.This underscores the need for further research to develop effective alternatives to the gluten-free diet [16].

Secondary plant metabolites, including polyphenols, terpenoids, alkaloids, and sulfur-containing compounds, have shown both positive and negative impacts on human health. Most studies suggested that polyphenols have potential protective effects against celiac disease. These compounds can function as natural gluten protein sequestrants, helping to diminish or modify gluten's immunogenic potential and alleviate its detrimental effects [17, 18]. These interactions depend on factors such as protein and polyphenol size, type, structure, and solution conditions (pH, ionic strength, and temperature) [17]. Gliadins, a component of gluten,

are of particular interest for polyphenol interactions due to their high proline content and flexible, polyproline II helical (PPII) structures. These features enable strong binding with polyphenols [19, 20]. Polyphenols are gaining research interest for their wide-ranging health benefits, including anti-inflammatory [21], anti-carcinogenic [22], antioxidant [23], antiallergenic [24], cardiovascular protective [25], and antimicrobial effects [26]. However, they can also hinder food protein digestibility and inhibit digestive enzymes, which may pose antinutritive effects [27]. With their widespread consumption and with these interaction capabilities, polyphenols present a promising avenue for therapeutic research in the context of celiac disease. This chapter explores the role of secondary metabolites from medicinal plants in regulating celiac disease, focusing on their potential therapeutic effects.

CELIAC DISEASES

Celiac disease, a severe autoimmune condition, is characterized by intestinal damage in individuals exposed to gluten, a protein present in wheat, rye, and barley. Approximately 1% of the population in Europe and North America is estimated to be affected by celiac disease. Celiac disease is an autoimmune disorder caused by the indigestion of gluten, a protein found in wheat, rye, and barley. The primary organ impacted by CD is the proximal small intestine, particularly the duodenum and jejunum. Therefore, it is now recognized as a systemic disease with symptoms that extend beyond the gastrointestinal tract [28]. If left untreated, CD can lead to significant health issues, increased risk of morbidity and mortality, and a lower quality of life for those affected [8]. Severe instances of celiac disease are marked by intestinal mucosal remodeling, villous atrophy, crypt hyperplasia, and lymphocytic infiltration, as well as significant

CHAPTER 8

The Significance of Secondary Plant Metabolites in the Development of Hashimoto's Thyroiditis

Vandana Bhatia[1,*], **Shagun Thakur**[1], **Anjali Chandel**[1] and **Yavnika Minhas**[1]

[1] *Department of Pharmacology, Laureate Institute of Pharmacy, Kathog 177101, India*

Abstract: The many facets of Hashimoto's Thyroiditis (HT), a common autoimmune disease marked by chronic thyroid gland inflammation that results in hypothyroidism, are explained in this chapter. It emphasizes how genetic predisposition, environmental variables, and immunological dysregulation interact intricately in the pathogenesis of HT. The chapter highlights the emerging significance of the thyroid-gut axis, emphasizing how gut dysbiosis, increased intestinal permeability, and microbiota-derived metabolites influence thyroid function and autoimmunity. It explores the roles of inflammatory cytokines, oxidative stress, and autoantibodies in exacerbating thyroid dysfunction and systemic symptoms. Furthermore, the chapter explores the therapeutic potential of secondary plant metabolites, particularly flavonoids, polyphenols, and terpenoids, which exhibit anti-inflammatory, antioxidant, and immunomodulatory properties. These metabolites are discussed in the context of their mechanisms of action, including inhibition of pro-inflammatory enzymes, downregulation of NF-I-B signaling, and modulation of immune cell activities. The chapter also addresses the impact of dietary factors, such as gluten, dairy, and goitrogens, on thyroid health. It provides practical dietary recommendations, emphasizing the inclusion of selenium, zinc, omega-3 fatty acids, and a variety of plant-based foods rich in beneficial metabolites. This comprehensive review integrates current understanding of HT's pathophysiology with emerging insights into the therapeutic potential of plant metabolites, offering a foundation for future research and personalized nutritional strategies in managing this complex autoimmune disorder.

Keywords: Anti-inflammatory, Antioxidant, Autoimmune thyroiditis, Flavonoids, Gluten-free diet, Gut dysbiosis, Hashimoto's Thyroiditis (HT), Hypothyroidism, Immune-modulatory, Inflammatory cytokines, Intestinal permeability, NF-I-B signaling, Oxidative stress, Polyphenols, Secondary plant metabolites, Selenium, Terpenoids, Thyroid autoantibodies, Thyroid-gut axis, Zinc.

[*] **Corresponding author Vandana Bhatia:** Department of Pharmacology, Laureate Institute of Pharmacy, Kathog 177101, India; E-mail: Vandana.bhatia40@gmail.com

GAINING KNOWLEDGE ABOUT HASHIMOTO'S THYROIDITIS

Introduction

Hashimoto's thyroiditis is a persistent autoimmune disorder of the thyroid gland whose aetiology remains unclear despite being identified more than a century ago. It is believed to be the most common autoimmune disease in existence today [1, 2]. Here are the most typical hormone imbalances and the causes of hypothyroidism. Based on the cause, HT is divided into primary and secondary types.

It is an illness characterized by the persistent autoimmune inflammation of the thyroid gland, first identified by Dr. Hakaru Hashimoto in 1912 through histopathological examination of thyroid tissue exhibiting various histological traits in affected patients [3]. Hypothyroidism combined with goitre is frequently caused by HT, commonly referred to as chronic lymphocytic thyroiditis [4]. The most common Autoimmune Thyroid Disease (AITD) is Hashimoto's Thyroiditis (HT) [1, 2], which results in hypothyroidism in approximately 20-30% of patients [5]. Hashimoto initially identified the most prominent symptoms of Autoimmune Thyroiditis (AIT) at the turn of the 20th century, noting the presence of goitre, fibrosis, lymphocytic infiltration, and follicular cell atrophy in affected individuals. About 0.3-1.5% people experience AITD each year; women experience it more frequently than males (4-10 times). Circulating anti-thyroid antibodies, hypoechogenic and dyshomogeneous gland parenchyma on ultrasonography, elevated TSH levels, and normal or low serum thyroid hormone levels (only in a small percentage of individuals) are some of the factors that are used to diagnose AIT [6].

The classic clinical manifestations of Hashimoto's Thyroiditis (HT) include both systemic and local symptoms, and they are usually absent in the early stages of the disease. Studies have shown that as the thyroid gland enlarges over time, symptoms such as pain, swallowing difficulties, throat discomfort, and neck enlargement often appear [7]. The frequency of systemic symptoms was increased in patients with thyroid impairment. Patients with hyperthyroidism frequently experience palpitations, tremors, sweating, heat intolerance, anxiety, restless nights, weight loss, and polydipsia [7].

Lymphocytic intrathyroidal infiltration of T and B cells, especially CD4+ Th1 cells, and the formation of anti-thyroid antibodies are linked to the aetiology of hypothyroidism [8, 9]. This results in long-term inflammation, which causes fibrosis and eventual thyroid tissue atrophy. HT is linked to a range of thyroid functioning conditions, including overt, subclinical, and euthyroidism. Overt hy-

pothyroidism manifests as elevated levels of thyrotropin (TSH) and reduced levels of free thyroid hormones [10].

Overview of Hashimoto's Thyroiditis

Hashimoto's illness is an autoimmune disease that causes inflammation of the thyroid gland. The thyroid is a butterfly-shaped gland located at the base of the neck, right below the Adam's apple, as shown in Fig. (**1**). The thyroid's primary function is to regulate the metabolic rate, which means it controls how the body converts food into energy. Although weight fluctuations are frequently linked to metabolism, they have a significant impact on all organ systems, including the heart and brain.

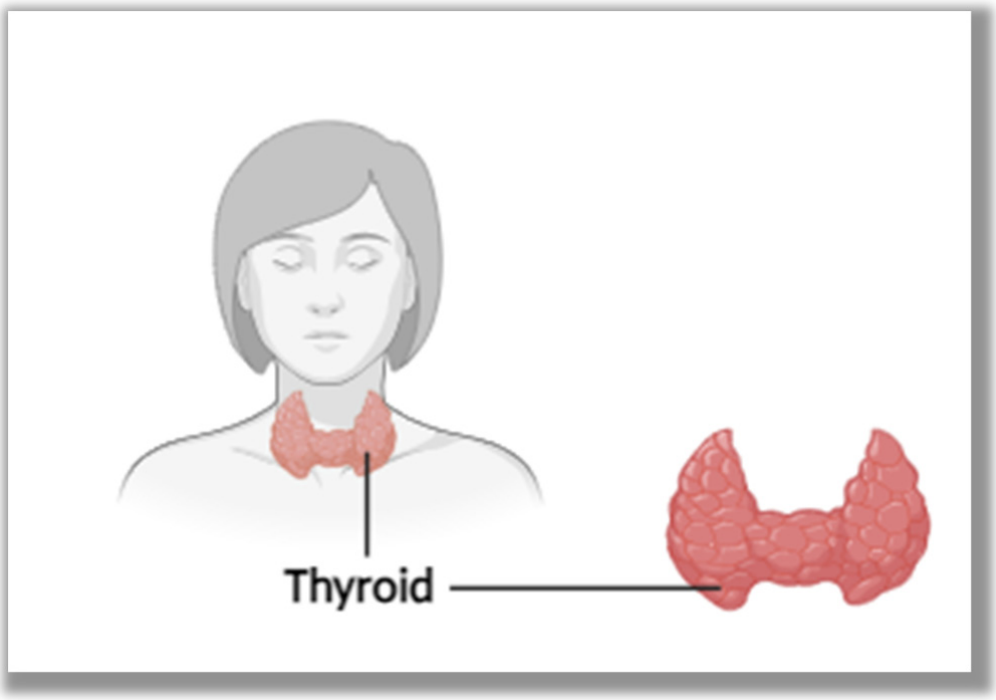


Fig. (1). Thyroid Gland.

Many bodily functions are regulated by the hormones produced by the thyroid gland. An autoimmune disorder is a medical illness in which the immune system attacks healthy tissues. The hallmark of Hashimoto's illness is the immune system-mediated destruction of thyroid hormone-producing cells. Hypothyroidism, the disease's typical outcome, is a decrease in hormone production. Hashimoto's illness can affect anyone, but middle-aged women are

SUBJECT INDEX

P

Q

R

S

T

U

V

W

X

Y

Z

M.S. Ashawat

Prof. (Dr.) M.S. Ashawat is the Director and Principal of Laurate Institute of Pharmacy (An Autonomous, NAAC- A Grade- H.P Technical University Off Campus Research Center), Himachal Pradesh, India. with over 25 years of experience in pharmaceutics and academic leadership. He has authored 13 books, published more than 130 research papers, and supervised multiple Ph.D. scholars. His expertise includes herbal cosmetics, intradermal delivery, nanocarriers, and regulatory science. He has served in key roles such as National Coordinator of APTI and is an active member of IPA and AAPS. Recognized with awards like "Principal of the Year," he has chaired national and international conferences and contributes significantly to research, academic governance, and editorial leadership in pharmaceutical sciences.

Aditi Kaushik

Dr. Aditi Kaushik is a Professor at Department of Pharmaceutical Chemistry, Laureate Institute of Pharmacy with over 17 years of academic and research experience. She specializes in molecular modeling, ADMET profiling, network pharmacology, and multi-target drug discovery, particularly for neglected diseases and antimicrobial resistance. She has published over 45 research papers, holds 10 patents, and has guided several undergraduate and postgraduate research scholars. Dr. Kaushik is actively involved in promoting IPR and entrepreneurship education, serves as a reviewer for Scopus-indexed journals, and contributes to analytical method development and regulatory compliance. As an editorial board member, she brings strong interdisciplinary expertise, advancing collaborative research and academic excellence in pharmaceutical sciences.

Akash Jain

Dr. Akash Jain is a Professor of Pharmacology at M.M. College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Haryana, with an extensive research profile including over 65 international publications. He holds 5 granted patents, 6 patents under process, and 5 copyrights, along with authoring books and book chapters. His key research areas include metabolic syndrome, neuropharmacology, and experimental pharmacology. Dr. Jain has guided students across all levels from B. Pharm to Ph.D. and has actively presented his work at national and international conferences. A member of the Indian Hospital Pharmacists' Association and a reviewer for reputed journals, he also contributes to organizing academic and research-focused events. His work reflects strong leadership, scholarly excellence, and impactful contributions to pharmaceutical education and research.

Jasmine Chaudhary

Dr. Jasmine is a Senior Associate Professor at Department of Pharmaceutical Chemistry, MM College of Pharmacy, MM(DU), Mullana with more than 17 years of academic and research experience. Her expertise includes the synthesis of analgesic and antimicrobial compounds and analytical method development. She has supervised B. Pharm, M. Pharm, and Ph.D. scholars and has published over 50 research papers, 15 book chapters, and holds 4 granted process patents. A reviewer for international journals and an active member of professional organizations, she frequently participates in scientific conferences and academic development programs. As an editorial board member, she contributes strong research insight, scientific rigor, and leadership to the advancement of pharmaceutical sciences.

Manish Kaushik

Manish Kaushik is an Associate Professor of Pharmacology at SBS College of Pharmacy, Palampur, with over 16 years of experience in academic teaching and institutional administration. His leadership roles include contributing to academic governance, regulatory documentation, and student welfare initiatives. His research focuses on metabolic disorders, antimicrobial resistance, and phytopharmacology, with publications in Scopus-indexed journals and contributions to Bentham Science titles. He is also the co-editor of a book on autoimmune disorders and secondary plant metabolites. As an editorial board member, he offers a multidisciplinary perspective that integrates research expertise with academic leadership to support high-quality scholarship and collaboration in pharmaceutical sciences.