

Biotechnology in the Modern Medicinal System

Advances in Gene Therapy, Immunotherapy,
and Targeted Drug Delivery



Editors: Rajesh K. Kesharwani | Krishna Mishra



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and Targeted Drug Delivery*

Edited by

Rajesh K. Kesharwani, PhD

Krishna Misra, PhD



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Professor Misra earned her PhD in 1964 from Delhi University under the supervision of late Prof T. R. Seshadri, FRS, and Padma Bhushan. From 1966 to 1999 worked at Allahabad University as lecturer, reader, and professor. She has supervised 55 PhD students, has published over 250 papers, three books, about 20 reviews, and a dozen book chapters. She has also presented papers at about 100 national and international conferences and holds several Indian and U.S. patents. Dr. Misra has visited Japan (as a UNESCO fellow), the U.K. (sponsored by the British Council), and the USA (invited for papers/talks/chair) a number of times to deliver lectures and to participate in scientific discussions. She has been awarded a large number of research projects, including three prestigious international projects from the USA. She has been member of a task force of biotechnology for Central government and is a founding member and fellow of a number of national and international science societies. She has been teaching graduate and postgraduate classes and also conducting research in organic chemistry, biochemistry, biotechnology, bioinformatics, biomedical engineering, and research methodology. Her fields of scientific research have been chemistry of naturally occurring herbal products of biological importance, DNA synthesis, oligonucleotide chemistry, tagging with fluorescent tags, antisense therapy, chemoinformatics, systems biology, computer-aided drug design, molecular medicine, biomedical engineering, targeted drug designing, nanotechnology, and nano-biotechnology. She has delivered lectures all over India and abroad about her research work on women empowerment, climate change, scientific writing, etc.

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Abbreviations

AAV	adeno-associated virus
ABC	ATP-binding cassette
ACT	adoptive T cell transfer
Ad	adenovirus
ADA	adenosine deaminase
AI	artificial intelligence
ANN	artificial neural network
AMT	adsorptive-mediated transcytosis
APCs	antigen-presenting cells
BBB	blood–brain barrier
BCSFB	blood cerebrospinal fluid barrier
BDNF	brain-derived neurotrophic factor
bFGF	basic fibroblast growth factor
CARs	chimeric antigen receptors
CAR-T	chimeric antigen receptor-T
CED	convection-enhanced delivery
CFTR	cystic fibrosis transmembrane conductance regulator
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CNTF	ciliary neurotrophic factor
CPP	cell-penetrating peptides
CRLBP	cathode ray local binary pattern
CSF	cerebrospinal fluid
DA	dopamine
DC	dendritic cells
DNNs	deep neural networks
ECs	endothelial cells
ELISA	enzyme-linked immunosorbent assay
EPO	erythropoietin
EPR	enhanced permeability and retention
EVAc	ethylene vinyl acetate copolymer
FDA	Food and Drug Administration
FP	heme iron

FUS	focused ultrasound
GA	genetic algorithm
GDNF	glial cell line derived neurotrophic factor
GHSR	growth hormone secretagogue receptor
GFP	green fluorescence protein
GM-CSF	granulocyte-macrophage colony stimulating factor
HaaS	healthcare-as-a-service
HDL	high density lipoproteins
HDR	homology-directed repair
hGDNF	human glial cell line derived neurotrophic factor
IFN	interferon
IoT	Internet of Things
LBP	local binary pattern
LDP	local derivative pattern
LDL	low density lipoproteins
k-NN	k-nearest neighbor algorithms
MAb	monoclonal antibody
MAS	macrophage activation syndrome
MHC	major histocompatibility complex
ML	machine learning
MLTs	machine learning techniques
MoA	mechanism of action
MSX1	msh homeobox 1
NGF	nerve growth factor
NHEJ	nonhomologous end joining
NK	natural killer
NPs	natural products
NTN	neurturin
OL	odorranalectin
PAMs	pharmacologically active microparticles
PBCA	polybutyl cyanoacrylate
PEG-PLGA	polyethylene glycol-poly(lactic-co-glycolic acid)
PgP	P-glycoprotein
POMC	pro-opiomelanocortin
RBCs	red blood cells
RMT	receptor-mediated transcytosis
SA	streptavidin
SCID	severe combined immunodeficiency

SHOX	short stature-homeobox
siRNA	small-interfering RNAs
SOMs	self-organizing feature maps
SVMs	support vector machines
TALENS	transcription activator-like effector nucleases
TCI	transcutaneous immunization
TCR	T cell receptor
TfR	transferrin receptors
TLR	toll-like receptor
TP	transportan
UN	urocortin
VBD	vector-borne disease
VLDL	very low density lipoproteins



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Foreword

It gives me great pleasure to write the foreword for the book, *Biotechnology in the Modern Medicinal System: Advances in Gene Therapy, Immunotherapy, and Targeted Drug Delivery*. It provides detailed information on the application of biotechnology in gene therapy, immunotherapy, drug delivery systems, and artificial intelligence in medicine.

This book covers medical processes such as, for example, designing of organisms to produce drugs, engineering of genetic cures through genetic manipulation (gene therapy), diagnostics, drug discovery, and targeted delivery. The drug delivery systems (DDS) that use a variety of carriers have been developed in order to minimize drug degradation, to prevent side effects, and to increase drug bioavailability. The DDS that were created for traditional oral and intravenous administration have been expanded to transdermal, nasal, ocular, buccal, intramuscular, rectal, intrauterine, vaginal, and pulmonary administration, ceramic implants, etc. These systems have been well described in this book.

The role of genes in therapeutics, termed as “gene therapy,” is emerging as a tool to provide treatment against numerous genetic and related deadly diseases. The authors have provided a of about ongoing research and trials on gene therapy for management of genetic disorders. A large number of genetic disorders are known to arise from either type of gene mutations and are almost lethal or may cause variety of abnormalities. Disease susceptibility of an individual depends on genomic conformation as well as external exposure.

This book provides a wealth of information that will be valuable to scientists, researchers, faculty, and students in the field of biomedical sciences. All the contributing authors demonstrate an exceptional expertise in the field of medicinal biotechnology research and development and provide a global perspective on current and future advances in new drug discovery.

I congratulate the editors for bringing together experts in the field of medical biotechnology and the authors for their excellent contributions.

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Preface

This book, *Biotechnology in the Modern Medicinal System: Advances in Gene Therapy, Immunotherapy, and Targeted Drug Delivery*, presents a full picture of the state-of-the-art research and development of actionable knowledge in medical biotechnology involving, specifically, gene therapy, immunotherapy, and targeted drug delivery systems. The book includes novel approaches for therapy of various ailments and the real-world challenges and complexities to the current drug delivery methodologies and techniques.

As is evident from latest discussions at various globally held conferences and seminars, several medical biotechnology methods have been used but only a few of them have been validated in actual practice. A major reason for the above situation, we believe, is the gap between academic research and real-time clinical applications and needs.

The present book includes eight chapters containing information about the role of biotechnology in the modern medicinal system for human welfare. This edited book also provides a detailed application of medical biotechnology in drug discovery and the treatment of various deadly diseases.

Chapter 1, entitled “Role of Naturally Occurring Lead Compounds as Potential Drug Targets Against Malaria,” authored by Neha Kapoor and Soma M. Ghorai, explains the diversity of natural products (NPs) obtained from telluric and marine plants as well as from microorganisms in the treatment of variety of communicable and noncommunicable diseases. However, this chapter is restricted to document those lead compounds that are used in the management of malaria, a mosquito-borne disease. A wide range of compounds resulting from natural product sources such as endoperoxide, isonitrile derivatives, alkaloids, and non-alkaloid derivatives (terpenes, flavonoids, quinones, phenols, polyethers, and peptides), have been found to have promise as antimalarials.

Chapter 2, entitled “Targeted Drug Delivery,” by Sangeeta Singh and Princy Choudhary, focuses on delivering the drug through drug-carrier complex at a higher concentration to targeted sites, resulting in minimum possible entry to nontargeted sites, minimizing the adverse effects. Administration of drugs to specific cavities, such as the like pleural

cavity, peritoneal cavity, cerebral ventricles, or tissues, such as tumors or Kupffer cells of liver and intracellular localization of drugs or drug carrier system or targeting of DNA and proteins to a cell, are all possible via targeted drug delivery. A wide range of carriers is available that are specifically used according to the requirements and nature of the route and the target site.

Author Vandana Patravale and her associates have written Chapter 3, entitled “Targeted Delivery of Biopharmaceuticals for Neurodegenerative Disorders,” which provides information about the role of alternative routes of drug targeting, such as intranasal and transdermal, resulting in improving the patient compliance. Similarly, noninvasive techniques have been successfully applied for brain delivery of biopharmaceuticals. In addition, several colloidal carriers have been explored for passive targeting of biopharmaceuticals whereas more precision has been achieved by active targeting with ligands. This chapter summarizes the advanced delivery approaches of biopharmaceuticals to the brain and the preclinical studies associated with them in treating complex neurodegenerative disorders. Nevertheless, a systematic clinical investigation is necessary before exploring their therapeutic translation.

The role of genes in various genetic diseases has been well described in Chapter 4, entitled “Genes in Genetic Disease,” by Rizvi and his associate. Genes are the hereditary factors that are passed from generation to generation and are responsible for determining the genotypic as well as phenotypic traits in an individual. Every human being has about 20,000–25,000 genes, which encode for a variety of polypeptides and proteins. A large number of genetic disorders are known that arise from either type of gene mutations and are almost lethal or may cause variety of abnormalities. Disease susceptibility of an individual depends on genomic confirmation as well as external exposure.

Chapter 5, entitled “Current Perspectives and Trends in Gene Therapy and Their Clinical Trials,” by Ashutosh Mani and his colleagues, well describes the need for target-specific modifications in human genome for the purpose of treating the genetic diseases. Gene therapy is known as a method of altering and mutating the genes to be used for therapeutic purpose. This approach is broad in an experimental sense and still needs various new developments and is still in its experimentally driven phase. This chapter focuses on the trends that are being followed up by the researchers now a days for current gene therapy-based clinical trials.

In the current drug discovery scenario, immunogenes are playing a very important role, and it is well documented in Chapter 6, entitled “Immuno-gene Therapy in Cancer,” by Pulakkat and Patravale, in a precise manner. Immunotherapy has long been investigated as a potent, alternative approach to conventional cancer therapy; however, the clinical translations are limited. Immuno-oncology and genomics have experienced vast advancements in the recent past, and this proliferation of knowledge gave birth to the field of cancer immunogene therapy. The different approaches explored in immuno-gene therapy including ex vivo manipulation of T-lymphocytes, transferring immunostimulatory genes to tumor cells and antigen-presenting cells, in vivo genetic modulation using viral and nonviral vectors etc. have been discussed in this chapter.

The role of genes in therapeutics, nowadays termed as “gene therapy” has a very important role against various diseases, including hemoglobin disorders, as described in Chapter 7, entitled “Gene Therapy for Hemoglobin Disorders,” written by Sona Yasri and Viroj Wiwanitkit. The chapter describes how gene therapy is emerging as a tool to provide treatment against numerous genetic and related deadly diseases. In the present chapter, the authors provide a glimpse of ongoing research and trials on gene therapy for management of hemoglobin disorders. Several in silico and in vitro studies prove that gene therapy is useful for management of hemoglobin disorders.

The role of computers in biotechnology accelerates the research and development specifically in modern medicinal field with better and optimum results. Nowadays artificial intelligence is playing a very pivotal role in many fields. Chapter 8, entitled “Artificial Intelligence and Biotechnology: The Golden Age of Medical Research,” by Upendra Kumar and Kapil Kumar, describes the significant improvement that has been observed in the development of a faster and less invasive diagnostic system for the treatment of diseases by utilizing both artificial intelligence (AI) and biotechnology. The biomedical research landscape is changing and evolving.

The present book, entitled *Biotechnology in the Modern Medicinal System: Advances in Gene Therapy, Immunotherapy, and Targeted Drug Delivery*, provides detailed information on the application of biotechnology in gene therapy, immunotherapy, drug delivery systems, and artificial intelligence in medicine. This valuable volume provides a wealth of information that will be beneficial to scientists and researchers, faculty, and students.



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CHAPTER 1

Role of Naturally Occurring Lead Compounds as Potential Drug Targets against Malaria

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ABSTRACT

This chapter overviews the diversity of natural products (NPs) obtained from telluric plants, marine-, and microorganisms in the treatment of variety of communicable and noncommunicable diseases. A historical perspective is being given to the readers about the discovery and use of various NPs as lead compounds for the synthesis of various drugs. Screening of natural resources to generate new lead compounds has been possible due to their enormous structural diversity and medicinal significance. Generation of many lead compounds with different structural analogs having fewer side effects and more pharmacological activity can be obtained by molecular modifications of their functional groups. Among others, much has been acknowledged about lead compounds that hold the promise as potential drug targets against almost all the vector-borne diseases. However, this chapter is restricted to document those lead compounds that are used in the management of malaria, a mosquito-borne disease. A wide range of compounds resulting from natural product sources such as endoperoxide, isonitrile derivatives, alkaloids, and nonalkaloid derivatives (terpenes,

flavonoids, quinones, phenols, polyethers, and peptides) have been found to have promise as antimalarials. Such lead compounds as antimalarials with unique functional groups and chemical backbones holds key to future drug synthesis against *Plasmodium* parasites.

1.1 HISTORICAL PERSPECTIVE

Every era had seen successive development of use of natural products (NPs) to benefit societies and is passed on to another with improvement in its effectiveness through generations. Approximately, 5000 years ago, medicinal plants' were the first candidates to be used and the early evidences have been found on a Sumerian clay slab from Nagpur. The inscriptions mentioned about 250 various plants and 12 recipes for drug preparation from plants like poppy, henbane, and mandrake (Kelly, 2009). The Chinese Emperor Shen Nung was the first to have documented a book called Pen T'Sao, circa 2500 BC, which defines 365 drugs from dried parts of medicinal plants including *Rhei rhisoma*, *Theae folium*, camphor, the great yellow gentian, podophyllum, ginseng, cinnamon bark, jimson weed, and ephedra (Wiar, 2006; Petrovska, 2012). Likewise, ancient Indian Vedas including the Charaka and Samhitas, which dates back to 1000 BC, recognized 341 medicinal plants and 516 drugs of the Indian Ayurvedic system (Dev, 1999; Kapoor, 2017). Many plant extracts of pomegranate, castor oil plant, senna, aloe, onion, fig, willow, coriander, juniper, common centaury, and so on have been mentioned along with garlic, a collection of 700 plant species used for therapeutics in Ebers Papyrus, circa 1550 BC (Tucakov, 1964). Talmud, the holy book of Jews, refers to the use of aromatic plants as incense or myrtle (Dimitrova, 1999). Homer's epics, *The Iliad* and *The Odysseys* (ca. 800 BC), also mentions use of 63 plant species as pharmacotherapeutic agents (Toplak Galle, 2005). Greek scholars such as Herodotus and Pythagoras (500 BC) mentioned about the therapeutic values of garlic, castor oil, mustard, and cabbage. Hippocrates (459–370 BC) categorized nearly 300 medicinal plants conferring to their functional effects. Common centaury (*Centaureum umbellatum* Gilib.) and wormwood were administered against fever; garlic was used against intestine parasites; opium, deadly nightshade, mandrake, and henbane were consumed as narcotics; haselwort and fragrant hellebore were considered emetics; oak and pomegranate as astringents; while sea onion, parsley, celery, garlic, and asparagus were used as diuretics (Bojadzievski, 1992;

Gorunovic and Lukic, 2001). Theophrast (371–287 BC), also known as the “Father of Botany,” was given due credit for cataloging more than 500 medicinal plants (Bazala, 1943; Nikolovski, 1995). The era from 23 to 79 AD was distinguished by two important contemporaries in pharmacy, Dioscorides (77 AD) and Pliny the Elder (23–79 AD). Both were credited to have traveled and documented more than 1000 medicinal plants (Tucakov, 1990; Toplak Galle, 2005). Galen (131–200 AD), a Roman physician, familiarized numerous new plants as remedial drugs which Dioscorides had not described, for example, *Uvae ursi folium* is used as an uroantiseptic and a mild diuretic. Some plants were used as insecticides, namely, *Veratrum album*, *Alium sativum*, *Urtica dioica*, *Cucumis sativus*, *Achillea millefolium*, *Lavandula officinalis*, *Artemisia maritime* L., and *Sambuci flos* (Bojadzievski, 1992) and by the seventh century, *Ocimum basilicum*, *Rosmarinus officinalis*, *Iris germanica*, and *Mentha viridis* were being used in cosmetics.

In the middle ages, particularly between 16th and 18th centuries, monasteries and churches took over the skills of healing and cultivation of medicinal plants, thereby; preparation of drugs were mostly restricted to a few handful of plants like sage, mint, anise, savory, tansy, and Greek seed (Tucakov, 1990). The silk route trade relations introduced the Arabs to numerous new plants in pharmacotherapy, mostly from India, and they used deadly nightshade, aloe, coffee, henbane, ginger, saffron, strychnos, pepper, curcuma, rheum, cinnamon, senna, and so forth. The European physicians consulted the Arab works, for instance; *De Re Medica* by John Mesue (850 AD), *Canon Medicinæ* by Avicenna (980–1037), and *Liber Magnæ Collectionis Simplicum Alimentorum Et Medicamentorum* by Ibn Baitar (1197–1248), in which over 1000 medicinal plants were documented (Tucakov, 1965). Though traditional people still used medicinal plants primarily as simple forms; the demand for compound drugs was increasing. During these period, simple pharmaceutical preparations by infusions, decoctions, and macerations using medicinal plants was also introduced and the compound drugs mainly contained of medicinal plants, rare animals, and minerals (Bojadzievski, 1992; Toplak Galle, 2005). Meanwhile, the great expedition by Marco Polo (1254–1324) and by Vasco dè Gama (1498) helped Europe develop rich cultivation of new medicinal plants like Cinchona, Cacao, Ipecacuanha, Ratanhia, Jalapa, Podophylum, Lobelia, Vanilla, Senega, tobacco, Mate, red pepper, as well as quinine bark *Cinchona succirubra*.

Early 19th century was marked by the beginning of scientific pharmacy. The earliest report of chemistry of NP was heralded by the work of Friedrich Wilhelm. With improved knowledge of chemistry and pharmacy; discovery, characterization, and isolation of lead compounds from the medicinal plants were available. Alkaloids were isolated from poppy (1806), ipecacuanha (1817), strychnos (1817), quinine (1820), pomegranate (1878), and other plants. Adam Serturmer (1803), a German pharmacist, was known to sequester morphine from opium poppy (*Papaver somniferum*) (Huxtable and Schwarz, 2001). Glycosides, tannins, saponosides, etheric oils, vitamins, hormones, and so on, were also characterized and substantiated (Dervendzi, 1992).

An impediment was observed in the use of medicinal plants as drugs in the late 19th and early 20th centuries, owing to shortcomings incurred during the process of drying of medicinal plants. Moreover, synthetic preparations of alkaloids and glycosides were being used in therapeutics. Much effort was devoted to study the cultivation of medicinal plants which ascertained numerous forgotten plants like *Aconitum*, *Hyosciamus*, *Punica granatum*, *Stramonium*, *Filix mas*, *Secale cornutum*, *Opium*, *Colchicum*, *Styrax*, *Ricinus*, with more stabilization methods being proposed, especially the ones with labile medicinal components. Laws on Drugs and Medical Devices (2007) legislated in the Republic of Macedonia clearly lay rules and regulations for the preparation of herbal drugs, herbal processed products, and traditional herbal drugs using dry and fresh parts of medicinal plants. The current law also has provision for use of herbal substances in homeopathic drugs and can be bestowed without a medical prescription, as over the counter preparations.

1.2 INTRODUCTION

Mankind has been on the pursuit of drugs from nature since time immemorial to alleviate pain and cure illness. Man has always been in harmony with nature to explore and harness NPs as healers of various diseases. Innumerable documentation either written or inscribed has been found to commemorate the usage of NPs as “lead compounds” to improve the quality of life. A lead compound is a novel natural chemical entity that has the potency to be a therapeutic agent by optimizing its pharmacokinetic parameters and minimizing its side effects.

It is of the highest prominence, given the random nature of discovery and the fake unfeasibility of innumerable invention of new active principles,

those decision-makers in the pharmaceutical industry should employ definitive strategies and that they must comprehend that these guidelines are not mutually exclusive. Hurriedly established any outcomes may lead to recognition of poor research wherein a brilliant study may remain dormant. Every possible effort should be made in the direction to study the molecular mechanism of action (MoA) of a lead compound once it is discovered and characterized. Therefore, a five-step approach should be embraced for the discovery of new lead compounds as possibly new drugs. These consist of the enhancement of already prevailing drugs, of methodical screening, of retroactive manipulation of biological information, of challenges toward coherent design, and of the use of the target protein structural data. In conclusion, all approaches ensuing in documentation of lead compounds are a priori equally good and prudent provided that the research they persuade is done in a cogent manner (Wermuth et al., 2015). A very recent study also has harnessed to target against cytochrome bc1 and dihydroorotate dehydrogenase by tapping onto the chemical diversity offered by the chemoprotective drugs (Antonova-Koch et al., 2018).

The broad chemistry know-how and industrial sustenance is of utmost importance once a lead compound is recognized. Optimization using medicinal chemistry for the drug development process is the most pertinent factor to develop the best pharmacokinetic profile leading to not only the desired formulation but also the preferred route of administration. Regrettably, this is the step where many possible therapeutic drugs miscarry as it needs to be coupled to biological assays for efficacy, safety, and pharmacokinetics. Therefore, manufacturing processes and procedures should include development of sufficient amount of lead compounds for preclinical evaluation and Phase I/II clinical trials (David and David, 2009).

Cohabitation of host–pathogen throughout evolutionary timeline has led humans to harvest a myriad of NPs from nature (plants, marine organisms, animals or microorganisms) as medical and therapeutic targets. (Butler, 2005; Newman and Cragg, 2007, 2016; Butler, 2008; Cragg et al., 2012). NPs are often stereochemically complex molecules marked with diverse functional groups and high specificity with biological targets. Thus, they are valued as health products or structural templates for drug discovery.

In the current scenario, 36% of all 1073 small-molecules-approved drugs are derivatives of NPs (Newman and Cragg, 2007; Newman and

Gordon, 2012). Data from World Health Organization (World Health Organization, 2009) establish that 80% of the world's population mainly from developing countries still relies mostly on traditional medicines for their primary health care. In advanced countries too, 119 chemical substances used as drugs are obtained from an odd 90 plant species and are a product of isolation of active chemicals from plants used in traditional medicines (Farnsworth et al., 1985). Over 68% of all anti-infectives (anti-fungal, antibacterial, antiviral, and antiparasitic compounds) are classified as naturally derived (Mukherjee et al., 2001; Lee, 1999), whereas 79.8% of compounds alone are used in cancer treatment (Paterson and Anderson, 2005; Koehn and Carter, 2005; Lee, 2004; Butler, 2004, 2005). Though much focus had been on anticancer drugs, NPs hold great promise in treating vector-borne disease (VBD) and it's the current global need where nearly half of the world's population is infected with at least one type of vector-borne pathogen (Cragg et al., 2011). More than 700,000 annual deaths are accounted globally; wherein more than 17% of all infectious diseases are VBDs (Jones et al., 2008). In over 128 countries, more than 3.9 billion people are at risk of suffering from dengue, with 96 million cases assessed per year. Malaria causes more than 400,000 deaths every year globally, most of them children under 5 years of age. Worldwide, hundreds of millions of people are affected by other diseases such as Chagas disease, leishmaniasis, and schistosomiasis (CIESIN, 2007; WHO, 2004). The risk of being afflicted by vector-borne pathogens has increased their severity with climate and environmental change due to increase in land use (2008).

Billions of people are at risk from vector-borne infectious diseases, such as dengue fever, malaria, yellow fever, and plague transmitted by mosquitoes, ticks, fleas, and other vectors. These diseases intensely restrict development in countries, many of which are located in the tropics and subtropics, with the highest rates of infection rendering poor socio-economic status. India, being a tropical developing country, faces high fatality in rural as well as urban areas owing to VBD and there is an imperative need for cost-effective, eco-friendly, and safe drugs harnessed from NPs. The most widely known VBD globally is malaria and India still face huge challenge in producing effective drugs against malaria. However in recent times, dengue, which is caused by an arbovirus virus, has become a major public health challenge (Bueno-Mari, 2013).

In this chapter, the authors have restricted in providing a complete account of lead compounds from NPs as potential drugs against malarial