# BENTHAM BRIEFS IN BIOMEDICINE AND PHARMACOTHERAPY

## BOTANICALS AND NATURAL BIOACTIVES: PREVENTION AND TREATMENT OF DISEASES

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## *(Volume 2)*

# *Botanicals and Natural Bioactives: Prevention and Treatment of Diseases*

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# FOREWORD

I am pleased to write this foreword for the e-book '*Botanicals and Natural Bioactives: Prevention and Treatment of Diseases*'. This outstanding endeavour by the editors represents a multi-disciplinary coverage of research in preventing and treating many diseases. This book embodies a compelling compilation of chapters on therapeutic aspects of natural bioactives against various physiological disorders. The authors deserve credit for their time and efforts to contribute excellent chapters relevant to their expertise. These chapters include timely discussions on ageing, infectious diseases, neurodegenerative diseases, osteoporosis, coronary heart diseases, and autoimmune disorders. I am confident this book will be a valuable addition to the bookshelves of teaching faculty, recognized investigators, and young graduate students. I wish you all the success for the launch of this book.

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# PREFACE

Scientific research in the diverse domains of biomedicine and pharmacotherapy has contributed much to the recent advancements in enhancing global health. Researchers have shown a great interest in exploring and enhancing the therapeutic assistance for a variety of diseases *via* vital understanding in areas of molecular diagnostics, immunobiology, regenerative medicine, drug development and discovery, cancer biology, functional genomics, pharmaceutics, chemical biology, human biology, and primary or scientific research. Following these, the book series *Bentham Briefs in Biomedicine and Pharmacotherapy* seeks to cover recent developments in various domains *via* various volumes.

The second volume "*Botanicals and Natural Bioactives: Prevention and Treatment of Diseases*" offers immense knowledge of the current research in the prevention and treatment of many diseases. This book volume provides recent and future trends in therapeutic aspects of natural bioactives against various physiological disorders. The pathogenic intervention of chronic ailments like cardiovascular diseases, neurodegenerative diseases, infectious diseases, age-associated diseases, and many cancers involves oxidative damage. The intensified pro-oxidant factors cause structural and functional defects at enzymatic and DNA levels. This leads to mutations and aberrations at the genetic level. The book chapters will captivate interest in the researchers for investigation and augmentation of the use of botanicals and natural bioactives in the remedial assistance against various ailments.

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# CHAPTER 1

# Food Color, Taste, Smell, Culinary Plate, Flavor, Locale, and their Impact on Nutrition: Present and Future Multisensory Food Augmentation and Non-communicable Disease Prevention: An Overview

**Douglas W. Wilson[1], Fabien De Meester[2], Toru Takahashi[3], Ram B. Singh[4]** and **Harpal S. Buttar[5,*]**

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**Abstract:** Cognizant that 'the world is one family', this overview describes chemosensory characteristics of food and related issues that may enable global inequalities in healthy food consumption to be improved with a reduction in non-communicable diseases (NCDs), preventatively. Past and modern aspects of food tradition are briefly described followed by titular chemosensory characteristics and their potential application to improving health in nutrition in the sense intended, including the culinary plate. Human-computer interface and food augmentation reality and commensal dining, in association with chemosensory properties, including sound concerning oral food processing, are described. Future research on arresting trends in the prevalence of NCD is suggested based on the literature. Visual cues for in-store food choice are discussed that potentially allow the consumer, through psychological processes and behavior outcomes, to be more discerning. Advertisements and store architecture *per se* are not discussed. The relatively high prevalence of anosmia caused by COVID-19 infection relative to non-infected subjects may alter taste and flavor perception and lead to changed dietary habits and metabolism. Most global consumers can practice the 'how' and 'when' to beneficially eat but food insecurity poses a global problem.

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**Keywords:** Commensal dining, Food augmentation, Global NCDs, Hidden hunger, Marketing, Robotics, Visual cues.

## INTRODUCTION

The subject matter of this overview topic is vast and only relevant scientific snippets and definitions have been embodied into a general framework of life on this planet. From a human perspective [1], sociological [2, 3], accessibility [4], environmental [5], locale [3], historiography [1], scientific [6 - 8], economic [9], feeding habits [10] and cultural [11] are among key factors/terms for food security [3, 12 - 14] and sustainability [5]; and even longevity [11]. From a philosophical/ religious point of view, food has a place in the concept that 'the world is one family' ('Vashudayo Kutumbakam' which comes from ancient Sanskrit वसुधेव कुटुम्बकम in the Maha Upanishad (VI,71-73) [15]), a motivation for the authors to write this overview in this world of inequality [16, 17]; *e.g.* low-income countries'-CVD deaths [18]. The layout of this article concerning the reduction in global NCDs using food chemosensory properties is shown in Fig. (**1**).

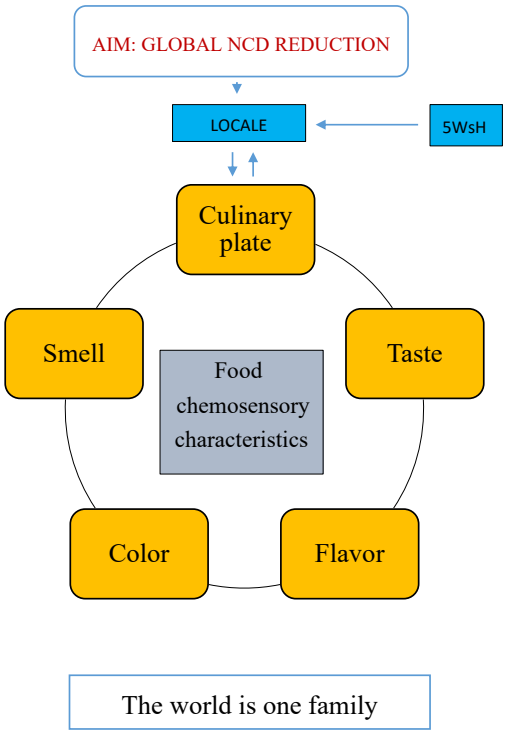


**Fig. (1).** Schema for reducing global NCDs using food chemosensory characteristics: health inequalities implicitly incorporate the '5WsH' circumstances which refer to the who, what, where, when, why and 'how' of food consumption.

## Food

This is a source of chemical energy [19]. The human body requires food, and just as the entire universe has been reportedly made up of the five elements *Viz.* earth, water, fire, air, and space, which according to Hinduism [20] ((assumed to be traced back to the Veda) are Prithvi/Bhudevi (Sanskrit: पृथ्वी: Earth), Apas/Varuna/Jal (Sanskrit: अप: Water), Agni (Sanskrit: अग्नि, Fire), Vayu (Sanskrit: वायु: Air), and Akasha/Dyaus (Sanskrit: आकाश, Space/Atmosphere/Ether)) whereas a similar system of cosmic rather than natural substances, arose in East Asia [21]. In Ancient Mediterranean tradition, food utility could be construed to involve the four classical Greek elements [22] *Viz.* fire (energy), earth (chemicals), air (oxygen/carbon dioxide), and water (*q.v.* Empedocles (c450 BCE) ([23], pp 62,75)), later aether (space) (*q.v.* Aristotle [22, 19], 350 BCE). It has been said, "No animal can live without food….(which) is about the most important influence in determining the organization of the brain and the behavior that the brain organization dictates." [24]. From birth, humans have different taste propensities [25], and presumably, this has developed throughout evolution [26, 27] and migration [28]: hence the subsection herein on 'locale'. Today researchers think of food as being necessary for sustaining metabolic processes essential for life [29] including reproduction and fertility [30] in terms of thermodynamic properties associated with evolved anaerobic and aerobic pathways involving the metabolism of fats [31], carbohydrates, proteins, *etc.*, and other essential ingredients. Descriptions of sensory and related characteristics are as follows.

## Color

This does not exist in the external world but luminance along with wavelength (color) is extremely important in natural selection and behavior. Color, which arose in common ancestors in Cambrian times in the Metazoa, arises from the visual perception by the brain of the light-spectrum (390-700nm) in humans and other animals [32 - 34] emanating from absorption, emission, and reflection from objects interacting with different retinal cells [35]. In humans "Color is the general name for all sensations arising from the activity of the retina of the eye and its attached nervous mechanisms, this activity being, in nearly every case in the normal individual, a specific response to radiant energy of certain wavelengths and intensities [36]". As a sensory property, this sense can affect food choice [37, 38]. Though in animals 'one cap does not fit all' there is an interplay between luminance and wavelength processing [32] *e.g.*, identifying brown [39], which drives behavior. Luminance and wavelength color/contrast are important in the co-evolution in plants and animals [40, 41]. Also, visual pictures of high-calorific food with contrasts were shown to women with binge-eating disorder or bulimia nervosa (with controls) and differential brain activation was found using

CHAPTER 2

# Oxidative Stress and Protein Misfolding in Skin Aging

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**Abstract:** Aging is a visible indicator of malfunctioning or toxic proteins that sensitize other proteins to oxidative damage which is most prominently observed on the skin. Protein misfolding is caused by the protein following an incorrect folding pathway which may lead to spontaneous misfolding while oxidative stress refers to the disruption of the balance between antioxidant defenses and reactive oxygen species production. Oxidation may alter noncovalent interactions within proteins, peptide chain fragmentation, and protein cross-linking, which causes protein misfolding and further skin aging. A feedback loop is observed in all three processes. A proper understanding of these events is significant in the formulation of anti-aging preparations and further understanding of the mechanism of aging. In this Chapter, we will be discussing some natural antioxidants available to combat oxidative stress which facilitate healthy aging and normal functioning of the body. We will be elaborating on the body's natural defense mechanism against these problems such as the role of Chaperones. We will be looking at the detailed mechanism of oxidative stress, protein misfolding, and their correlation with skin aging along with factors influencing it. The biomarkers for oxidative stress will be enlisted. A brief correlation between these processes in a test worm and how it correlates to humans and its importance will be explained in this chapter.

**Keywords:** Antioxidants, Biomarkers, Chaperones, *Caenorhabditis elegans*, Oxidative stress, Protein misfolding, Reactive oxygen species, Skin aging.

## INTRODUCTION

The term "oxidative stress" refers to an imbalance favoring oxidants over-reactive oxygen species in an antioxidant defense system [1]. Protein misfolding is caused by the protein following an incorrect folding pathway which may lead to spontaneous misfolding. Aging is a visible indicator of the accumulation of mal-

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functioning or toxic proteins that sensitize other proteins to oxidative damage which is most prominently observed on the skin [2].

## Oxidative Stress – The Underlying Mechanism

The term "oxidative stress" refers to an imbalance favoring oxidants over the antioxidant defense system, which disrupts redox signaling and may be accompanied by molecular damage [1]. Reactive oxygen species (ROS) that are commonly involved include hydroxyl radicals (OH), superoxide radicals ($O_2$), singlet oxygen, and hydrogen peroxide ($H_2O_2$), which are metabolic by-products of biological systems [3, 4]. Apoptosis, immunity, differentiation, and phosphorylation of proteins are a few processes depending upon correct ROS production and occurrence within cells and both should be maintained at a low level [2]. As ROS production increases, crucial cellular components like proteins, nucleic acids, and lipids are negatively impacted [5]. The fundamental premise is that there is a maintenance of a constant balance of redox in an open metabolic system at a specific setpoint, providing the redox tone a base. Any change from the constant redox balance is considered stress, triggering a stress response. According to the definition of oxidative stress, there are two types of aberrations: physiological deviations, known as "oxidative eustress", and supraphysiological deviations, known as "oxidative distress". Redox regulation and physiological redox signaling depend on oxidative eustress. This idea and the redox equilibrium being the "golden mean" are related [1, 6, 7]. Oxidant signaling is specific to a target while higher exposure of oxidants beyond the normal causes damage due to reaching unspecified targets. Fig. (**1**) exhibits the oxidative stress mechanisms and its therapy.

## Biomarkers Involved in Oxidative Stress

Biomarkers are biomolecules altered upon interaction with antioxidant system molecules or ROS' in the microenvironment and those that change in response to increased redox stress are two categories of biomarkers of oxidative stress. Molecules like proteins, carbohydrates, lipids (including phospholipids), and DNA are some of those that can be altered *in vivo* owing to too many ROS'. A crucial factor involved in the determination of the validity of the marker is the causal effect or the functional importance of oxidative alteration on the functioning of the cells, organs, and the system. The availability of a suitable biological specimen, the biomarker's stability when subjected to various storage conditions and during preparation of the specimen process, and the specificity, sensitivity, and repeatability of the assay used to measure the modification are additional factors that affect a ROS biomarker's clinical applicability [8]. Table **1**

enlists the various biomarkers of oxidative stress along with their advantages, and problems encountered along with some remarks regarding the same.

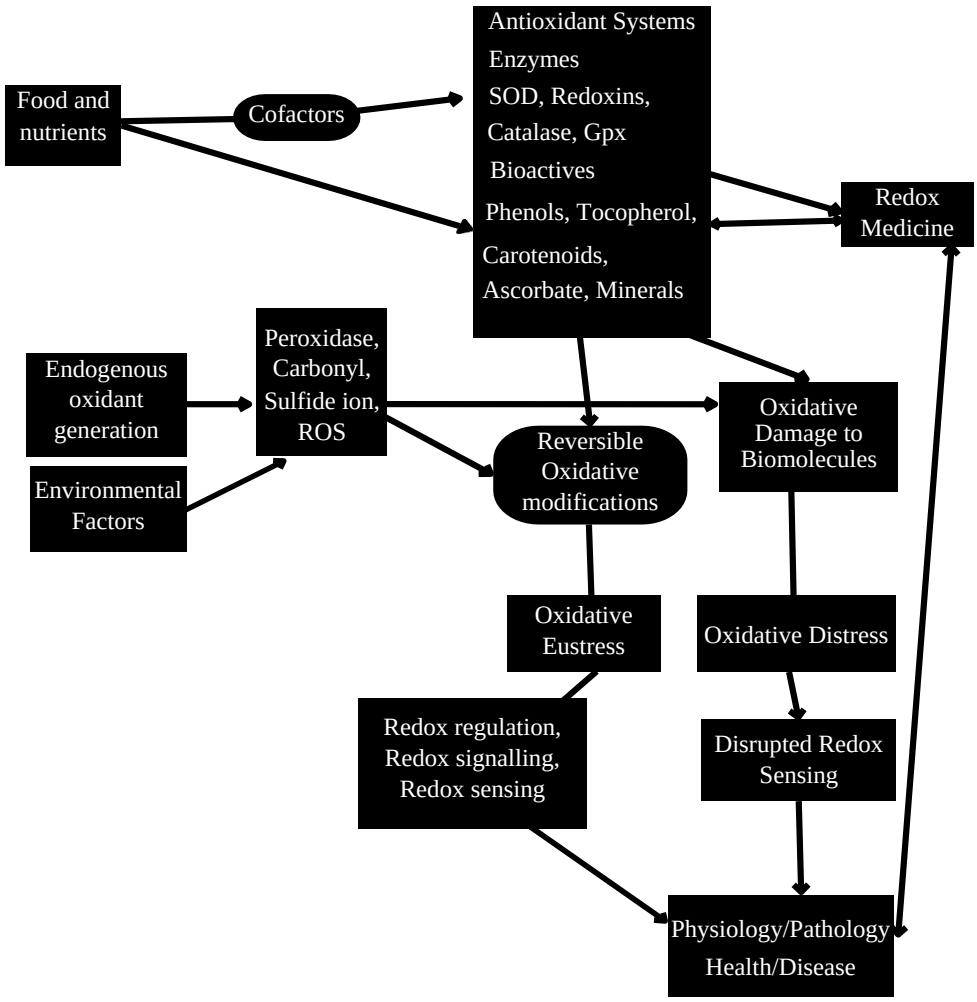


**Fig. (1).** Oxidative stress mechanism and therapy.

**Table 1. Biomarkers, their advantages, and disadvantages.**

| Biomarker | Advantages | Problems | Remarks | References |
|---|---|---|---|---|
| IsoPs | Detectable in various samples (urine, serum) easily. | Current quantification techniques are not suitable, and modifications are required. | Lack of evidence linking biomarkers to their clinical outcomes. | [9 - 11] |

# CHAPTER 3

# Therapeutic Scope and Application of Mushroom-Derived Pharmacoactives in Enhancing Health

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**Abstract:** In the present era, the notion that "prevention is better than cure" has gained impetus with increased incidences of infectious and degenerative lifestyle diseases. Recent years have seen many people choosing functional food such as probiotics, plant-based nutritional supplements, and their normal dietary needs. Studies have shown significant health benefits in using these nutraceuticals as they aid in the body's general well-being. Among food varieties, edible mushrooms have also become a functional dietary food. It has been used as a source of nutrition in many parts of the world. Oriental medicine has been using mushrooms as a component in various medicinal concoctions for several decades. Today, with the advent of scientific know-how, around 2,000 edible mushrooms have been identified; among them, 700 possess bioactive compounds. Both *In vitro* and *In vivo* studies have shown immunomodulatory effects *via* the regulation of innate, complement-mediated, and adaptive immunity by enhancing the active mechanisms of immune systems such as the macrophages, IL, TNF-α, IFN-γ, NO, and the complement system. The possibility of modulating these immune system players by the bioactives may pave the way to side-effect-free anticancer and immunosuppressant drugs. Recent studies have also elucidated the neuroprotective effect induced by mushroom-derived compounds through ROS scavenging and antioxidant activity. This chapter highlights the recent findings and the importance of these mushroom-derived compounds and their anti-inflammatory, anti-cancerous antioxidant, and immunomodulatory roles.

**Keywords:** Antioxidant, Anti-cancer, Functional food, Immunomodulatory, Mushrooms, Therapeutic.

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## INTRODUCTION

The search for a "Wonder drug" that can cure all diseases efficiently for many populations is a far future, as drugs that can be repurposed to cure many diseases are either less or do not exist. The COVID-19 pandemic caused by the SARS-CoV-2 virus has changed the outlook of drug discovery and forced us to look for options from nature to combat the outbreak [1, 2]. Nature is a diverse repository of bioactives that could be derived from flora and fauna. Human medical knowledge using these has been documented in texts and practices followed from time immemorial but without much scientific evidence to validate the mechanism of action and its effects against diseases [1, 3]. Food habits, health, and disease are interlinked. The primary role of food is to provide sufficient nutrients essential for metabolic processes, health benefits including reduction and prevention of diseases, and mainly to satiate hunger [4].

Mushrooms are known to be treasures of the forest [5] and have been part of many traditional foods and medicines. It has been distinguished and marketed as a superfood due to its functional and nutraceutical importance, becoming a vital part of the human diet for improving health and promoting quality of life [6]. Mushroom extracts and powder-based studies have shown excellent pharmaceutical activities such as neuroprotective, anti-ageing, immunomodulatory, anti-microbial, anti-diabetic, hypocholesteraemia, anti-cancer, and antioxidant activity [6]. The present chapter intends to highlight the recent findings and the importance of these mushroom-derived compounds and their immunomodulatory roles in inflammation and cancer research.

### Mushrooms as a Valuable Source of Nutrition and Nutraceuticals

Mushrooms belong to the phyla Basidiomycota, with over 30,000 known species worldwide, and the ones that are of pharmaceutical importance belong to the order Agaricales, Aphyllophorales, Auriculariales, and class Gasteromycetes [7]. Previously, mushrooms were used in the human diet as a culinary delight or a component of traditional medicine. They were forged from the forest by knowledgeable people and were considered expensive and exquisite due to their rarity. Still, with modern agricultural practices, it is possible to optimise the requirements for the growth of desired species of edible mushrooms. Furthermore, various techniques are being used and researched for biomass production through fermentation methods [8]. Current mushroom production has increased five-fold compared to data from the 1990s. With the increase in awareness and appeal for a healthy and clean plant-based diet, mushrooms are a sustainable replacement for meat in terms of protein and essential fatty acids [9]. It is well known that these are rich sources of proteins, unsaturated fatty acids (when compared to a plant-

based diet), fibres, carbohydrates (fruiting body contains about 50-60%), water (as moisture content, varying from 70-95%), micronutrients such as vitamins (like vitamin B complex, E, D, and folate) and minerals (including K, P, Na, Ca, Mg, Cu, Fe, Zn, Mo and Cd) [10, 11]. Besides nutritional constituents, the mushroom also comprises compounds that promote health and protect the body against infection and diseases. These are called nutraceutical compounds, namely, lectins, triterpenoids, ganoderic acid, β-glucan, phenolics, flavonoids, hispolon, calcaelin, proteoglycan, lentinan, laccase, nucleoside, nucleotides and ergosterol [11]. In general, the biological activity showed by different mushrooms, such as anti-bacterial, anti-viral, anti-mutagenic, anti-inflammatory, anti-carcinogenic, anti-tumour, anti-obesity, and anti-hypercholesterolemic potential, could be attributed to the presence and interaction of these nutraceuticals with host biochemical processes as shown in Fig. (**1**) [4, 6, 11].

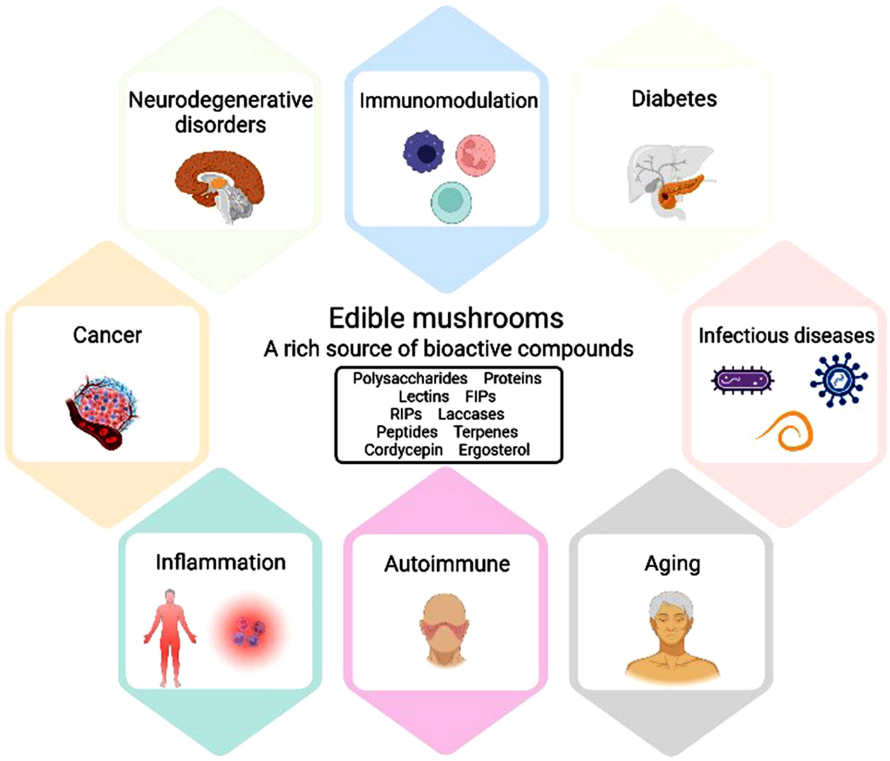


**Fig. (1).** Functional roles of mushroom-derived bioactive compounds. Due to their pharmaceutical activities, a variety of bioactive compounds in mushrooms have been demonstrated to fight against numerous illnesses including those associated with neurodegenerative disorders, immunomodulation, inflammation, autoimmune, cancer, diabetes, aging and infectious diseases.

# CHAPTER 4

# Natural Products as Antioxidant Adjunct Therapy for Blood Parasitic Infections

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**Abstract:** Human blood protozoa infections cause oxidative stresses from the parasites, host's defense systems, and administered drugs. Oxidative stress is an important tool to eliminate parasites from the host's body. However, the host's cells, tissues, and even organs would be damaged along with parasites. Many pathologies such as cerebral malaria, and renal or hepatic failures are a result of the unbalanced oxidative condition. Many medicinal plant extracts show both anti-protozoa and antioxidant activities simultaneously. Therefore, the administration of medicinal plant extracts in combination with chemical drugs should be beneficial for patients with blood-protozoa infection, by both eradicating the parasites and alleviating the oxidative stress. In addition, the combination might also help prevent parasite resistance to chemical drugs as the extract and chemical drugs aim at different targets simultaneously. In this chapter, the properties and benefits of medicinal plant extracts are discussed.

**Keywords:** Acute respiratory distress syndrome (ARDS), Aldo-keto reductase (AKR), Anti-plasmodial, Antimalaria, Anti-babesia, Anti-leishmania, Anti-oxidant, Antioxidant adjunct therapy, Catalase, Glutathione (GSH), Malondialdehyde (MDA), Natural product, Nicotinamide adenine dinucleotide phosphate reduced (NADPH) oxidase, Nitric oxide synthase (NOS), Oxidative burst, Oxidative enzyme, Oxidative stress, Reactive oxygen species (ROS), Superoxide dismutase (SOD), Xanthine oxidase (XO), 2,2-Diphenyl-1-picrylhydrazyl (DPPH).

## INTRODUCTION

Human blood protozoans continue to cause serious parasitic diseases around the globe. According to World Health Orgainisation (WHO), Malaria infections were

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241 million cases and 627000 deaths in 2020 [1]. Malaria infections remained endemic in impoverished countries with transmission-suitable climates [2]. Despite the general waning trend of *Plasmodium falciparum* malaria in Africa, from 40% (1910–1929) to 24% (2010–2015), a new rising trend was reported in 2016 compared to that of 2015 by WHO [2]. Five species of human *Plasmodium* parasites are *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi* [3]. Malaria causes fever and flu-like maladies, such as shaking chills, headache, muscle aches, tiredness, nausea, vomiting, diarrhea, anemia, and jaundice [3].

In addition to numerous species of *Babesia* reported to infect wild and domestic animals including livestock, six species have up till now been established as human parasites: *Babesia crassa*-like agent, *Babesia divergens*, *Babesia duncani*, *Babesia microti*, *Babesia motasi*, and *Babesia venatorum* [4]. Human babesiosis is acquired mainly in the temperate zone. The predominant *B. microti* was endemic in the northern United States and southwestern China [4]. Even with the low global prevalence of human *Babesia spp.* infection of 2.23%, the increasing cases of immunocompetent patients are alarming. Approximately half of the infections are commonly asymptomatic or mistaken for malaria [5]. The usual symptoms are fever and hemolytic anemia. However, in immunocompromised persons, *Babesia spp.* triggers hemolytic anemia, intravascular coagulopathy, hepatomegaly, and splenomegaly, and results in respiratory distress syndrome, heart failure, inflammation of the central nervous system, and death [5].

700,000 to 1 million *Leishmania* new cases are estimated per year [6]. Visceral leishmaniasis (VL), otherwise known as kala-azar, has an estimated 50,000 to 90,000 new cases worldwide per annum. Above 90% of VL new cases reported in 2020, were from Brazil, China, Ethiopia, Eritrea, India, Kenya, Somalia, South Sudan, Sudan, and Yemen. VL is lethal in 95% of untreated cases. The symptoms are irregular fever sessions, weight loss, spleen and liver enlargement, and anemia. Most cases were reported in Brazil, East Africa, and India. VL is still one of the leading parasitic ailments with a high potential for outbreak and mortality. The most common cutaneous leishmaniasis (CL) has an estimated new case of 600,000 to 1 million worldwide annually. Roughly 95% of the cases take place in the Americas, the Mediterranean basin, the Middle East, and Central Asia. In 2020, above 85% of new CL cases were in Afghanistan, Algeria, Brazil, Colombia, Iraq, Libya, Pakistan, Peru, the Syrian Arab Republic, and Tunisia. Mucocutaneous leishmaniasis (ML) causes skin lesions, developing into fractional or entire damage of mucous membranes, such as in the nose, mouth, and throat. More than 90% of ML cases were in the Plurinational State of Bolivia, Brazil, Ethiopia, and Peru [6].

The life-threatening human African trypanosomiasis predominantly impacts poor people and travelers in rural endemic areas. Since the WHO's reinforced control and surveillance program in 2001, human African trypanosomiasis infections diminished significantly to less than 1,000 cases in 2019, with 2.5 million people screened yearly [7]. However, the disease is considered fatal if not treated [7].

These parasites cause enormous economic expenditure and remain one of the major causes of death. Therefore, new anti-parasite agents are still urgently and persistently explored.

Natural products from medicinal plants and fruits hold great potential for fighting against parasites as well as the free radicals produced during infections. Natural products have more possibility than artificial compounds to contain multiple and/or novel targets, owing to their structural features: multiple stereocenters, flexible conformations, and heteroatom presences [2].

## OXIDATIVE STRESS IN BLOOD PARASITE INFECTIONS

Oxidative stress is a consequence of the broken balance between oxidizing species and antioxidants. Blood protozoa usually have many stages inside hosts, such as erythrocytic, hepatic, or muscle stages. Protozoa, host defense system, and antimicrobial drugs are responsible for oxidative burdens inside host cells and tissues. The high oxidative stress during malarial infection is accountable for both tissue and systemic oxidative damages, involving crucial organs like the brain and lungs. Consequences of the most life-threatening cerebral malaria, brain parenchyma lesion, leading to physical and cognitive impairments are thus possible [8, 9].

Janka, *et al.* [10] described the oxidative stress affecting the myocardial wall and causing high pulmonary pressure in children with severe malaria. This cardiopulmonary effect was initiated by intravascular hemolysis and a decreased nitric oxide (NO) generation [10].

Also, in an experimental malaria study, oxidative damage markers linked to kidney acute tubular damage, 4-hydroxynonenal (4-HNE), and heme oxygenase-1 (HO-1), were found to be increasingly expressed [11].

Percário *et al.* [12] proposed that oxidative stress induction in malaria is a result of various factors. These considerations are: 1) the consumption of hemoglobin producing free radical assembly *via* Fenton and Haber–Weiss reactions, 2) the host's immune response against the parasites, 3) microvascular cytoadherence and anemia leading to ischemia and reperfusion syndrome, 4) free radicals directly created by the parasites, and 5) anti-parasite drugs used. At least some of these

# CHAPTER 5

# Natural Products as a Therapeutic Approach in Regulating Autophagy for the Management of Neurodegenerative Diseases

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**Abstract:** Autophagy is a complex phenomenon that occurs constantly in cells for maintaining the well-being of individuals. However, any dysregulation in the mechanism or the proteins involved leads to detrimental effects on several diseases including cancer, diabetes, and neurodegenerative diseases (NDs). Autophagy dysfunction is involved in the progression of NDs including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). With the involvement being identified, autophagy has become a prospective target in ameliorating NDs. Natural products in the form of extracts and bioactive compounds were repeatedly reported for targeting autophagy-related proteins and the mechanism making them promising drug candidates against NDs. The current chapter briefly outlines the role of autophagy in NDs and the effect of selected natural products in restoring pathological outcomes.

**Keywords:** Autophagy, mTOR, Neurodegenerative diseases, Oxidative stress, Polyphenols, Phytomedicine.

## INTRODUCTION

Autophagy is a form of cellular survival during nutrient starvation, which helps to clear the damaged and degraded cell structures such as proteins, lipids, and other cellular organelles from the system, thereby providing nourishment and energy to the cells. These organelles are engulfed by membrane-bound vesicles termed autophagosomes, which fuse with the lysosomes and form autolysosomes further leading to the degradation of dysfunctional materials by lysosomal acid hydrolases [1, 2]. However, the process is age-dependent; in other words, the rate

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of autophagy decreases during aging [3]. There are different types of autophagy such as macroautophagy, microautophagy, chaperone-mediated autophagy, mitophagy, and lipophagy, depending on the activity involved.

Macroautophagy deals with the clearance of damaged cell organelles and proteins from the cells [4 - 6]. It is one of the most studied processes in autophagy and several genetic players have been identified. In case of microautophagy, the cell debris is directly taken to the lysosome, and the autophagosome is not essential for the process [4, 7]. The chaperone-mediated autophagy can function without autophagosome, as the cytosolic chaperons aid in the transportation of degraded proteins into the lysosome. This process is connected to the pathogenesis of neurodegenerative diseases and cancer; however, the complete mechanism is still unclear. The other processes such as mitophagy deal with the degradation of damaged mitochondria and lipophagy deals with the degradation of damaged lipids [4].

Different molecular pathways have been reported to mediate autophagy. It is already known that the disruption and dysfunction of autophagy can occur *via* mTOR mediated pathway and can also take place independently of the pathway [8]. In the mTOR-dependent regulation, phosphatase and tensin homolog (PTEN) induce autophagy by blocking mTOR, while the class I PI3 kinase, and AKT inhibit autophagy by activating mTOR [9]. In mTOR-independent regulation, autophagy can be modulated through cAMP-Epac-PLC-ε, phosphoinositol, and $Ca^{2+}$-calpain-GSα pathways [10]. In addition, oxidative stress can activate autophagy *via* an mTOR-mediated/independent pathway [11].

## AUTOPHAGY IN NEURODEGENERATIVE DISEASES

In a normal healthy human brain, the proper functioning of cells depends on the periodic clearance of misfolded, unused, and damaged proteins. In contrast to most cell types, neurons are post-mitotic, and therefore their cell division process will not dilute any toxic materials. In this regard, autophagy is essential for the survival and functioning of neurons, and it must prolong until the organism's lifetime. It should be noted that autophagy occurs constitutively in neurons [12, 13]. Abnormal protein aggregation, which could eventually lead to neurodegeneration can occur by the suppression of this neuronal autophagy, which highlights the prominence of autophagy in maintaining neuronal homeostasis and survival [14, 15]. Disruption in autophagy has been reported to be involved in aging and age-associated degenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) [16]. Autophagy plays a significant role in eliminating the build-up of amyloid-β, hyperphosphorylated tau protein, α-synuclein, and clearing

malfunctioning organelles. However, autophagy has been reported to show both decreases [17 - 20] and increases in amyloid-β expression [21, 22], indicating the paradoxical relationship. For instance, autophagic vacuoles act as sites of abnormal APP cleavage leading to Aβ generation [23, 24]. More in-depth studies on the contradictory reports imply that during the initial phase of AD, the accumulating Aβ can activate autophagy, and thereby the autophagosome-lysosomal system. However, during the later stages, the continuous accumulation of Aβ leads to abnormal autophagy and neuronal dysfunction, which accelerates AD symptoms [25 - 28]. Similar to AD, compelling pieces of evidence point to the link between PD and autophagy dysfunction, as the α-synuclein inclusions have been reported to modulate autophagic function [29], leading to decreased lysosome - autophagosome fusion and reduced protein degradation, genetic mutations in phosphatase and tensin homolog-induced putative kinase 1 (PINK1) and E3 ubiquitin ligase (Parkin) [30 - 33].

Moreover, autophagy could also play a key role in the incidence and development of ischemic stroke through HiF-1α/BNIP3, PINK1/Parkin, PKC/JNK, PI3K/Akt-mTOR, AMPK/mTORC1, and other pathways [34 - 39]. Oxygen glucose deprivation/reoxygenation can activate PINK1-mediated mitochondrial autophagy and play a role in its pathophysiological process. Also, ROS can activate mitochondrial autophagy *via* the PINK1/Parkin pathway [40], and remove damaged mitochondria [41]. Under normal conditions, the optimum level of ROS developed in the body aids in cell growth, development, and immunity. Despite that, during brain ischemia, there would be a decrease in cerebral blood flow leading to oxygen and glucose deficiency, causing oxidative stress. During this stage, FOXO3A mediates autophagy by inducing LC3, BNIP3, Beclin1, and Atg12, which may result in cell lysis and promote cell death [42 - 45].

Targeting autophagy can play a role in mediating neurodegenerative diseases, as suggested by some recent shreds of evidence. Compounds that could block the mTOR-C1-kinase activity, and can further reduce Aβ and tau pathologies, such as rapamycin, CCI-779, Torin1, or PP242, can be used as an activator of autophagy [46 - 48]. However, blocking the mTOR pathway completely might have a negative impact, as it plays a role in normal growth and metabolism [6]. Therefore, mTOR-independent pathways that could modulate autophagy can be focused. Autophagy is a complex process involving different and diverse mechanisms, it would be ideal to aim multiple targets using a cocktail of drugs to induce autophagy in subjects with neurodegenerative diseases [48]. However, this could also lead to disastrous effects, as too much autophagy may lead to the accumulation of large chunks of autophagosomes and undigested autolysosomes, which too can hinder axonal activity [3].

CHAPTER 6

# Propitious Effects of Natural Bioactives for Osteoporosis: Special Emphasis From Marine Source

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**Abstract:** Osteoporosis is one of the most significant health issues on the globe. The activity of osteoclast cells is connected to altered hormone levels and other factors such as age. The condition is characterized by increased bone fragility and loss of bone tissue. Osteoporosis, osteopetrosis, and Paget's disease are frequently caused by an imbalance in the production and function of osteoclasts and osteoblasts. The disease's early signs are scarcely noticeable. It results in gradual bone loss, which eventually makes the patients more prone to fractures. Osteoporosis must be avoided since the fractures caused by it have substantial medical expenses and morbidity. Bisphosphonates are used in the treatment of osteoporosis, along with hormone therapy, selective estrogen receptor modulators (SERMs), calcitonin, strontium ranelate (SR), and other treatments. Marine Natural Products (MNPs) have also had a significant impact on bone metabolism by preventing osteoclastogenesis. These MNPs are generated from a variety of marine resources, including marine cyanobacteria, soft corals, mollusks, fish, dinoflagellates, algae, sponges, and mangroves. Numerous plant and herb species are also effective in the treatment of osteoporosis. We check if these plant-based bio-actives may replace hormonal and synthetic drug-based treatments. This chapter also throws light on any possible effect of COVID-19 that might be on the body, particularly the musculoskeletal system.

**Keywords:** Bisphosphonates, COVID-19, Hormone therapy, Marine natural bio-actives, Osteoporosis, Plant-based bio-actives.

## INTRODUCTION

Osteoporosis is called a “silent” disease as its indications generally do not appear until a bone is broken with one or more vertebrae fractures. Systemic skeletal

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osteoporosis is a disorder hallmarked by lower bone density, micro-architectural degradation of bone tissue, and greater fracture risk. It is one of the most frequent reasons for fractured bones in older people [1].

Our bones are living tissues that continuously repair themselves all our lives to help give shape, movement, and support to our bodies. During childhood and adolescence, the body replaces old bone faster, and after the age of 20, we may begin to lose bone faster than it is formed [2]. Exercise, $Ca^{2+}$, and vitamin D are essential for maintaining bone density and preventing bone loss. One should also avoid too much alcohol consumption and smoking. Bone diseases can make bones brittle, and the most common reason for fractures is osteoporosis. The onset of osteoporosis is one of the realities of aging. Other examples of bone problems include low bone density, Paget's disease, and osteogenesis imperfecta [2].

The most serious issue caused by osteoporosis is fracture, which may be the primary recognizable sign of the disease in patients. Annually, approximately 15 lakh people experience severe fractures because of bone disease. Fracture risk increases with age, and it occurs more in women. Commonly broken bones include vertebrae in the spine, forearm, and hip (Fig. **1**).

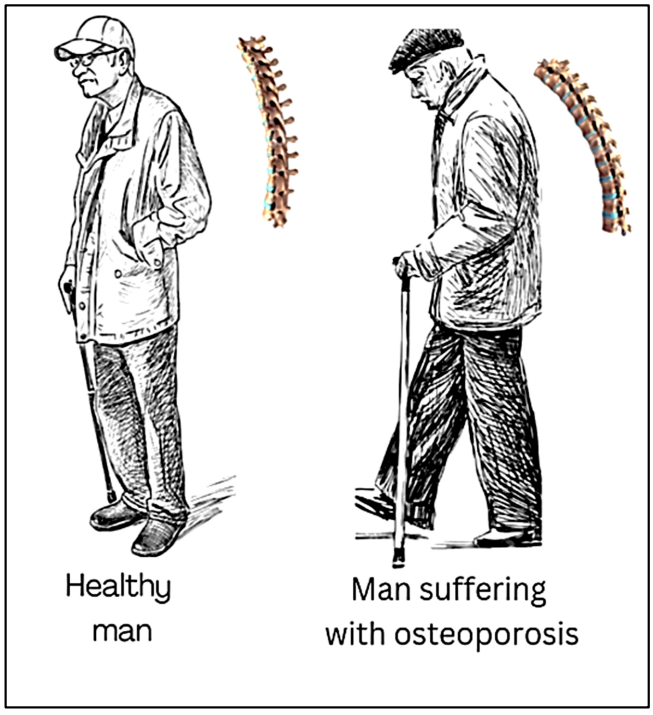


**Fig. (1).** Internal structure of a healthy bone and a bone affected with osteoporosis.

The global prevalence of osteoporosis is about 18.3% reported based on the incidences from 86 studies spanning five continents [3]. The latest studies from Africa indicate that osteoporosis and associated fractures are on the rise across the continent (Fig. **2**).

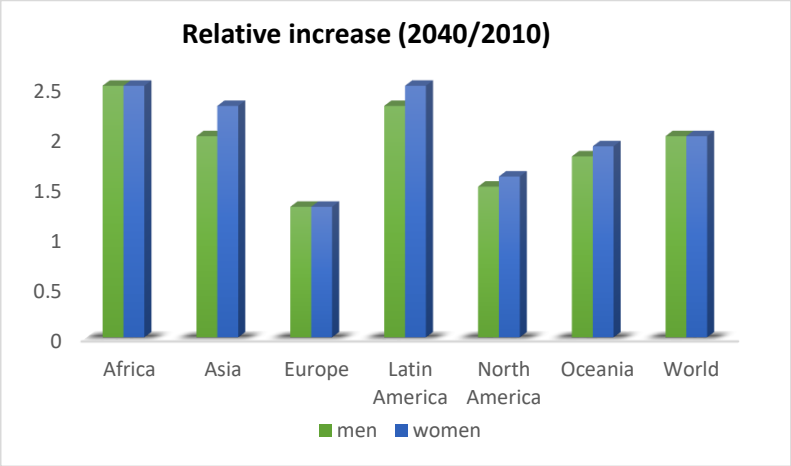


**Fig. (2).** High fracture risk in men and women in 2040 relative to 2010 by world region.

Other studies indicate strongly that the occurrence of osteoporosis and other bone diseases will continue to rise due to a sedentary lifestyle and lack of physical exercise. Earlier people used to work in agriculture farms and household chores were manual which involved a lot of physical work, however with the advent of the digital revolution, the job profile has changed over the last decade and more and more people are involved in the IT industry which involves sedentary lifestyle, which has resulted in a reduction of age with the onset of bone disease.

Their risk factors for osteoporosis have been categorized into modifiable and non-modifiable types. Modifiable risk factors can be controlled by bringing in some adjustments in our daily lifestyle whereas non-modifiable risk factors are beyond our control. Alcohol consumption, weight, smoking, dietary calcium deficiency and physical inactivity are modifiable osteoporosis risk factors. For non-modifiable osteoporosis, risk factors include sex, age, nationality, and genetic characteristics. These factors might be more common in terms of gender as well [3].

## OSTEOPOROSIS- PATHOGENESIS AND MORPHOLOGIC FEATURES

Osteoporosis is traditionally categorized into two types. Primary osteoporosis is a result of osteopenia in the absence of an underlying disease or medication. It is

# CHAPTER 7

# Pathogenesis of Atherosclerosis and Coronary Heart Disease: Epidemiology, Diagnostic Biomarkers and Prevention by Nutraceuticals, Functional Foods, and Plant-Derived Therapies

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**Abstract:** Atherosclerosis is characterized by hardening/narrowing of arteries and reduction of blood flow to vital organs. Animal models and human research show that endothelial dysfunction and plaque development precede the pathogenesis of atherosclerosis, and related coronary heart disease, neurological, and renal disorders. Cardiac CT-scans are used to detect atherosclerosis. Early diagnosis of atherosclerosis reduces mortality, morbidity, and healthcare expenditures. Biomarkers like C-reactive protein, IL-6, IL-8, phospholipase A2, cardiac troponin, MicroRNA, miR-21, and other endothelial inflammation biomarkers are novel targets for monitoring atherosclerosis-related cardiovascular disorders. Anti-platelet and anti-cholesterol drugs are used in the treatment of atherogenesis and blood vessel clots. However, cholesterol-lowering drugs may cause serious adverse effects. Thus, safe and cost-effective non-pharmacological anti-atherogenic and anticoagulant therapies are urgently needed. Nutraceuticals, functional foods, plant-derived therapies, antioxidant/anti-inflammation, foods/fruits/vegetables, and lifestyle changes (*e.g.*, physical activity, less alcohol, smoking cessation) reduce atherogenesis, diabetes mellitus, obesity, hypertension,

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LDL, and C-reactive protein in all age groups, especially younger people. Overwhelming evidence suggests that regular physical activity (30 min/day), cessation of cigarette smoking, and consumption of antioxidant nutraceuticals rich in flavonoids and retinoids, fresh vegetables and fruits, omega-3 PUFA, culinary spices, probiotics, Mediterranean-type diet, and "DASH DIET" lower the risk of atherogenesis and cardiovascular diseases. This review summarizes current advances in the diagnosis and management of atherosclerosis and related cardiovascular illnesses with plant-based and wholesome diets, including the Mediterranean diet, DASH DIET, and lifestyle changes. New preventative measures and alternative therapies, including dietary interventions and plant-based foods may be the most cost-effective ways to manage atherosclerosis and cardiovascular illnesses.

**Keywords:** Coronary heart disease, Culinary spices, DASH diet, Diagnostic biomarkers, Healthful foods, Mediterranean diet, Nutraceuticals, Pathophysiology of atherosclerosis, Stroke.

## INTRODUCTION

Cardiovascular diseases (CVDs) are among the most prevalent chronic illnesses that affect the people worldwide. In both developed and developing nations, CVDs continue to be the main cause of morbidity and mortality [1]. CVDs include atherosclerosis, hypertension, myocardial infarction, heart failure, arrhythmias, valvular heart disease, coagulopathies, and stroke. According to the Registrar General of India (2001–2003), CVDs are the main cause of mortality and morbidity in India, with the highest percentage (25%) recorded in Southern India. Additionally, it was mentioned that CVDs contributed nearly 26% of adult fatalities all across India in the years 2001 to 2003, and that number is predicted to rise to 32% in the years 2010 to 2013 [2]. Globally, the incidence of CVD-related fatalities increased by 41% between 1990 and 2013, and about 17.6 million deaths were attributed to CVDs in 2016. The CVDs not only place a very high financial and emotional strain on families but also escalate the economic healthcare burden on society [3].

Atherosclerosis has been identified by several researchers as the primary underlying cause of many CVDs. The word *athero* means hardening and *sclerosis* means gruel in the Greek language which gave us the phrase atherosclerosis, *i.e.*, accumulation of lipids in the endothelium. In 1904, Marchand originally identified atherosclerosis as the fatty degeneration and stiffness of the blood vessels [4]. It was further characterized as a progressive degenerative process with cholesterol buildup in the small and medium arterial walls and intimal plaque formation in the endothelium [5, 6]. The slow arterial inflammation leads to the buildup of macrophages and white blood cells, which triggers a chronic inflammatory response in the arterial walls (Fig. **1**). Low-density lipoproteins (LDL), which carry triglycerides and cholesterol, further encourage this

pathological process without providing enough high-density lipoprotein (HDL) to remove triglycerides and cholesterol from the macrophages [6].

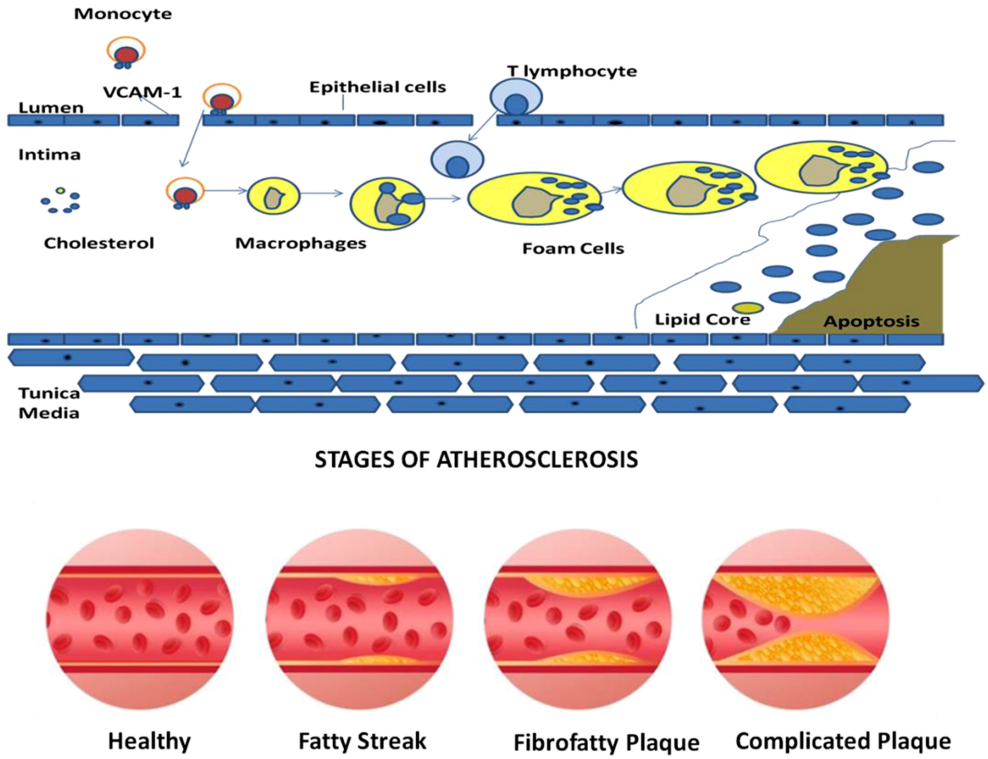


**Fig. (1).** Schematic illustration of the development of atherosclerosis, including stages of arterial plaque formation.

Atherosclerosis, hypertension, hyperlipidemia, and hyperglycemia are typical CVD risk factors. Tobacco smoking, poor nutrition, lack of exercise, and low socioeconomic level lead to obesity, diabetes mellitus, and CVD in children and adults. Particularly hazardous risk factors are sugary drinks and salty foods. Atherosclerosis, plaque formation, obesity, and diabetes are the main cardiovascular risk factors linked to poor diets and lifestyles. Heart-healthy meals and exercise are the most cost-effective ways to preserve cardiovascular health. Diet and cardiovascular health are strongly linked [7]. This study emphasizes on early atherosclerosis diagnosis with blood-based biomarkers and CVD prevention with dietary treatments, plant-derived medicines, probiotics, exercise, and smoking cessation.

# CHAPTER 8

# Immunomodulating Botanicals: An Overview of the Bioactive Phytochemicals for the Management of Autoimmune Disorders

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**Abstract:** Immunomodulation refers to the mechanism by which the response of the immune system is modified by the regulation of antibody synthesis, leading to either an increase or a decrease in its levels in the circulation and body organs. Owing to their immunomodulation and remedial benefits, a broad range of herbal remedies have been shown to be effective in the treatment of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, myasthenia gravis, and systemic lupus erythematosus. The ancient Indian system of Ayurveda and different other alternative therapeutic methods have acknowledged the potential benefits of herbal-based remedies to upregulate or suppress the immune response in the human body. The conventional pharmacotherapies used for the management of autoimmune ailments are documented to cause serious drug-induced adverse reactions (ADRs). Whereas, some phytotherapies have proven safe, reliable, and efficient alternatives for the existing drug regimens with lesser ADRs. For instance, *Withania somnifera*, *Andrographis paniculate*, *Tinospora cordifolia*, *Glycyrrhiza glabra,* and *Berberis arista* are a few herbs whose bioactive phytoconstituents have been reported to possess powerful immunomodulation properties. Based on their purported immunomodulatory mechanisms, they can be used for the management of autoimmune conditions. The focus of this review is to highlight the key inflammatory biomarkers such as TNF-α and interleukin 1, 6 involved in the distortion of the immune system in humans. Also, we will discuss the usefulness of animal models for understanding the underlying mechanisms of autoimmune disorders. In addition, we will describe the patents of phytomedicine formulations filed by different manufacturers for the management of autoimmune disorders, as well as futuristic opportunities that should be explored for discovering the therapeutic functions of alternate remedies for treating autoimmune diseases.

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**Keywords:** *Andrographis paniculate*, Autoimmune disorders, Animal models of autoimmune diseases, *Berberis arista*, Formulation patents, *Glycyrrhiza glabra*, Immunomodulators, *Tinospora cordifolia*, *Withania somnifera*.

## INTRODUCTION

Antimicrobial resistance can be tackled by improving the host immune system [1]. The immune system is highly precised and developed, and prevents the host from the spectrum of foreign substances and infections [2]. The host immune system developed largely to protect the host against pathogenic germs, providing a survival benefit. The hosts try to resist the diseases, while the pathogens try to avoid the host's developing defenses [3]. Activated immune system causes coordinated release of various cells like natural killer cells, T cells, polymorphonuclear leukocytes, dendritic cells, macrophages, and B cells. These cells elimate the pathogens and maintain host immunity. The immune cells are produced by the primary lymphoid organs, like bone marrow, thymus, and secondary lymphatic tissues, like the spleen and lymph node [4]. Development of T cell and B cell occurs in thymus and bone marrow respectively [5]. Various immune cells are stored in the spleen and are circulated through the blood throughout the body when required. The lymphatic nodules contain plenty of white blood cells and the nodules present near the throat prevent the host from foreign particle invasion [6]. Natural killer cells can detect and eliminate tumor cells without any prior antigenic activation and secrete cytokines such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) to improve immune responses [7].

The immune system consists of cells and chemical mediators that protect the organism's integrity against foreign microorganisms, and its perfect operation and stability are required to avoid a variety of immunomodulatory diseases [8]. Rheumatoid arthritis (RA) is an immunomodulatory condition that affects synovial joints. RA begins as painful inflammation of the joints and worsens, leading to joint deterioration and irreversible damage to joints [9]. The predominant factors involved in acute and chronic inflammation are cytokines, such as IL-17, IL-7, IL-1β, IL-6, IL-35 and TNF-α. They stimulate and activate dendritic cells, B cells and T cells, thereby leading to the activation of receptor complexes through Janus kinase (JAK). Furthermore, monocyte recruitment and macrophage differentiation lead to the inflammation of synoviocytes in RA [10]. Multiple sclerosis (MS) is a neurodegenerative disorder of the central nervous system leading to chronic inflammation and demyelination of neurons that is affected by both genetic and environmental factors [11]. In systemic lupus erythematosus (SLE), the cells are attacked by the host’s own immune system, resulting in widespread inflammation and tissue damage in the affected organs.

Body parts most likely to be affected include the brain, kidneys, lungs, skin, joints, and blood vessels [12]. The pathogenesis is mediated by cytokine IFN-α, which upon induction by the immune complexes upregulates several inflammatory proteins. T cell-derived cytokines like IFN-γ, IL-2, IL-6, IL-17, and IL-21 are dysregulated in SLE. A T cell phenotype is induced by the T cell-derived cytokines, characterized by the enhanced secretion of B cells and proinflammatory cytokines, and reduced expression of suppressive T cells, as well as a decrease in activation-induced cell death [13]. The neuromuscular disorder, myasthenia gravis (MS), weakens skeletal muscles due to impairment in the signalling between muscles and nerve cells [14]. In addition to cytokines, *anti-acetylcholine receptor* antibodies and complement proteins significantly contribute the progression of inflammation at the neuromuscular junction. The pathogenesis of MS can be attributed to the increased proportion of Th1 (type 1 helper T cell) and Th17 cells, whereas its development is ameliorated by Th2 and Treg (regulatory T cell) cells. Downregulation of IL-4 levels and upregulation of IL-17 are reported in patients with MS [15]. Fig. (**1**) shows the various immune cells that lead to immunomodulation in various diseases.

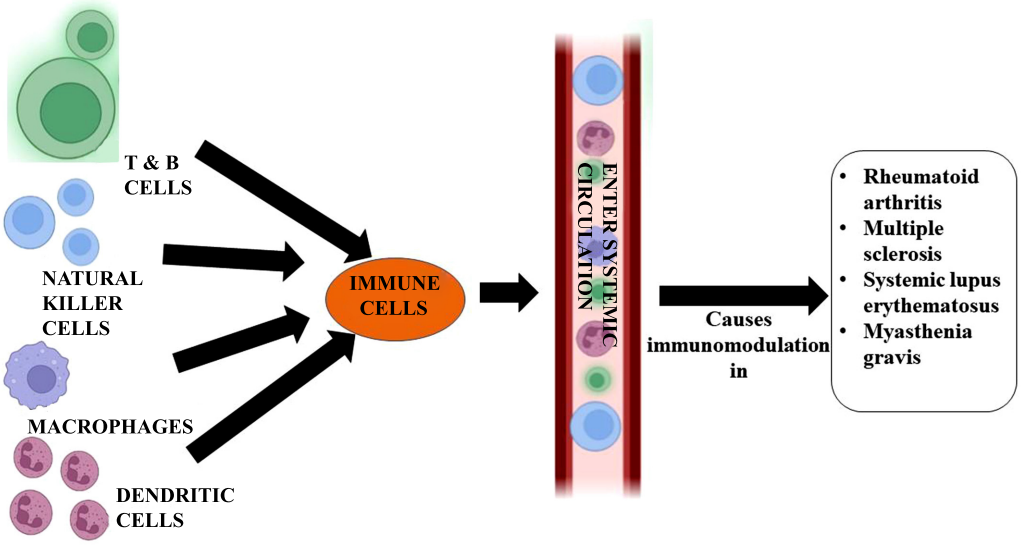


**Fig. (1).** Illustrates various immune cells that enter into the systemic circulation leading to immunomodulation [16, 17].

Research on these autoimmune illnesses has been conducted using a variety of animal models, each of which has a specific objective, rationale, and approach. Animal models have been utilized not just for fundamental scientific study but

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## Tewin Tencomnao

Dr. Tewin Tencomnao is an assistant professor in the Department of Clinical Chemistry, Faculty of Allied Health Sciences, Chulalongkorn University, Bangkok, Thailand. He obtained Ph.D. from Commonwealth University, USA. He did his postdoctoral study at the Institute of Molecular Medicine and Genetics, Medical College of Georgia, Georgia Health Sciences University, Augusta, Georgia, USA. His research interests include genetic polymorphisms, transcriptional regulation, genome-wide screening, and the identification of diseased tissue. His lab has focused on studying the molecular mechanisms of natural products against neurodegeneration and aging. The study models in the lab include cell culture and in vivo studies, such as C. elegans.

## Robin

Dr. Robin is an application scientist in the Regional Water Testing Laboratory, Amritsar, Department of Water Supply and Sanitation, Government of Punjab, India. He obtained M.Sc. (Hons.), M.Phil., and Ph.D. in environmental sciences from Guru Nanak Dev University, Amritsar. With expertise in plant extraction and activity-guided fractionation, he has over ten years of research experience and an in-depth specialization in analytical instruments. He has published several research articles in journals of international repute. His research interests are anticancer medicinal plants, natural plant products, food chemistry, evaluation of isolated compounds for different bioactivities (antioxidant, anti-mutagenic, anti-proliferative, and anti-topoisomerase activities), and determining the molecular mechanisms of action.

## Rajendra G. Mehta

Dr. Rajendra G. Mehta is an internationally known researcher in the area of cancer chemoprevention, drug discovery, and molecular mechanisms of drug action. The main focus of research in his laboratory has been in the area of carcinogenesis and chemoprevention for the past 40 years. Over the years, his group has discovered several products as possible cancer preventive and therapeutic agents. These include resveratrol (from red wine), 1 alpha hydroxy-Vitamin D5 (vitamin D analogue), deguelin (from African plant) and fenretinide (retinoid, vitamin A analogue). In addition, he developed a procedure called the mouse mammary gland organ culture (MMOC) model to screen newly identified (or synthesized) chemicals from plants for their cancer-preventive properties. The National Cancer Institute (NCI, USA) is using this procedure for screening compounds.