General introduction

Chapter 1
Introduction

Natural products have been an important resource for the maintenance of life for ages. Already in the earliest written traditions, e.g. the Rigveda of South Asia (ca. 1500-900 BC), it is evident that plants played an important role in daily life. One of the best-known examples is Soma, a plant that was pressed to yield juice, which was used as a medicine (Mukhopadhyaya, 1922-1929, Mahdi Hassan and Mehdi, 1989). The interest in medicinal plants has never ceased since. Even today, natural products become increasingly important as a source of pharmacotherapeutics, either directly, for example in the application of herbal drugs for the treatment of chronic diseases, or as raw material from which more or less complex chemical structures with particular biological activity are isolated. Cragg et al. (1997) reviewed the role of natural products in drug discovery, and concluded that for the disease indications anticancer and anti-infection, more than 60% of new approved drugs are derived from natural sources. Furthermore, there is a global concern about emerging infectious diseases, and an urgent need to identify novel means for effective treatment thereof.

The National Cancer Institute has screened randomly a hundred thousand plant extracts for antineoplastic, anticarcinogenic, and antitumor activity in several model systems. This strategy did not prove very effective (Reynolds, 1991). Traditional systems of medicine, however, provide an extremely vast body of source material for the development of new drugs (Holland, 1994). Evaluation of traditionally used medicines, keeping into account the traditional principles that are applied in drug therapy, may supply leads towards effective drug discovery.

One of the species that emerged from such an inventory is Picrorhiza kurrooa Royle (Labadie et al., 1989). This plant has been the subject of another thesis, which focused on its modulatory effects on complement activation and the production of chemiluminescence by activated neutrophils. Two macromolecules have been isolated that interfered with the classical pathway and the alternative pathway of complement activation, respectively. Furthermore, several phenols were isolated that inhibited the production of chemiluminescence by activated neutrophils. One of these, apocynin, also reduced the severity of symptoms in experimentally induced arthritis (Simons, 1989, ’t Hart et al., 1990). Because oxidative stress due to reactive oxygen species is a major contributor to joint damage in rheumatoid arthritis (Halliwell and Gutteridge, 1999), these data suggest the usefulness of Picrorhiza in the treatment of this disease. This impelled further research into active constituents of Picrorhiza that may be modulating immune responses.

Objective

The objective of this thesis was the further pre-clinical evaluation of the immunomodulatory activity of Picrorhiza and the activity-guided isolation of other active constituents, in order to assess its usefulness in rheumatoid arthritis or related conditions. This assessment is presented from a pharmacognostic perspective. The ultimate biomedical goal of pharmacognosy is “to contribute to the causal and hence rational relationships between the chemical constituents of medicinal plant preparations and the biological and therapeutic effects they generate” (Labadie et al., 1989). Traditional systems of medicine provide an
extensive source of material, which may demonstrate such relationships. To investigate the
nature of these relationships, a multidisciplinary approach is required, ranging from
anthropology, via philology, botany, phytochemistry, pharmacology, to medicine. In this
thesis, several of these fields are taken into consideration in answering questions pertaining to
the usefulness of *Picrorhiza* in chronic inflammation.

Rhizomes of two *Picrorhiza* species happen to be available on South-Asian markets: *P. kurrooa* Royle and *P. scrophulariiflora* Pennell (Scrophulariaceae). Both species are known under the same local name, and used for similar purposes. The material under investigation, which was obtained from the market, was identified as *Picrorhiza scrophulariiflora* Pennell (Scrophulariaceae). This species is categorized into a separate genus by Hong (1984), who named it “*Neopicrorhiza scrophulariiflora*”. For reasons of clarity, however, described in chapter 2, the name *Picrorhiza scrophulariiflora* is maintained throughout this thesis.

**Outline**

Chapter 2 deals with taxonomical and geographical information concerning the proper identity of the plant material used. This chapter is partly based on fieldwork performed in the Himalaya regions of Nepal and India. Chapter 3 elaborates on the traditional use of *Picrorhiza* in Āyurveda, a traditional life science of South Asia, as known from ancient Sanskrit literature, as well as from contemporary use. Two approaches have been followed, one based on the direct exploitation of empirical knowledge, and the other on the specific application of generalized traditional principles. In chapter 4, an overview is given of metabolites that have been isolated from *Picrorhiza*, and their biological activity is discussed with regard to immunomodulation. Chapter 5 gives a limited overview of the background necessary to understand the assays and models used, and describes the *in vitro* and *in vivo* immunomodulatory activity of *Picrorhiza* extracts. Chapter 6 describes the activity-guided fractionation of extracts that interfere with the classical pathway of complement activation. Activity-guided isolation of two cucurbitacins that inhibit proliferation of activated T lymphocytes is described in chapter 7, while chapter 8 elaborates on the mechanisms of action involved. Finally, chapter 9 provides a summary and a general discussion of the topics that were elaborated in this thesis, and extends the discussion to further perspectives. In addition, appendices have been included as reference to Sanskrit words and abbreviations.

**References**


