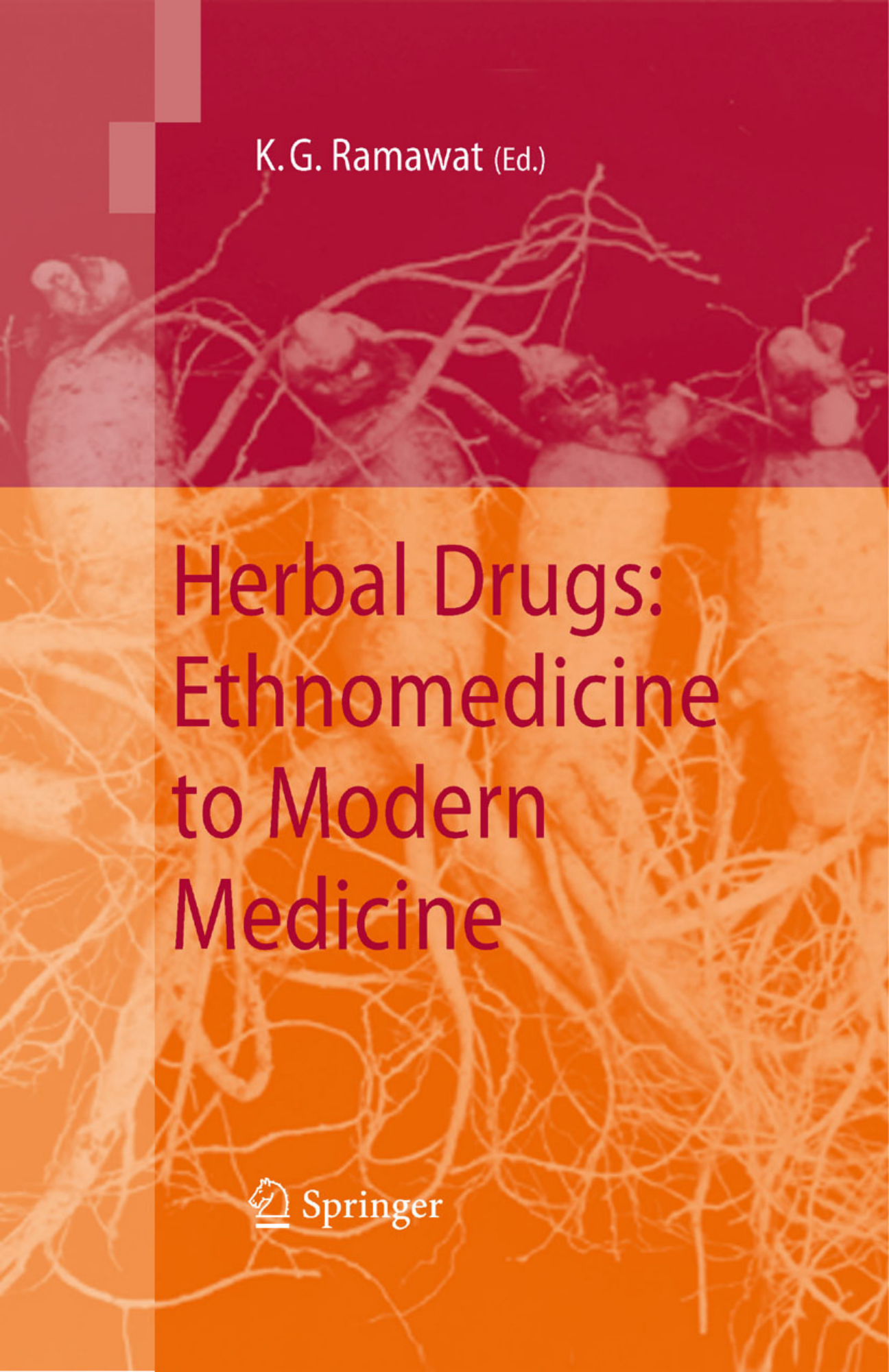
K. G. Ramawat (Ed.)
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About the editor

Professor K.G. Ramawat (born in 1952) received his M.Sc. (1974) and Ph.D. (1978, Plant Biotechnology) from the University of Jodhpur, Jodhpur, India and became a faculty member in January of 1979. He joined M.L. Sukhadia University as an Associate Professor in 1991 and became a Professor in 2001. He served as Head of the Department of Botany (2001–2004), was in charge of the Department of Biotechnology (2003–2004), was a member of the task force on medicinal and aromatic plants at the Department of Biotechnology (Government of India, New Delhi; 2002–2005), and was a coordinator of the UGC-DRS and DST-FIST programs (2002–2007). He did his postdoctoral study at the University of Tours, France (1983–85) and subsequently worked as visiting professor at the University of Tours (1991) and University of Bordeaux 2, France (1995, 1999, 2003, 2006). He visited Poland under the auspices of an INSA-PAN academic exchange program (2005). He has published more than 100 research papers and review articles in reputed journals and books. He has edited two books on the biotechnology of secondary metabolites and of medicinal plants (Scientific Publishers, Enfield, USA and Springer verlag, Heidelberg, Germany). Professor Ramawat has completed several major research projects from UGC, CSIR, ICAR, DBT, and DST, and has supervised the doctoral theses of 16 students. He has been a member of the Plant Tissue Culture Association of India since 1991.

Preface

Considerable progress has been made in our healthcare system, in particular with respect to sensitive diagnostic tools, reagents and very effective and precise drugs. On the other hand, high-throughput screening technology can screen vast numbers of compounds against an array of targets in a very short time, and leads thus obtained can be further explored. In developing countries, the exploding population exerts pressure not only on natural resources but also on the human population itself, whose members strive to become successful and advance in society. This leads to increased blood pressure, anxiety, obesity-associated lipid disorders, cardiovascular diseases and diabetes. Most of these diseases result in disturbed family life, including sexual behaviour.

Despite technological developments, herbal drugs still occupy a preferential place in a majority of the population in the Third World and terminal patients in the West. Herbal drugs, in addition to being cost effective and easily accessible, have been used since time immemorial and have passed the test of time without having any side effects. The multitarget effects of herbs (holistic approaches) are the fundamental basis of their utilization. This approach is already used in traditional systems of medicine like Ayurveda, which has become more popular in the West in recent years. However, the integration of modern science with traditional uses of herbal drugs is of the utmost importance if ones wishes to use ancient knowledge for the betterment of humanity. This book will try to bridge this gap and will be a valuable source for herbalists, traditional and modern medical practitioners, and researchers in botany, ethnobotany, pharmacy, phytochemistry and agriculture. Contributions on herbs used for beneficial effects on memory, sexual behaviour, neurodegeneration, erectile dysfunction, inflammation, cardiovascular diseases, cancer prevention, stroke and central nervous system disorders will provide vital information to readers.

Finally, I would like to acknowledge my contributors, who have gone to great lengths to ensure the high scientific quality of the book. I would also like to thank my colleagues at Springer.

July 2008 *K.G. Ramawat*

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Chapter 1
Medicinal Plants: A Renewable Resource for Novel Leads and Drugs

R. Verpoorte

Abstract Present-day drug development is strongly focused on finding active compounds on well-defined targets using high throughput screening approaches. Unfortunately it seems that this approach is becoming less and less successful, as in most cases already good compounds are on the market, and the rapidly rising costs of drug development will make it increasingly difficult to make an economically competitive novel drug for any major disease. In other words, the reductionist approach presently used is becoming less successful. The time has come to rethink drug development. Many Western medicines are based on traditional knowledge from Europe and the Mediteranean region. This is why interest is rapidly increasing in Indian and Chinese medicine, both of which represent a very long tradition of apparently safe use. However, these healthcare systems are different from Western medicine, so novel methods are required to verify the efficacy and safety of the therapies. As it often concerns personalized medication with complex mixtures, a reductionist approach of screening for a single active compound on a known target will in many cases not be successful, as more than one target may be involved; in addition, and complicating the situation even more, synergism and prodrugs may be involved. Systems biology as a novel holistic way of dealing with biological problems seems here an interesting option. Systems biology means proceeding without a hypothesis, just observing, measuring as many parameters as possible in a biological system and afterwards using chemometrics to reveal any meaning in the data. This approach has already proven successful in studying medicinal plants and, in combination with the classical natural-product-based drug lead finding, is expected to be a major issue in the coming years. As present-day patent laws require innovative and unexpected findings, the development of old knowledge does not fit this requirement. Therefore, to support the development of evidence-based traditional medicines, it would be of great interest if some sort of protection could be obtained for companies developing such medicines so that they could earn back their huge R&D investments.

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1.1 Introduction

Since ancient times humans have explored their environment for plants that could be used to cover all their basic needs: food, shelter, fuel and health. This has resulted in the use of a large number of plants; in particular, food plants' extensive breeding has resulted in high-yield crops. In the case of medicinal plants, such breeding has largely not yet taken place as nature could provide a sufficient supply. The number of medicinal plants has been estimated to be on the order of 40,000 to 70,000 [1], which means that almost 25% of all plant species have some sort of medicinal use somewhere in the world. This heritage from our ancestors has continued to develop in Western medicine and has resulted in the isolation and production of pure active compounds (e.g. morphine, atropine and digoxin) and later in the development of novel synthetic compounds based on this knowledge (e.g. local anaesthetics based on cocaine, analgesics based on morphine). Some of these synthetics based on natural products have been very successful, e.g. acetylsalicylate, which development was based on the use of Salix bark as analgesic. In other cases the result has not been so successful, e.g. the acetyl derivative of morphine (heroin). This illustrates that many medicines in the West have originated in phytotherapy, as occurred in European/Mediterranean region.

In addition, the statistics on novel drugs developed in recent decades show that natural products are a major source of inspiration for drug development [2], with only 30% of all novel molecules (of the 1184 so-called novel chemical entities or NCEs) introduced into the market in the period 1981–2006 being pure synthetic and all others being natural products or natural product related. These statistics also show that the number of novel chemical compounds reaching the market is decreasing every year. The high costs (approx. 1000 million euros) and long duration (more than 10 years), as well as the fact that for most major ailments good medicines that are already available hampers the development of novel drugs by the pharmaceutical industry. Recently problems with serious side effects caused that several novel medicines had to be taken of the market shortly after their introduction. This does not also help to increase efforts at novel drug development.

At the same time the strong emerging economies of countries like India and China have led to greater interest in local healthcare systems, which are even considered an important (cheap) alternative to expensive treatments using Western drugs (see Chapters written by Pandey et al., Melzer and Saller, and McGregor (this volume)). Moreover, after thousands of years of extensive and widespread use of traditional medicines, the question arises as to why we should not consider these medicines again using all the tools of modern science [3, 4]. Further studies may lead to the discovery of novel modes of action, novel biologically active compounds, confirmation of traditional use, or, in the worst case, the fact that no activity is present and even that a given medicine's use can carry risks of toxicity (see Chap-

ters written by Cuzzolin and Benoni, and Benoni and Cuzzolin (this volume)). With 80% of the world's population using such traditional medicine, it makes sense to devote much more resources to such studies. The discovery of the antimalarial compound artemisinin in traditional Chinese medicine some 30 years ago has led to an efficient novel medicine used to treat malaria. But it has also led to totally new potential applications, e.g. in treating cancer (see Chapter written by Efferth (this volume)). Many more hidden gems may be found through studies of traditional medicine (Please specify the title and author you are referring to.).

One of the problems in studying traditional medicines is the totally different healthcare systems they are embedded in, e.g. different ways of classifying diseases, personalized medicines, and the complex mixtures of ingredients in traditional medicines. Current approaches to drug development may pick up some interesting compounds with high activity, but high throughput screening (HTS) will only detect compounds with strong affinity to a target enzyme or receptor; it will miss prodrugs (such as salicin the compound in Salix bark that in the human body is converted via glucolysis and oxidation into salicylate). Also, the synergy between compounds will not be observed in HTS, as one may, for example, envisage that artemisinin may have synergy with other antitumor compounds in a plant. The study by Stermitz et al. [5] showing the synergy between berberine and 5′-methoxyhydnocarpin is now a classical example of synergy between two compounds from one plant. The way traditional Chinese medicines are made and the different roles that each plant traditionally was thought to play in fact point to the possible importance of synergy between ingredients [6]. A recent study on the effects of ginkgo on peripheral blood flow is a beautiful example of the totally different concept of activity of such a traditional medicine and present-day Western pharmacology. Boelsma et al. [7] showed in a placebo-controlled, double-blind clinical trial that a standardized ginkgo preparation caused different effects in different subjects, which would be unacceptable to the Western way of thinking. However, their systems-biology-type of approach showed that in fact the preparation lowered peripheral blood flow in those people who had an above-average peripheral blood flow level, increased it in those who had a below average level, and in the case of the average level did not produce any effect. In other words ginkgo normalizes peripheral blood flow, a concept that does not match the reductionist approach of drug development, using the single-target, single-compound paradigm.

On the other hand, HTS may pick up well-known compounds such as adenosine and GABA in their respective receptor binding assays, thus masking possible other active compounds, but it would confirm the rationale behind the traditional use of a traditional medicine used to treat hypertension [8].

In fact the holistic ideas of traditional healthcare systems demand a holistic approach to studying their activity [4]. First, instead of trying to find an active compound, clinical trials could be considered as a way to confirm activity before trying to understand the activity. In well-established ancient healthcare systems such as in Asia, such experiments could be done in relation to current treatments. The fact that these medicines have been used for several thousand years and are still used extensively means that acute toxicity is unlikely to occur,

though long-term toxicity might be a point for some further research (see also Chapters written by Cuzzolin and Benoni, and Benoni and Cuzzolin (this volume)).

In an approach using clinical studies, systems biology enters the picture. Systems biology aims at studying an organism under different conditions without a working hypothesis. Instead one tries to measure as many parameters as possible and use multivariate analysis or other related statistical tools to asses all the data and draw conclusions from this, i.e. the hypothesis comes afterwards. These data may include physiological parameters (e.g. blood pressure, pulse), chemical parameters (using metabolomics to measure e.g. metabolites in body fluids, metabolites in a medicinal plant), the proteome and the transcriptome. Using such a holistic approach prodrugs and synergy may be found. Also new modes of action can be revealed in this way. In any case I think that the different medical systems could learn from each other and in that way make some major steps forwards and become the source of novel ideas and concepts. Combining the best of all approaches would be to the great benefit of all people's healthcare the world over.

That said, one may also wonder why the pharmaceutical industry shows such little interest in traditional medicine. Besides the fact that the above-described problems of prodrugs and synergism do not fit their present expertise for drug development, the major reason might be that of patents. It is not impossible that the activity of a traditional medicine is due to a well-known compound, e.g. GABA or adenosine, which would thus not lead to a novel active and patentable compound. Moreover, patenting of a traditional medicine might be difficult, as a patent requires some sort of innovation, something unexpected [9]. Finding antidiabetic activity in a traditional antidiabetes medicine would thus not be accepted as an innovation, and even a compound isolated for such a plant might be difficult to patent. It would be of great value to all of humanity if any industry developing a traditional medicine with a view towards an evidence-based medicine would also be given some years of protection to be able to earn back the enormous investment needed to develop an evidence-based traditional medicine.

Ginkgo may again serve as an example. There is one ginkgo preparation (see also Chapters written by Howes and Houghton, Bhatnagar, Shah, Lehotsky et al., Melzer and Seller (this volume)) that has been studied extensively in clinical trials and shown to be active. An analysis of six different preparations for sale as an over-the-counter drug on the Dutch market, one of them being an evidence-based preparation, showed that the other five had lower, and some even very low, levels of the compounds thought to be involved in the activity, but the health claims were the same as for the proven one [10, 11]. One problem facing a country such as the Netherlands that has no clear legislation regarding phytotherapy, as the government is in general unfavourably disposed towards phytomedicines, is that a de facto laissez-faire policy is established that leads to the suboptimal use of herbal medicine.

1.2 Conclusion

There is an urgent need to convince Western pharmacologists that traditional medicines can be a major source of novel medicines, as well as novel concepts, but that a different approach to studying these medicines is required.

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