Hypertension

ABOUT THE VOLUME

Hypertension is a chronic metabolic disorder characterized by a persistently elevated blood pressure—which increase the risk of heart disease and stroke. Hypertension can also lead to other conditions such as congestive heart failure, kidney disease and blindness. Many anti-hypertension agents are used for treatment of hypertension. But these drugs have some side effects like diuretics etc. The use of medicinal plants for treatment of hypertension is very common because these remedies are easily available at low cost than novel pharmaceuticals. The present volume has been compiled and edited for selected eighteen medicinal plants worldwide used for hypertension. The medicinal plants namely Acacia sp., Allium hookeri, Bacopa monnieri, Centella asiatica, Citrus sp., Cocos nucifera, Clerodendrum colebrookiannum, Convolvulus pluricaulis, Coriandrum sativum, Elettaria cardamomum, Nardostachys jatamansi, Nigella sativa, Olea europaea, Phyllanthus urinaria, Rauwolfia serpentine and Tribulus terrestris have been reviewed in sixteen different chapters received from far and east countries like India, Malaysia, Netherland, Saudi Arabia, Spain, Tunisia, USA. Besides, two chapters are covered on the various patho-physiological process of hypertension, regulatory mechanism of blood pressure and pharmacology of anti-hypertensive and treatment options.

In the volume, major emphasis has been given on the pharmacology and phytochemical composition of medicinal plants that acts in prevention, management and treatment of hypertension. Simultaneously, the results reviewed in the articles have also provided an ideal platform for the isolation, purification and characterization of known bioactive / novel compounds present in these plants for future potential drugs against hypertension.

The volume is aimed at a wide range of audience of ethnobotanists, phytochemists, pharmacologists, pharmacists, pharmacognosists and other research scientists engaged in the search of new drugs from natural resources for Hypertension treatment.
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RECENT PROGRESS IN MEDICINAL PLANTS

Series Editor: J.N. Govil

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Vol. 10: Phytotherapeutics (2005)
Vol. 15: Natural Products (2007)
Vol. 16: Phytomedicines (2007)
Vol. 18: Natural Products II (2007)
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RPMP Vol. 48—Metabolic Disorders: Hypertension

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Vol. 26: Cumulative Index to Abstracts Vols 1-25 (2010)
Vol. 27: Drug Plants I (2010)
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Vol. 32: Ethnomedicine and Therapeutic Validation (2012)
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Vol. 41: Analytical and Processing Techniques (2016)
Vol. 43: Phytotherapeutics II (2016)
Vol. 44: Phytotherapeutics III (2016)
About the Series

Medicinal plants are value added for the content and chemical composition of their active components. Therefore, the demand on plant based therapeutics has increased many fold in both developing and developed countries due to the growing recognition that they are natural products, being non-narcotic, having no side-effects, easily available at affordable prices. In a wider context, there is a growing demand for plant-based medicines, health products, pharmaceuticals, food supplements, cosmetics etc. International market of medicinal plants is over US $ 60 billion per year, which is growing at the rate of 7% and expected to be US $ 5 trillion by 2050. Herbal remedies would become increasingly important especially in developing countries.

Progress in medicinal plants research has undergone a phenomenal growth during last two decades. The input of biochemistry to pharmacology has grown. Molecular pharmacology puts more emphasis on the mode of action of drugs. Worldwide trend towards the utilization of natural plant remedies has created an enormous need for information about the properties and uses of the medicinal plants. Based on this rationale, the present series *Recent Progress in Medicinal Plants* brought out eight volumes, in the first phase, providing edited information from over 225 original and review papers by eminent scientists and researchers from India and abroad on a wide range of topics in the areas of Ethnomedicine, Pharmacognosy, Phytochemistry, Pharmacology, Aesthetics, Biotechnology, Genetic Engineering, Crop Improvement, Production Technology, Trade and Commerce, Diseases and their Management etc. In continuation to these foregone efforts, further eight volumes (9-16) viz., *Plant Bioactives in Traditional Medicine; Phytotherapeutics; Drug Development from New Molecules; Globalisation of Herbal Health; Search for Natural Drugs; Biopharmaceuticals; Natural Products; Phytomedicines*, providing recent research data in the areas of medicinal plants investigations, aimed at discovering new drugs of plants origin, were presented.

Continuing with the ongoing efforts and over-whelming response, the Series editors have been hard pressed to bring out further nine volumes (Vols: 17-25) of the series on herbal drugs containing recent researches on bioreactive components based on their phytochemistry and phytopharmacology in order to discover potential drugs coupled with their therapeutic values. In this direction, nine volumes (17-25) on *Phytochemistry and Pharmacology III, Natural Products II, Phytopharmacology and Therapeutic Values I, II, III, IV & V, Standardization of Herbal/Ayurvedic Formulations and Chemistry and Medicinal Value* were published.

Thus the publication of 25 volumes of “Recent Progress in Medicinal Plants” (2002-2009) provides a comprehensive account of nearly 1800
important medicinal plants for producing drugs, cosmetics, perfumery etc. Hence, it was felt that there is an urgent need to document these 25 volumes in a more condensed form for scientist’s desk reference in day to day research activity. Considering the importance of such a resource book, it was planned to bring out Vol. 26 containing the abstracts of papers published in 25 volume-set of *Recent Progress in Medicinal Plants*. The Vol. 26-“Cumulative Index to Abstracts, Vols. 1-25”- provides information on some 1282 abstracts of original and review papers published in the aforesaid volumes.

Considering the fact that many traditional remedies are back to therapeutic use, including plants as such, or extracts prepared in accordance with the pharmacopoeia of the country where they are used. These medicinal plants are increasingly used as (i) *source of direct therapeutic agents*, (ii) *as a raw material base for the elaboration of more complex semi-synthetic chemical compounds*, (iii) *as models for new synthetic compounds*; and, (iv) *as taxonomic markers for the discovery of new compounds*. In addition to these applications in developed countries, naturally, the medicinal plants will continue to be used increasingly in developing countries, where they are a traditional source of medicine for generations. This has created renewed interest of scientists in medicinal plants and research is at phenomenal rate. We have received excellent studies for publication. It was, therefore, felt desirable to bring out further Volumes of the series, covering recent global updates in medicinal plants researches. This includes 3 specialized Vols (Vol. 36-38) on *Essential Oils*. Learning, recently, the intense research activities in biotechnology, pharmacology and biochemical actions and the rapid increase of knowledge in the field of traditional medicine, it appeared desirable to bring further specialized volumes on *Biotechnology and Genetic Engineering II* (Vol. 39), *Flavonoids and Antioxidants* (Vol. 40), *Analytical and Processing Techniques* (Vol. 41), *Nutraceutical and Functional Foods* (Vol. 42) and *Phytotherapeutics II & III* (Vols. 43 & 44).

The Chief Editor Dr. J N Govil was hard pressed by Academicians, Researchers, Industries & Relevant Govt. Agencies to further bring *disease-oriented* volumes in the Series. Considering the great demand, the editors have brought out four volumes on Metabolic Disorders. Two volumes on Diabetes I & II (Vols 45 & 46), while one volume each on Hyperlipidemia (Vol. 47) and Hypertension (Vol. 48) publication of these volumes incorporating the articles contributed by eminent scholars over the globe in the field of Medicinal Plants will definitely be useful by way of providing latest upcoming advances and developments in the field of Herbal Drugs.

It is hoped these volumes will open new vistas of knowledge and the information presented will lead to further research in the discovery of new drugs of natural origin and serve as good source of material for future work.

*J.N. Govil*
“Save plants to save lives” was the call given by the World Health Organisation a few years ago to stress the role of medicinal plants in achieving the goal of “health for all”. Unfortunately, a high percentage of plant species used in the Indian Systems of Medicine like Ayurveda, Unani and Siddha are still being collected from forests and from natural vegetation. With a rapid rise in the national and global understanding of the importance of herbal medicines in preventive and curative medicine, the pace of exploitation of medicinal plants from the wild state has increased. Consequently, several important medicinal plant species occurring in forest canopies are being threatened with extinction and are being listed in the Red Data books of IUCN and the Botanical Survey of India. Our first task is to bring about a paradigm shift from collection to cultivation. Species occurring in the wild should be domesticated and cultivated in accordance with market demand. Conservation, sustainable use and equitable sharing of benefits are all vital for developing a sustainable medicinal plant industry. At the same time, we should accelerate our efforts in the areas of validation and identification of the biomolecules responsible for specific medicinal properties. Medicinal plants are equally important in veterinary medicine and our vast livestock wealth can be made more productive only by attending to their health and nutrition.

Dr. J.N. Govil and Dr. V.K. Singh deserve our gratitude for their painstaking efforts to compile 40 volumes containing a wealth of information on all aspects of medicinal plants with particular reference to the formulation of both traditional and novel drugs. Volumes 13 to 40 in the series Recent Progress in Medicinal Plants contain valuable ideas on the botanical,
biochemical and pharmaceutical aspects of herbal drugs. Volume 16 deals with recent work on medicinal plants, including information on bioprospecting. This timely series of books reinforce the views expressed by Charaka centuries ago that there are no useless plants in our planet. We must preserve our heritage in herbal medicine and also add to scientific knowledge relating to their properties and active principles. Dr. J.N. Govil, Principal Scientist, Indian Agricultural Research Institute, New Delhi and Dr. V.K. Singh, Assistant Director (Botany), Central Council for Research in Unani Medicine, New Delhi, have rendered valuable service in drawing attention to the vast scope in medicinal plants research and drug development.

I hope these books will be widely read and used by all interested in promoting sustainable health security.

\[\text{\textit{(M.S. Swaminathan)}}\]

New Delhi
Dated: 4th October, 2005
Foreword to the Volume

Metabolic Disorders: Hypertension

Vaidya K.S. Dhiman

I am glad to learn that the Studium Press LLC, USA is publishing recent volume (48) on Metabolic Disorders –Hypertension compiled by Dr. J N Govil and Dr. Anita Bhardwaj in the series of Recent Progress in Medicinal Plants.

Hypertension is a foremost common health problem and important area of research due to its high prevalence and being major risk factor for cardiovascular diseases and other complications. Aging in both men and women is characterized by increases in Blood Pressure (BP). Raised Blood Pressure is a major risk factor for chronic heart disease, stroke, and coronary heart disease. There are numerous factors predisposing to hypertension. These factors vary from country to country and even there is difference between urban and rural regions of the same place. Rapid urbanization rising aged inhabitants, mechanization sedentary life and dietary changes act together as a snare of possibility factors which entangles people in it and leads to several chronic diseases. In order to take effective prevention measures identification of the risk factors in an essential prerequisite. The use of medicinal plants for treatment of hypertension is very common because these remedies are easily available at low cost than novel pharmaceuticals.
India is having immeasurable repository of medicinal plants that are used in traditional medical treatments. Herbal medicines which formed the basis of health care throughout the world since time immemorial and are still widely being used and have considered importance in National and International health sectors especially in Indian systems of hypertension. Each reflects at various pharmacological properties, their mechanisms of action and medical preparations used in management of hypertension. And also main focus has been given on the pharmacology and phytochemical composition of medicinal plants that acts in prevention, management and treatment of hypertension. The results of these studies will provide an ideal platform for the isolation, purification and characterization of known bioactive/ novel compounds present in the plants for future potential drugs against hypertension.

Author has put forth the concept of Indian Traditional Systems especially Ayurveda on the disease and medicinal herbs used in various metabolic disorders including hypertension. The selection of medical ingredients in the diseases are individual’s pathology specific in Ayurveda system and others too, hence some herbs may not be directly anti-hypertensive but important for breaking the pathogenesis. What I propose to emphasize that it is equally important to select an anti-hypertensive plant according to the origin of the disease. This unique approach can provide more opportunities to the future scientists in the field of research and drug developments.

(Prof. Vaidya K. S. Dhiman)
J.N. Govil

J.N. Govil (b. 1945): Obtained his Master’s and Doctorate degrees from Agra University, Agra, India. In his career span of 41 years research experience at the Indian Agricultural Research Institute, New Delhi, Dr. Govil has been involved in the breeding of cross-pollinated, often cross-pollinated, and self-pollinated crops. His research was mainly focused on breeding for better quality, disease resistance, and for higher productivity in Pennisetum, Sorghum, maize, chickpea, and pigeonpea. During these years at IARI, he has released nine varieties of early pigeonpea in arhar-wheat rotation. Dr. Govil has been well exposed to the international scientific community through various programmes at UK, Denmark and Thailand. He also participated in various international seminars and conferences. Dr. Govil is credited with more than ninety research papers in various journals of national and international repute in various aspects of genetics, crop breeding, and topics on general agriculture. He has also guided more than a dozen post-graduate students. Dr. Govil is recipient of no. of Awards and Honor presented by ICAR and Agricultural Societies. He has written and edited a number of books on Medicinal Plants and other books with international authors. A new series “Recent Progress in Medicinal Plants” has been published by Studium Press, LLC, USA in 48 volumes under Dr. Govil’s Chief Editorship. Dr. Govil has been the main resource person as Executive Editor in Execution, Co-ordination and Completion of Projects in bringing 12 Vols Set each on Nanotechnology, Biotechnology, Energy Science and Technology, and Environmental Science and Engineering. Simultaneously, Dr. Govil has brought four volumes set of Chemical Technology Series comprising 2 vols each on Advances in Fertilizer Technology as well as on Petroleum Engineering under the capacity of Acquisition Editor of the Series. Dr. Govil retired from ICAR service during the year 2007. Presently, he is working as Publishing Director and Managing Editor with Studium Press LLC, USA (Camped at New Delhi, India) and has brought out nearly 310 scientific books publication during last eleven years. E-mail: jngovil@gmail.com; jngovil@hotmail.com
Dr. Anita Bhardwaj, BAMS, MHA, PGDHRM (Amity), PGDHJ, Joint Medical Director, Six Sigma Star Healthcare, Delhi. A member of the founding family, Dr. Anita Bhardwaj actively participated in the inception of Six Sigma Healthcare & Global Institute of Healthcare Management. Recently Govt. of India awarded her with India’s Most Prestigious National eGovernanace Award 2016-17. She is the recipient of “Kalpana Chawla Shaurya Award 2016” by the Government of Haryana, DCW Achievement Award by Govt. of Delhi & High Altitude Medical Services Award by Six Sigma High Altitude Medical Services. Dr. Anita Bhardwaj has been pivotal in directing operations for the entire Six Sigma Group and under her able stewardship Six Sigma emerged as India’s first Healthcare consultancy. Instrumental in growing the group’s High Altitude Medical Services at Uttrakhand Flood, Nepal Earthquake, Kailash Mansarover Yatra at China and Manimahesh Yatra 2015, Manimahesh Yatra Medical Services 2017. Dr. Anita steers Six Sigma thrust on research, innovation, Ayurveda and healthcare initiatives. She is also the member of High Altitude Medical Rescue team. Dr. Anita Bhardwaj graduated from the University of Delhi, India. She had taken post-graduate and executive courses in Hospital Administration, Journalism and Human Resource Management.
Preface

Medicinal plants used for treatment and management of Hypertension in Traditional Medicines are the focus of this volume. Hypertension is one of the most important diseases in developing countries. Statistics show that more than seven million people worldwide are affected by this disease each year. The allopathy medicines used for hypertension usually have side effects, therefore, the use of medicinal plants as natural and healthy source of medicines appears essential. The hypotensive and antihypertensive effects of 16 plants namely *Acacia sp.*, *Allium hookeri*, *Bacopa monnieri*, *Centella asiatica*, *Citrus sp.*, *Cocos nucifera*, *Clerodendrum colebrookianum*, *Convolvulus pluricaulis*, *Coriandrum sativum*, *Elettaria cardamomum*, *Nardostachys jatamansi*, *Nigella sativa*, *Olea europaea*, *Phyllanthus urinaria*, *Rauwolfia serpentine* and *Tribulus terrestris* have been validated in the present volume. It contains 18 chapters contributed from 9 far & east countries namely Brazil, Egypt, India, Malaysia, Netherland, Spain, Saudi Arabia, Tunisia and USA. Each reflects at various pharmacological properties, their mechanisms of action and medical preparations used in management of hypertension. Overview of each chapter and its conclusions are presented below.

The first Chapter revealed the various pathophysiological process of hypertension, regulatory mechanism of blood pressure and treatment options. Some of the medicinal plants like *Hibiscus sabdariffa*, *Kelussia odoratissima* and *Eucommial cortex* were highlighted in the regulation of blood pressure.

The second Chapter listed forty five commonly available medicinal plants for use in hypertension. These herbal drugs are generally considered safe being from natural sources. Studies are required for their toxic effects. Therefore, traditional herbal medicines could be another option on which a huge population depends for their primary care.

The highlight of third Chapter is to review the medicinal values of *Acacia* species. Besides, its use as texturing additive, the combine’s functionality of *Gum arabic* is an advantage over other edible biopolymers that do not show antioxidant activities. The special natural characteristic of *Gum arabic* helps it to be best candidate as a natural prebiotic. It can resist the acidic effect inside the stomach and withstand the alkaline effect of bile salts and other digestive enzymes inside the lower bowel.
The Chapter 4 summarizes the photo-chemical and pharmacological properties of *Bacopa monneiri* based on several pre-clinical trials and major bioactivities with currently available reports. In Indian Ayurvedic medicine system, this plant has shown a significant role for its application in the development of different formulations.

Chapter 5 emphasized that traditional herbal medicines are need of the hour in preventing any hypertension complications like nephropathy, stroke, heart attack and retinopathy. One such herbal used since ancient times is *Centella asiatica* which has pharmacological properties such as antidepressant, wound healing, neuroprotection and so on. Anti-hypertension property of *Centella asiatica* is attributed by bioactive compounds like triterpenoids, steroids, flavonoids, glycosides, alkaloids and fatty oils that act synergistically and can be used as antihypertensive herbal approach in near future.

In Chapter 6, using wide range of fruits belonging to *Citrus* species, the study was designed to investigate the role of naringin and hesperidin in two kidney on clip (2K/C) induces renovascular hypertension in rats. The anti-hypertensive effect of naringin and hesperidin may be useful in herbal medicines for the management of hypertension due to its potential free radical scavenging, inhibition of lipid peroxidation and plasma renin inhibitory action.

In Chapter 7, the authors have discussed about diagnosis of hypertension against various living organism by several constituents of *Cocos nucifera*. The medicinal properties of coconut water and especially the antihypertensive activity of coconut water is definitely as easy, cheap and the safest way to control hypertension and also various risks of hypertension such as cardiovascular risks diabetes lipid profile etc. They have concluded that coconut water can be considered as a trusted natural source over many drugs giving no side effects in treating hypertension.

The next Chapter 8 is inclined towards the pharmacological therapeutic and safety aspects of *Convolvulus pluricaulis* along with outlining the future avenues that may be explored. It has been reported that convoline raises the sensitivity of M- receptors that are involved in a large number of physiological functions including the release of neurotransmitters that may reduce hypertension.

In another Chapter on *Convolvulus pluricaulis* an attempt has been made to evaluate *Convolvulus pluricaulis* through any exploited mechanism that is still required to study for the development of potential antihypertensive drug from targeted plant.
Chapter 10 attempts to summarize the medicinal importance of *Coriandrum sativum* and its bioactive constituents in the management of hypertension from the available literatures and highlights the future reason directions on the use of *C. sativum* in hypertension.

The Chapter 11 on *Elettaria cardamomum* clearly indicated that Cardamom could serve as a potential dietary spice to control hypertension with added advantage of antioxidant, anti-inflammatory, anti-platelet, aggregating, hypolipidemic, immunomodulatory and fibrinolysis enhancing properties.

Chapter 12 has provided an insight into an array of phytoconstituents present in *Nardostachys jatamansi* DC with special attention on its antihypertensive and neumprotective properties. Similarly in Chapter 13, the authors have discussed in details the pharmacology and phytochemical composition of *Nigella sativa* that acts in prevention, management and treatment of hypertension.

The data presented in Chapter 14 are encouraging and suggested that the beneficial effects of Olive tree (*Olea europaea*) products on health particularly hypertension are due not only to the favorable fatty acid composition, but also to the abundance of bioactive minor components. The review on *Phyllanthus urinaria* presented in Chapter 15 updates the information on the medicinal properties of the plant that justified its use for hypertension.

The review on *Rauwolfia serperntina* in Chapter 16 focuses mainly on medicinal uses, chemical constituents, pharmacological activities, clinical studies and hypertensive effects. The new findings of getting reserpine from leaves rather than sacrificing whole plant and tuber will help to play an important role in quality control and prevention of adulteration as well as to conserve dwindling population of endangered important medicinal plant *Rauwolfia serperntina* by its medicinal use.

The review of *Tribulus terrestris* has elaborately described the traditional uses, phytochemistry, pharmacology and toxicology of this plant. Simultaneously, review summarizes the results related to the antihypertensive and cardioprotective properties. It also emphasizes the aspects that warrant future research to establish its activity and utility in prevention and treatment of hypertension.

The last Chapter 18 covered two native plants namely *Allium hookeri* Thwaites and *Clerodendrum colebrookianum* of North East India being widely used by the local people (Mizorum) to garnish cooking and as ingredients in cooking popular dishes. In the sturdy, plants based antioxidant and bioactive compounds with focus on the impactful usage of medicinal
plants in the treatment of hypertension are emphasized and could facilitate meaningful public health benefits in the context of prevention, delaying and curing of cardiovascular related diseases.

The overview of unique collection of scientific information including mechanism of action presented in 16 plants included in the volume for Metabolic Disorders: Hypertension clearly indicates the antihypertensive properties and probably determine the mechanism of action and bioactive principles of these plants. The information provided thus will be useful for pharmacologists, herbal medicine preparations and practitioners, drug developers, phytochemists, medicinal chemists, phytologists and researchers.
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The Black Seed, *Nigella sativa* (Ranunculaceae), for Prevention and Treatment of Hypertension

NELISSA PACHECO VAZ1*, DANIELA RODRIGUES DE OLIVEIRA2, GALAL A. ABOUELELLA3, NOUR A. ABOUELELLA3 AND HANEM FATHY KHATER4*

**ABSTRACT**

Hypertension is a crucial risk factor for cardiovascular diseases. Diuretic drugs are frequently used to reduce blood pressure, even though many possess harmful and undesirable side effects. Therefore, the use of alternative treatments such as medicinal plants are considered a good strategy to treat hypertension and its related diseases. Fortunately, many efforts have been made to verify the efficiency of traditional medicinal plants such as the black seed *Nigella sativa* (Ranunculaceae) in benefit of health. Its seeds exhibit a wide variety of pharmacological actions to control diabetes, hypertension, cancer, inflammation, hepatic disorder, arthritis, kidney disorder, and cardiovascular complications. Several mechanisms have been proposed in the literature to explain the effect of *N. sativa* supplementation on lowering blood pressure levels. In this chapter, we discuss in detail the pharmacology, and phytochemical composition of *N. sativa* that acts in prevention, management, and treatment of hypertension.

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1. INTRODUCTION

Hypertension is a public health problem and a term used to describe elevation of systolic blood pressure higher than 140 mmHg and/or diastolic blood pressure higher than 90 mmHg, and it’s classified as either essential (idiopathic) or secondary hypertension. Essential hypertension is a complex interplay between lifestyle and environmental influence, genetic predisposition, and disturbance in vascular, kidneys and neurohumoral control mechanisms.

Hypertension takes a long time before being diagnosed, thereby causing major health problems as stroke and coronary heart disease. In addition, complications of elevated blood pressure can include heart failure, peripheral vascular disease, renal impairment, retinal hemorrhage and visual impairment.

Lifestyle modification is the cornerstone for the prevention and treatment of primary hypertension, and it can be equivalent to drug monotherapy (Caligiuri et al., 2016). These changes include the reduction of salt intake, avoid alcohol consumption, the high consumption of food rich in phytochemicals, weight reduction, and regular physical exercises. At the same time, the use of alternative treatments such as ingestion of medicinal plants and their components can contribute to reducing global cardiovascular risk and the further development and progression of hypertension and other several diseases such as hyperlipidemia and diabetes.

Medicinal plants and essential oils had been used for medicinal purposes in ancient civilizations (Khater, 2017a,b), but one of the main problems faced by doctors and also by users of medicinal plants are the lack of information in the field of natural drug safety and its action on disease and in the organism. Fortunately, many efforts have been made over the last three decades to develop new drugs from natural products, and also to verify the efficiency of traditional medicinal plants such as the black seed Nigella sativa (Ranunculaceae) in benefit of health. To the best of our knowledge, more than two-thirds of the active agents of drugs are at least related to natural sources. For instance, between the years 2005–2010 among 19 natural based drugs that have been approved for worldwide marketing, 7 were classified as natural products, 10 as semi-synthetic natural products, and 2 as natural product-derived drugs.

The seeds of N. sativa are widely used in the Middle East and South Asian countries for the treatment of a large variety of ailments and are
accepted as a panacea, exhibiting a wide variety of pharmacological actions. To illustrate this fact, the seeds or its oils have been used to control diabetes, hypertension, cancer (leukemia, liver, lung, kidney, prostate, breast, cervix, skin), inflammation, hepatic disorder, arthritis, kidney disorder and cardiovascular complications.

This review is therefore aimed to discuss clinical and pharmacological highlights of *N. sativa* in prevention and treatment of hypertension as we discuss the pathophysiology, pharmacology, phytochemical composition of *N. sativa* that acts in prevention, management, control and treatment of hypertension.

2. NIGELLA SATIVA

The use of medicinal plants in several human disorders dates back to the earliest years of man’s evolution (Biradar, 2015). *Nigella sativa* L. (Ranunculaceae) is an indigenous herbaceous plant native to Southwest Asia including Iran, India, and Pakistan. The plant grows to a maximum height of about 40–70 cm and has finely divided foliage and pale blue and white flowers. From the fruit capsules, many small caraway-type black seeds are produced (length: 2.5 to 3.5 mm and width: 1.5 to 2 mm) and it’s reported as the main source of the active ingredients of this plant (Amin and Hosseinzadeh, 2016).

Black seed (*Nigella sativa* L.) is one of the most revered medicinal seeds in history. Hurayrah (RA) narrated that the Islamic prophet Mohammed [peace be upon him] said: “Use black seed regularly, because it is a cure for every disease, except death”. The curative “black seed” it is also explained in the Holy Bible and is described as Melanthion by Hippocrates and Dioscorides and as Gith by Pliny (Tarik *et al.*, 2008; Salem *et al.*, 2005).

The seed was called ‘Panacea’ in old Latin that means ‘cures all’ (Desai *et al.*, 2015). In other languages the plant is known locally by several names:

- Black cumin, black caraway, fennel flower, love-in-a-mist, Roman coriander (English);
- Habbah Al-Sauda, (seed of blessing), Habatut Barakah Shooneez, Habba Sauda, ‘Habbah Sawda’, Habb al-barka ‘Habbat el Baraka’ (Arabic);
- Cominho-preto (Portuguese);
- Chernushka (Russian);
- Çörek otu (Turkish);
- Cyah-daneh, siah dana (Persian);
- Krishana-jiraka, upakunchika (Sanskrit);
Schwarzkümmel (German);
Pei hei zhong cao, hak jung chou (Chinese);
Cheveux de vénus, nigelle (French);
Kalonji (Hindi and Urdu);
Kalonji jire (Marathi);
‘Kalo jeera’ (in Bengali) and
Punjabi in Kalvanji.

Having a strong, hot peppy taste, the black seed seeds are much appreciated. The best seeds are considered to come from Egypt (Ramadan, 2007) where they grow in oasis conditions considered almost ideal, being watered until the seed pods form. Called as “Pharaohs’ oil” and recognized as a very precious remedy from Egyptian culture, the oil extracted from the seeds has much benefits (Ramadan, 2007). Besides the medicinal use of nigella (Khater, 2015, 2017b), it has insecticidal properties as well (Khater, et al., 2003, 2012, 2013).

For thousands of years, the seeds of this plant have been used as a spice and additive in bread, cookies, and other dishes in many Asian and Eastern countries. Therapeutic benefits of black seed and its active ingredients have been demonstrated in many investigations (Amin and Hosseinzadeh, 2016) and were published in several reviews available in the literature (Khan, 1999; Salem et al., 2005; Ramadan, 2007; Paarakh, 2010; Khan et al., 2011; Mathur et al., 2011; Leong et al., 2013; Bahmani et al., 2015; Khan et al., 2016; Amin and Hosseinzadeh, 2016).

3. TRADITIONAL USES OF NIGELLA SATIVA

Traditional uses of this amazing herb originate from the ancient Egyptians, Greeks and Romans. Black seed and their constituents are used to treat various diseases since thousands of years ago and also take an important place in Chinese Traditional Medicine. Black seed is also considered a vital drug in the Indian traditional system of medicine, prevention, and long life uses of black seed for its capability to heal nervous disorders, anorexia, and gynecological problems. In many Arabian, Asian and African countries, black seed oil is used as natural remedies for several diseases including various allergies (Rahmani et al., 2015). Both seeds and oil extracted from this plant are used for medicinal purposes (Khan et al., 2011).

Unani medicine is substantially based on Ibn Sina’s (Avicenna) The Canon of Medicine (11th century) and the most famous physician and philosopher of the Islamic world. He had been advocated black seed, as the body’s energizing compound and as a remedy for fever, headaches, toothaches, and common colds (Amin and Hosseinzadeh, 2016).
It was also recommended as a soothing agent for skin disorders, wounds, and external irritations. In folklore medicine, the seeds and oil of *N. sativa* have been frequently prescribed as a natural remedy for a diverse range of diseases, such as fever, cough, nasal congestion, bronchitis, asthma, dyspnea, hypertension, diabetes, inflammation, milk production, eczema, dizziness, and gastrointestinal disturbances. It is also used in case of pain conditions such as headaches, toothaches, and back pain has also been recommended.

In the traditional system of medicine practiced in the Arabian Gulf region, black seed is recommended for a wide range of diseases, including the following analgesic, anti-inflammatory, fever, cough, bronchitis (acting as bronchodilator), asthma, chronic headache, migraine, dizziness, chest congestion, dysmenorrhea, obesity, diabetes, paralysis, hemiplegia, back pain, infection, inflammation, immunopotentiation, rheumatism, hypertension (hypotensive effect), and gastrointestinal problems such as dyspepsia, flatulence, dysentery, and diarrhea. It has been used as a stimulant, diuretic, emmenagogue, lactagogue, anthelmintic, carminative, antibacterial, antifungal. Black seed has also been used externally where it is applied directly to abscesses, nasal ulcers, orchitis, eczema, and swollen joints (Tarik, 2008). The extracts from their seeds are used by Unani Physicians of Traditional Medicine (Hakims or Tabibs) and Ayurvedic Practitioners (Vaids) in the treatment of several medical disorders including dyslipidemia, obesity, and hypertension (Qidwai *et al.*, 2009).

Besides, the use of *N. sativa* seeds is claimed to be free from major side effects including hepatic or renal toxicity, but cases of contact dermatitis have been reported with local applications (Qidwai *et al.*, 2009).

Amin and Hosseinzadeh (2016) have reviewed recently the analgesic and anti-inflammatory effects of *N. sativa* and its main active constituent thymoquinone. In this work, they report many studies showing the different doses and administration forms of *N. sativa* seed components that were tested in models of nociception and inflammation.

This plant has been a great focus of research and has several traditional uses and consequently has been extensively studied for its chemical constituents and biological activities. Moreover, it worth to mention that nigella has anti bacterial activity against clinical isolates of methicillin resistant *Staphylococcus aureus* (MRSA) (Hannan *et al.*, 2008), antidiabetic properties (Mathur *et al.*, 2011), antiepileptic effects in children with refractory seizures (Akhondian *et al.*, 2007), as well as tumor and immunomodulatory properties, augmenting the T cell- and natural killer cell-mediated immune responses (Salem, 2005). A lot of animal studies have already been done to determine the various activities of *N. sativa* oil on different components of the metabolic syndrome for example blood sugar and blood pressure but no clinical studies have been done in patients with
metabolic syndrome. This clinical study was undertaken to know the adjuvant effect of *Nigella sativa* oil on various clinical and biochemical parameters of the metabolic syndrome (Najmi et al., 2008). Most of the studies have reported the favorable effect of *N. sativa* on various components of the metabolic syndrome (Najmi et al., 2008). *N. Sativa* has beneficial effects on fasting blood sugar, total cholesterol, and LDL. However, more research is required to determine mechanisms by which *Nigella sativa* acts on various components of the metabolic syndrome. *Nigella sativa* is one such remedy that may prove beneficial in the future for the prevention and treatment of the metabolic syndrome (Najmi et al., 2008).

4. CHEMICAL COMPOSITION OF BLACK SEED

In the last five decades, there are reports of more than 150 studies that have been conducted to investigate the chemistry and pharmacological properties attributed traditionally to black seed (*Nigella sativa* L.) and their constituents. Most of these studies are usually aimed in the search for a link between seeds’ chemical composition and their traditional uses (ethnopharmacology), focusing on obtaining enough information to elucidate under the light of modern science, their biological action mechanisms, identifying the active substances and understanding their effectiveness. Thus, many of the traditional medicinal uses of black seed have been tested (Tariq, 2008). Taking into account the latest phytochemical studies performed on black-seed seeds, researchers worldwide have reported the presence of more than 100 constituents. However, many of them lack on properly chemical identification and/or characterization and/or pharmacological effectiveness.

In 1880, the first chemical study performed on *N. sativa* seeds was reported by Greenish (Gholamnezhad et al., 2016) and included seeds basic composition: basically oils, proteins, carbohydrates, fibers, ash and moisturizers. Since that pioneering study, many were the *N. sativa* investigated pharmacological and nutritional properties: those were mainly attributed to the identified components (Table 1) from diverse chemical classes including proteins, amino acids, carbohydrates, vitamins, fibers, oils (combination of fatty acids, especially polyunsaturated fatty acids), volatile oil, minerals, alkaloids, flavonoids, saponins, and other organic compounds.

It’s worthy to point that chemical composition of vegetable species like *N. sativa* seeds are usually very diverse, comprising besides active secondary metabolites, moisture, oil, proteins (eight of the nine essential amino acids), carbohydrates, vitamins, and minerals as well. It is well established that the percentage of such components varies according to geographic distribution, plant’s amount of sunlight exposure, time of harvest, and other cultivation parameters.
The Black Seed, *Nigella sativa* (*Ranunculaceae*), for Prevention...

Table 1: General chemical composition of *N. sativa* seeds*

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Chemical composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil</td>
<td>Linoleic acid (omega-6), oleic acid, palmitoleic acid, α-linolenic acid (omega-3), myristoleic acid (omega-5), dihomolionolenic acid, stearic acid, eicosadienoic acid, myristic acid, arachidic acid, behenic acid, sterols (β-sitosterol, avenasterol, stigmasterol, campesterol and lanosterol), tocopherols (α, β, and γ) thymoquinone, retinol (vitamin A), carotenoids (β-carotene), dihomo-γ-linoleic acid,</td>
</tr>
<tr>
<td>Volatile oil</td>
<td>Thymoquinone, p-cymene, carvacrol, α-pinene, β-pinene, longifolene, trans-anethole, thymol, thymohydroquinone, dithymoquinone (nigellone)</td>
</tr>
<tr>
<td>Proteins</td>
<td>Glutamic acid, arginine, aspartic acid, leucine, glycine, valine, lysine, threonine, phenylalanine, isoleucine, histidine, methionine</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Glucose, rhamnose, xylose, arabinose</td>
</tr>
<tr>
<td>Minerals</td>
<td>Ca, P, Fe, K, Na, Zn, Mg, Mn, Cu, Se</td>
</tr>
<tr>
<td>Saponins</td>
<td>α-Hederin (melanthin), hederagenin, (melanthigenin)</td>
</tr>
<tr>
<td>Alkaloids</td>
<td>Nigellicine, nigellimine, nigellidine</td>
</tr>
<tr>
<td>Other vitamins</td>
<td>Vitamin A, folic acid thiamin, riboflavin, pyridoxine, niacin, folacin, vitamin C, and vitamin E</td>
</tr>
</tbody>
</table>

*Adapted from Amin and Hosseinzadeh, 2016

It is believed that the chemical composition of essential (volatile) and fixed (stable) oils are the main source of beneficial and active substances found in *N. sativa* seeds (Amin and Hosseinzadeh, 2016). Hence, great part of the published research papers about this subject reports the investigation of black seed chemical composition relating it to some biological and/or pharmacological effectiveness.

4.1. Essential Oil Composition

After literature survey, it was possible to perceive that *N. sativa* seeds essential oils possess a wide range of organic compounds from several chemical classes. A GC-MS analysis of the volatile seed extracts performed by many research groups has shown it to have a rich mixture of volatile compounds many of them shown in Table 2.

Table 2: *Nigella sativa* seeds essential oil composition

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Structural formula</th>
<th>Concentration (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymoquinone (1)</td>
<td><img src="image" alt="Thymoquinone structure" /></td>
<td>27.8–57.0</td>
<td>Ali, 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6</td>
<td>Nickavar, 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.1</td>
<td>Delkordi, 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23.25</td>
<td>Sultan, 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>traces</td>
<td>Wajs, 2008</td>
</tr>
</tbody>
</table>

*Table 2: (Contd…)*
### Table 2: (Contd...)

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<thead>
<tr>
<th>Constituent</th>
<th>Structural formula</th>
<th>Concentration (%)</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Dihydrothymoquinone (thymohydroquinone)</td>
<td><img src="image1" alt="Structural formula" /></td>
<td>3.84</td>
<td>Sultan, 2009</td>
</tr>
<tr>
<td>p-Cymene</td>
<td><img src="image2" alt="Structural formula" /></td>
<td>7.1–15.5</td>
<td>Ali, 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.8</td>
<td>Nickavar, 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41.5</td>
<td>Dehkordi, 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60.2</td>
<td>Wajs, 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32.02</td>
<td>Sultan, 2009</td>
</tr>
<tr>
<td>Carvacrol</td>
<td><img src="image3" alt="Structural formula" /></td>
<td>5.8–11.6</td>
<td>Ali, 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2</td>
<td>Dehkordi, 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.0</td>
<td>Wajs, 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.38</td>
<td>Sultan, 2009</td>
</tr>
<tr>
<td>Trans-anethole</td>
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<td>0.25–2.3</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>38.3</td>
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</tr>
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<td></td>
<td></td>
<td>2.10</td>
<td>Sultan, 2009</td>
</tr>
<tr>
<td>4-Terpineol</td>
<td><img src="image5" alt="Structural formula" /></td>
<td>2.0–6.6</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>0.7</td>
<td>Nickavar, 2003</td>
</tr>
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<td></td>
<td></td>
<td>0.9</td>
<td>Wajs, 2008</td>
</tr>
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<td>Thymol</td>
<td><img src="image6" alt="Structural formula" /></td>
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<td>Concentration (%)</td>
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</tbody>
</table>
Other compounds that were identified in *N. sativa* seeds essential oils include: nonterpenoid hydrocarbons like *n*-nonane (1.7%), 3-methyl nonane (0.3%), 1,3,5-trimethyl benzene (0.5%), *n*-decane (0.4%), 1-methyl-3-propyl benzene (0.5%), 1-ethyl-2,3-dimethyl benzene (0.2%), *n*-tetradecane (0.2%) and *n*-hexadecane (0.2%) (Nickavar et al., 2003); camphene, (Z)-β-ocimene, (E)-β-ocimene, *cis*-thujan-4-ol, *cis*-4-methoxythujane, β-thujone, bornol, α-terpineol, cyclosativene, α-copaene, *allo*-isolongifolene, β-*cis*-farnesene, β-bisabolene, β-caryophyllene oxide, pentadecan-2-one (all compounds present in trace concentration ≤ 0.05%), camphor (0.1%), terpinolene (0.6%), *trans*-thujan-4-ol (0.5%), *trans*-4-methoxythujane (4.0%), *trans*-verbenol (0.3%), *cis*-chrysanthenyl acetate (0.1%), bornyl acetate (0.1%), longicyclene (0.4%), tridecan-2-one (0.1%), β-selinene (0.1%), γ-cadinene (0.1%) and farnesal D (cis, trans) (0.2%) (Wajs et al., 2008) among others unidentified yet.
The major identified terpenes for some samples are thymoquinone (1), dithymoquinone (28) (Fig. 1), \(p\)-cymene (3), carvacrol (4), trans-anethol (5), the terpene limonene [also called carvene (16)] and the unsaturated ketone carvone (21). According to Khan et al. (2011) some of these compounds are discovered to be cytotoxic for various types of tumors. Besides these, thymohydroquinone (2), thymol (7) and \(a\)-pinene (17) are also considered to be pharmacologically active constituents (Ramadan et al., 2007). The crystalline active principle, nigellone (dithymoquinone), is the only constituent of the carbonyl fraction of the oil (Ramadan et al., 2007).

![Fig. 1: Dithymoquinone structure: produced by photodimerization of thymoquinone (1) in consequence of sunlight exposure during separation and extraction of the seed quinones.](image)

Thymoquinone [2-isopropyl-5-methyl-1,4-benzoquinone (Compound 1)] is the major and the most reviewed component of the seed (Amin and Hosseinizadeh, 2016; Gholamnezhad et al., 2016; Rahmani and Ali, 2015) and it is attributed a wide range of biological activities for (1), being considered to be the principal seed active ingredient: it possesses antioxidant, anti-carcinogenic and antimutagenic activities. Furthermore, when given orally to experimental animals (1) is considered a relatively safe compound (Al-Ali et al., 2008).

### 4.2. Fixed Oil Composition

It has become evident that black seed seeds hold nutraceutical potential against various physiological threats due to its phytochemical richness, mainly because of the presence of vitamins, minerals and other nutritive and/or active compounds (Table 1). Sultan and collaborators (2009) after performing the evaluation of nutritional and antioxidant effects of *N. sativa* seeds fixed and essential oils have suggested that oils supplementation in bakery items and other food products is achievable and can be employed to reach the allied health demands (Sultan et al., 2009).

It is extensively reported that fixed oil of black seeds contains valuable quantities of unsaturated healthy fatty acids like, linoleic acid (omega-6), oleic acid and small amounts of linolenic acid (omega-3, ALA), among others, as well as saturated fatty acids in minor amounts like arachidonic and eicosenoic acids which are considered to have rare occurrence in nature. The fatty acids in this seed may have roles in the hypolipidemic effect while...
the presence of dihomo-γ-linoleic acid could partially explain the powerful antioxidant effect observed for this seeds.

Besides the fatty acid profile, the seeds are considered to be very nutritive as well, once it is a natural source of several vitamins like retinol (vitamin A), carotenoids (β-carotene), and vitamin E (tocopherol α, β, and γ) in considerable amounts (Fig. 2) (Salem et al., 2005).

There are reports citing that the consumption of tocopherols (α-, β-, γ- and δ-) in different isomeric forms, is strongly recommended once this class of substances contributes substantially towards the health improvement (Sultan et al., 2009). It is estimated that fat-soluble vitamins represent more than 0.2% of the black seed total oil content. Beyond the presence of vitamin A (32) in the seeds, there is the presence of β-carotene (33) that can also be converted by the liver to more vitamin A after seed consumption (Salem et al., 2005).

Black seed has been known to contain also considerable quantities of phytosterols (Fig. 3) including β-sitosterol (35), stigmasterol (36), avenasterol (37), campesterol (38), lanosterol (39), cycloartenol (41), sterol esters and sterol glucosides with some other minor lipidic constituents such as methylmonadeca-15, 17-dienoate, pentyl hexadec-12-enoate, and pentyl pentadec-11-enoate (Nickavar et al., 2003). It is believed that the presence of phytosterols further strengthens its hypoglycemic and hypercholesterolemic perspectives of seed in meals (Sultan et al., 2009).

It was found also many non-oily and non-caloric components in black seed seeds in trace amounts. Such compounds include diterpenes, triterpenes and terpenic alkaloids. Some alkaloids (Fig. 4) with the isoquinoline and indazole backbones have been isolated in the N. sativa seeds extracts (Khan, 1999; Khan et al., 2016). The isoquinoline alkaloids include nigellimine (42)
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and nigellimine-N-oxide (43), while the indazole alkaloids include nigellicine (44) and nigellidine (45).

Though thymoquinone (Table 2) is the main bioactive compound of black seed seeds, other compounds like β-carotene (Fig. 2), phytosterols (Fig. 3), alkaloids (Fig. 4), flavonoids, and saponins (Fig. 5) do contribute their bit toward the immense benefits that this seed possesses (Khan et al., 2016). Pursuant to, the saponin α-hederin (a water-soluble pentacyclic triterpene) is reported to be a potential anticancer agent once it showed potent in vivo antitumor activity (Huat and Swamy, 2003).

![Fig. 3: Main phytosterols identified in black seed (Nigella sativa) seeds.](image)

![Fig. 4: Alkaloids found in Nigella sativa seeds](image)
Other ingredients present in *N. sativa* seeds include minerals such as potassium, phosphorus, calcium, and iron, in greater quantities, as well as zinc, magnesium, manganese, selenium, and copper in fewer amounts (Tarik, 2008).

Notwithstanding the phytochemical composition of the *N. sativa* seeds extract or oils (fixed and volatiles) have been intensively studied, there are only a few clinical studies available in the literature, evaluating the possible correlations between chemical composition, pharmacological activities and action mechanisms in molecular levels. However, there is more research showing some effects of black seed on parameters related to metabolic syndromes, such as the influence on blood glucose levels, lipid profile, and blood pressure (Shah *et al.*, 2012; Desai *et al.*, 2015; Tabatabaei-Malazy *et al.*, 2015; Mohtashami *et al.*, 2016) among others. Despite all those published studies, we have realized that there is still a lack of studies on the effect of *N. sativa* on human hypertension which could explain or at least scientifically prove its ethnopharmacological use. Furthermore, it was found sufficient evidence to infer that *N. sativa* contains many active substances that may be responsible for antioxidant activity and diuretic effect, which may play key roles in prevention and the cure of hypertension as will be discussed properly ahead.

5. PATHOPHYSIOLOGY OF HYPERTENSION

The human body uses different mechanisms to maintain blood pressure within a certain range. Blood pressure is a product of peripheral vascular resistance and cardiac output, and control is exerted by influencing one of these two components. Pathogenesis of essential hypertension is only partially understood. Due to a big number of factors and pathogenic mechanisms that participate in the development and progression of hypertension, its pathogenesis is rather complicated. Most of the theories which try to explain the pathogenesis do agree on that there is a disorder in
blood pressure regulation (this disturbance may probably affect any parts of the regulating chain), that is due to some endogenous or exogenous factors. Endogenous factors are multifactorial, including genetic ones. However, exogenous factors include primarily high salt intake, high energy provision, and some psychogenic factors. The following gives an overview to explain the principal pathogenesis of essential hypertension:


Aldosterone increases the volume of body fluids by the reabsorption of $\text{Na}^+$ and hence water in the distal tubules. Angiotensin II is a pressor factor. It stimulates vasoconstriction via a direct mechanism. It enhances the synthesis and the release of noradrenaline from the nerve endings and it also blocks its uptake by the nerve terminals. Apart from this, it stimulates adrenaline and aldosterone release from the adrenals as well as the vasopressin from the neurohypophysis, what will consequently lead to an increased vascular susceptibility to vasoconstriction agents (Pessôa *et al.*, 2013).

5.2. **Sympathetic Nervous System**

An overactive of sympathetic system that leads to the release of catecholamines from the adrenal medulla, leading to increased stress response. Along with the stimulation of the sympathetic nervous system and the adrenal medulla, there will also be a releasing of hormones of the anterior lobe of the pituitary (adenohypophysis), from which the most important one in stressful situations is the adrenocorticotropic hormone (ACTH) (Fisher *et al.*, 2012).

5.3. **Peripheral Resistance**

During the initial stage of essential hypertension, the cardiac output is increased by sympathetic-adrenal activity. It acts directly on the heart and the vascular structure, where there is an increased tension of the vascular wall in the resistant and the capacitive (venous) field. But during vasoconstriction that is caused by high sympathetic tonus, concentration of $\text{Na}^+$, $\text{Ca}^{2+}$ and water content in the vascular wall also increase. Later there will be some structural changes in the wall of the vessels: Thickening of the wall due to the hypertrophy of the media and hyperplasia of the collagen fibers. That is the cause of the changes in the relation between the thickness of the vascular wall and its lumen. In that case, increased peripheral resistance means that in order to maintain the same perfusion, it is necessary to increase the systemic pressure; thus greater cardiac work is needed, leading to further fixation and progression of hypertension.
5.4. Psychoemotional Stress

The Central Nervous System reacts to exogenous stress factors via activating the sympathetic system and antidiuretic hormone (ADH). Its action lies in enhancing the reabsorption of water. Apart from this, it shares the modulation of blood pressure (Bolivar et al., 2013).

5.5. Oxidative Stress

This could be described as an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense systems. The excess of ROS generation (e.g., superoxide anion, hydroxyl radical, hydrogen peroxide, and singlet oxygen), decreases nitric oxide (NO) levels and reduce the antioxidant capacity (enzymes) in the vessels, heart, brain and kidneys. Major enzymatic antioxidants are superoxide dismutase (SOD), catalase, glutathione peroxidases, thioredoxin, and peroxiredoxin. Reduction in SOD and the peroxidase activity of glutathione peroxidises, have been observed in newly diagnosed hypertensive subjects. On the other hand, hydrogen peroxide production is also higher in these subjects. Subcellular processes have been described to ROS. It stimulates mitogen-activated protein kinases (MAPK), tyrosine kinases, Rho kinase and transcription factors (NF κB, AP-1, and HIF-1), inactivate protein tyrosine phosphatases (PTP), and increases intracellular free Ca$^{2+}$ concentration and upregulates proto-oncogene and pro-inflammatory gene expression activity. All alteration described above induces an endothelial dysfunction reduces vasodilatation, increases contraction, and structural remodelling causing increased peripheral resistance and elevated blood pressure (for more detail about the described mechanism see Montezano et al., 2014).

5.6. Endothelial Cells

Endothelial cells have a crucial role in the modulation of total peripheral vascular resistance and control vascular tone. Endothelial dysfunction including altered anticoagulant and anti-inflammatory properties in the endothelium, impaired modulation of vascular growth, and deregulation of vascular remodeling, decreased the production of NO and unbalanced production of other different vasoactive substances (endothelin-1, thromboxane A2, and angiotensin II). This dysfunction has been demonstrated in subjects with different risk factors for atherosclerosis including arterial hypertension, and in coronary atherosclerotic disease. Oxidative stress plays an important role in the development of endothelium injury. Formation of ROS, resulting in scavenging of NO and reduced NO bioavailability, has been suggested as a hallmark of endothelial dysfunction. Increased production of vascular ROS, especially superoxide anion
contributes significantly to functional and morphological alterations in hypertension (Higashi et al., 2012).

5.7. Genetic Factors

It was proven that some biochemical and other markers, and even some reactions to different stimuli - that are present in people with essential hypertension - can be noticed also instill healthy normotensive members of hypertensive families:

- Fast release of noradrenaline from the thrombocytes.
- Low contents of kallicrein (a depressor factor).
- Changes of the release of catecholamines and metabolism.
- High sensitivity to Na⁺.
- Transport abnormalities for Na⁺, K⁺, Ca²⁺ (in the kidneys and the vascular wall, in erythrocytes, leukocytes, and lymphocytes).

In summary, in most patients with incipient essential hypertension, there is an increase in cardiac output, whereas the peripheral resistance and the extracellular fluid volume stay normal. Later, as blood pressure increases, the cardiac output decreases again to physiological or mildly increased values just as well as the volume of extracellular fluid, whereas the peripheral resistance increases. In advanced stages of the disease because of the damage incurred to target organs, the glomerular filtration decreases (the extracellular volume increases), and the perfusion of the brain and coronary vessels also decreases. In this phase, the maintenance of high blood pressure is inevitable to procure sufficient perfusion of brain and kidneys. Hypertrophic heart muscle without the respective growth in coronary perfusion, however, is not able to provide sufficient perfusion pressure against the increased vascular resistance. The activation of the renin-aldosterone system and the retention of fluids theoretically improve this state, yet eventually, they bring about further fixation and progression of hypertension. As a result of progressive damage to nephrons, a decrease in glomerular filtration takes place in advanced stages of the disease and further contributes to the retention of sodium and extracellular fluid. Consequent comprehension of the pathophysiology mechanism of hypertension needs to consider all the possible disorders in the regulation of individual physiological components, determining the development and maintenance of increased blood pressure, cardiac output, and peripheral resistance.

Several studies point to the important role of local inflammation and autoimmunity alterations in development and progression of essential hypertension. What knows that inflammation and oxidative stress are
frequently coupled? This interaction can be explaining changes that drive the stage for developing essential hypertension. Vessel stiffening is associated with the development of hypertension. A common denominator of various conditions associated with the vessel is increased oxidative stress in the vascular wall, inflammatory infiltration, fibrosis and ensuring elevated blood pressure (Harrison et al., 2011).

6. THERAPEUTIC ROLE OF N. SATIVA TO DECREASE BLOOD PRESSURE IN ANIMALS AND HUMANS

Evidence exists to support several potential mechanisms whereby N. sativa might decrease blood pressure and decrease the severity of hypertension in animals and humans. These mechanisms are a decrease in oxidative stress, interference with the renin-angiotensin-aldosterone system, and/or improving vascular function in an endothelium-dependent or -independent manner.

6.1. N. sativa and Oxidative Stress

Oxidative stress has been linked to impaired vasodilation and kidney function in animal models of hypertension; many studies have examined the role of antioxidants to treat hypertension. Previous studies found that a decrease in blood pressure in hypertensive animals and humans treated with N. sativa is due to decrease in oxidative stress. For example, Khattab et al. (2007) found that treatment with thymoquinone (1) (0.5 and 1 mg/kg/day, orally) reduced the increase in hypertensive rat induced by L-NAME in a dose-dependent manner via antioxidant effects. Treatment-rat with (1) inhibited production superoxide radical decreased the elevated creatinine and increase in kidney GSH. Another animal study has also found that both (1)-rich fraction and (1) markedly improved plasma antioxidant status by inhibiting the formation of hydroxyl radicals. In the same study, (1)-rich fraction and (1) caused an enhanced expression of antioxidant genes (SOD-1, catalase CAT, and GPx-2) in hypercholesterolemic rats (Ismail et al., 2010). In these studies, the authors concluded that the antioxidant effect of thymoquinone (1) is a potent free radical scavenging in the treatment of hypertension which is closely associated with oxidative stress.

6.2. N. sativa and RAAS

As mentioned, RAAS plays a major role in the regulation of blood pressure. The use of angiotensin-converting enzyme (ACE) inhibitors or subtype-specific angiotensin receptor blockers can interfere with this system and lead to a decrease in blood pressure. N. sativa oil has been shown to inhibit an ACE in vivo (Jaarin et al., 2015), presumably through its ability to a reduction in Ang II synthesis. Interestingly, the cardiac HO-1 activity shown a significantly increased in rat treated with N. sativa oil at dose of 2.5 mg/
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kg. for 8 weeks. It is known that HO-1 plays an important role in reducing blood pressure by reducing Ang II and NADPH oxidase-mediated oxidative stress (Jaarin et al., 2015).

6.3. *N. sativa* and Calcium Channel Blockade

An active compound from *N. sativa*, thymol, has been showed to reduce blood pressure by block calcium (Ca\(^{2+}\)) channels. It can be explained by mechanisms involving inhibition of Ca\(^{2+}\) releases from sarcoplasmic reticulum, reduced Ca\(^{2+}\)-sensitivity, and/or blockade of calcium influx across the membrane in endothelium cells (Peixoto-Neves et al., 2010). Electrophysiology studies from canine cells showed that thymol inhibits L-type Ca\(^{2+}\) current in a dose-dependent (10–1000 mM) manner (Magyar et al., 2004). It’s known that Ca\(^{2+}\) channels are blocked, Ca\(^{2+}\) entries into vascular smooth muscles are decreased leading to an increase in vasorelaxation and decrease blood pressure. It is also reported that the compound nigellone (28) from the crude extract of *N. sativa* seeds acts as a calcium channel blocker(s), which might explain the beneficial traditional therapeutic uses of *N. sativa* toward diarrhea, asthma and hypertension (Salem et al., 2005).

7. SAFETY OF *NIGELLA SATIVA*

The toxicity of the fixed oil of *N. sativa* L seeds in mice and rats through determination of LD50 values and examination of possible biochemical, hematological and histopathological changes was evaluated. The acute toxicity of *N. sativa* fixed oil was investigated in mice. LD50 values, obtained by single doses, orally and intraperitoneally administered in mice, were 28.8 ml/kg body wt. p.o. [26.2–31.6] and 2.06 ml/kg body wt. i.p. [1.86–2.26], respectively. In addition, chronic toxicity was investigated in rats treated daily with an oral dose of 2 ml/kg body wt. for 12 weeks. Changes in key hepatic enzyme levels, as aspartate-aminotransferase, alanine-aminotransferase, and gamma-glutamyltransferase and histopathological modifications in orans as heart, liver, kidneys and pancreas were not observed in rats treated with *N. sativa* after 12 weeks of treatment. The serum cholesterol, triglyceride and glucose levels and the count of leukocytes and platelets decreased significantly, compared to control values, whereas hematocrit and hemoglobin levels increased significantly. A slowing of body weight gain was also recorded in *N. sativa* treated rats, as compared to control animals. The low toxicity of *N. sativa* fixed oil, as indicated by high LD50 values, key hepatic enzyme stability and organ integrity, propose a wide margin of safety for therapeutic doses of *N. sativa* fixed oil, but the changes in hemoglobin metabolism and the fall in leukocyte and platelet count must be taken into consideration (Zaouia et al., 2002). Furthermore, There was no evident of hepatotoxicity following administration of *N. sativa* (Tennekoon et al., 1991).
8. CONCLUSIONS

*N. sativa* is proven to be the real “seed of blessing” providing many health benefits and nutritionally essential components (unsaturated fatty acids in fixed oil and essential oil, vitamins, and minerals). Due to its richness in phytochemicals from different classes, black seed seeds are formed by a complex mixture of more than 100 compounds (especially thymoquinone, alkaloids, saponins, and other trace elements) some of which have not yet been studied or even identified but are often associated with several pharmacological effects and protection against notorious ailments *i.e.*, cancer, cardiovascular health problems and hypertension.

Although the safety of *N. sativa* essential oils and their active constituents particularly thymoquinone, have been investigated by some authors, data on the pharmacokinetic parameters and bioavailability of this amazing herb are not completely understood. Health benefits of the *N. sativa* seeds have been proven in *vivo* and *in-vitro* types of studies. Research of this herb is furthermore recommended: especially those that are related to chemical modifications in molecular structures of *N. sativa* active components that may lead to the discovery of important novel medicines. Furthermore, broad spectrum studies on specific cellular and molecular mechanisms of action as well as controlled clinical trials to prove its efficacy in humans are some urgent needs to further assess the application of *N. sativa* action on hypertension and other illnesses. We expect that this chapter inspires awareness encouraging researchers worldwide to increase investigation about the potential health benefits of *N. sativa* especially on hypertension.

9. FUTURE PERSPECTIVES

Mechanism of *Nigella sativa* action at molecular levels needs to be further explored to comprehend the cellular anti-hypertensive effect. Notwithstanding the phytochemical composition of the *N. sativa* seeds extract by oils (fixed and volatiles) have been extensively studied, there are few clinical studies available in the literature, evaluating the possible correlations between chemical composition, pharmacological activities and action mechanisms in molecular levels. Despite several published studies, we have realized that there is still a lack of studies on the effect of *N. sativa* on human hypertension which could explain or at least scientifically prove and encourage its ethnopharmacological use. Furthermore, it was found sufficient evidence to infer that *N. sativa* contains many active substances that may be responsible for antioxidant activity and diuretic effect, which may play key roles in prevention and the cure of hypertension that is worthy to be further investigated. However, the reverse pharmacological approach methodology revalidating scientifically this ancient but still neglected herbal medicine can reshape our outlook toward nature as an amazing source of substances with biological action potential. We hope that this review article
would offer a primary source of information to researchers in hypertension research field and *N. sativa* plan chemistry to conduct their experiments as future studies on this subject are guaranteed.

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11. REFERENCES


