

# **CHAPTER 1**

## **INTRODUCTION**

## 1 Introduction

Harnessing nature in search of remedies for an array of diseases has been an old practice. Folkloristic use of flora, fauna, and mineral sources for the treatment of a range of ailments and diseases paved the way for the discovery of natural products or their derivatives [1]. Since 1980, approximately 51% of approved drugs have been derived from natural products. By 2050, the international herbal market is predicted to generate a turnover of \$5 trillion [2]. Since the inception of human civilization, the process of curing disorders and healing ailments has centred on medicinal plants, contributing to the Traditional Systems of Medicine (TSM). From time to time, plant-based drugs proved clinically significant in alleviating several diseases, thereby encouraging the researchers to discover and develop natural products with improved efficacy and safety. However, only 15% of the higher plants have been screened for phytoconstituents and about 6% for their pharmacological effectiveness (between 300,000 and 500,000) [3]. Emerging risks to human health necessitate a concerted effort to find both preventive and therapeutic approaches, with natural products at the centre of initiatives to develop novel treatments and lower disease transmission and associated mortality [4]. Natural products do, however, also present difficulties for drug discovery, such as technical obstacles in compound isolation, characterization, and optimization, which led to the waning interest of pharmaceutical companies in natural product development [5]. Similarly, natural crude extracts contain trace amounts ( $\mu\text{g}$  to  $\text{mg}$  range) of bioactive natural products, but sometimes these amounts are insufficient to carry out biological analyses in a series of phenotypic or target-based assays. Despite these bottlenecks, natural product research has seen a remarkable renaissance in the past few years. The advent of robust modern analytical technologies, including chemotaxonomic studies, chemical fingerprinting, dereplication techniques, bioinformatics, chemoinformatics, and metabolomics, has made significant contributions to NP-based drug discovery in recent times [5, 6]. Natural product research has gradually

embraced computational approaches involving artificial intelligence and machine learning algorithms [6].

A limited number of studies are devoted to elaborating on the composition of various plant extracts, and the studies conducted revealed only the metabolite classes. Coping with the resurgence of natural product-based drug development [7], many in the natural product research community are focused on the isolation of compounds, both known and unknown. The variation in the concentration of metabolites in different parts of the plant growing in varying regions under vivid environmental conditions can also be determined to hunt for new chemical factories. Scientific advancement in the tools of trade like analytical tools, genome mining, engineering strategies, microbial culturing techniques, and instrumental technology is uplifting the exploration and exploitation of these natural resources in association with pharmacotherapy [8, 9].

In spite of a strong leap in the investigation process, the lack of a quality control profile for raw materials and the deliberate or accidental act of adulteration remains unsettled areas for the makers and users of the drugs discovered from such natural resources. Additionally, the pharmaceutical industry's pursuit of them may have slowed down as a result of these reasons [9]. Hence, the authentication of medicinal plants holds paramount significance in providing an unambiguous confirmation in a number of ways [10]. Making use of authentic starting material, forging reproducibility, and minimising batch-to-batch variation are the first steps in the quality check of medicinal plants, which is complicated by the complexity of the composition of crude drugs used as a whole plant, plant parts, or plant extracts. Prior to urbanization, vaidyas and hakims, who were well acquainted with the identity of medicinal plants, shouldered the responsibility of collecting, processing, storing, preparing, and distributing crude drugs. With the passage of time, the closeness with nature became disoriented, as did the mastery of identifying medicinal plants. Linguistic diversity, the

existence of homonyms and synonyms, and the pervasiveness of local dialects are the cherries on top, leading to the debatable botanical identity of a number of medicinal plants. The rightly identified plant is the basic and preconditioned factor in the domain of medicine and science that will yield a standard drug to be administered to patients, which, along with the physician's calibre, is to be credited in any system of medicine. Henceforth, to obtain up-to-par outcomes and sustain the efficacy and therapeutic properties of plant-based preparations, the authentication of the botanical source of medicinal plants engrossed in health-giving utility and research is an obligation [10]. Advancements in DNA sequencing technology and bioinformatics tools have projected DNA barcoding as a renaissance for taxonomy as an independent source of information to delimit and identify a species. The Plant Working Group of the Consortium for the Barcode of Life recommended ribulose-1,5-bisphosphate carboxylase/oxygenase large subunit (*rbcL*) and maturase K (*matK*), plastid barcode loci, as standard due to their universality, relatively high overall sequence quality, low cost, and high discriminatory power between angiosperms. The success rate of PCR amplification of *rbcL* is relatively higher [11–13].

Quality control studies of the plants based on the guidelines of the regulatory bodies may give an insight into the quantitative and qualitative aspects of the same. The relevant positive attributes of the various plant preparations in treating ailments and disorders indicate the presence of therapeutically active phytoconstituents, and their synergistic effects to some extent. The mere association of biological activity with the crude extract is not enough. Bioassay guided fractionation and subsequent isolation of phytochemicals may be attempted. Unequivocal identification of bioactive compounds and elucidation of their mechanism of action will only rightfully validate the remedial claims of folkloristic medicine. A basic understanding of plant metabolites and their biosynthetic pathways is another important area to be looked into. Structure-activity relationship (SAR) studies and their associated physico-

chemical properties are also paradoxically overlooked. Lack of awareness about the possible existence of toxicity usually leads to the indiscriminate use of medicinal plant preparations [14]. Therefore, a pharmacological and toxicological investigation of the crude extracts and/or the biologically active phytoconstituent(s) should be conducted to prevent the patient population from being exposed to unhealthy and unsafe treatment strategies. The results obtained in *in vitro*, *in silico*, or *ex vivo* studies should be re-evaluated using animal models so that one is in agreement with the other. Henceforth, a hasty expansion of this age-old knowledge is the need of the hour, as it is likely to vanish under the wrap of modernization. The majority of the ethnopharmacological investigations conducted are mainly limited to the pre-clinical level without further investigation into the mechanism of action or the compound(s) responsible for it and lack a toxicity profile. Considering the increasing demand for herbal medicines, manufacturers and regulatory authorities must make consumer safety a top priority. Many factors (both plant-related and environmental) may be contributing to the toxicity of therapeutic botanical products, making the assessment of their toxicological potential a complex procedure. The scientific community is making a concerted effort to enhance the approaches used for the validation of herbal species, the identification of toxic phytochemicals, the elucidation of toxicity mechanisms, and the quantification of environmental pollutants in botanical products. To assess acute and chronic toxicity, the Organization for Economic Cooperation and Development (OECD) developed testing guidelines for chemical compounds.

It is anticipated that drug discovery must be integrated with systems-level polypharmacology approaches to overcome the unabating problems, including emerging resistance, associated with single-targeted drugs. With the modernization of the scientific field, network pharmacology has been introduced to exploit the mechanisms of action of drugs and their interactions with multiple targets in different pathways [15]. Network pharmacology utilises

computing power to systematically analyse the underlying complex interactions and relationships between phytochemicals and the different pathways of the body [16, 17]. By integrating systems biology and network pharmacology, it is expected to rationally design and develop the next generation of promiscuous drugs by utilising traditional knowledge [18, 19]. Network pharmacological analysis has gained traction as a novel platform, particularly for elucidating traditional knowledge to find answers to the current problems confronting the drug discovery industry. NP has been advantageous for drug research, which contributes to the revitalization of traditional knowledge. This technique utilising in silico data is quickly gaining popularity due to its low cost and comparable predictability. Consequently, network analysis has multiple applications and promising prospects in relation to the drug discovery and development process. NP analysis not only introduces novel therapeutic options, but also seeks to enhance the safety and efficacy of existing drugs [20].

*Natsiatum herpeticum* Buch.-Ham. ex Arn. is a very less exploited shrub found in evergreen forests and scrub jungles of South Asia and Southeast Asian countries. However, there exist lacunae in the present knowledge about the experimental validation of the traditional claims as available in the literature. We anticipate this lacuna in the current research to be associated with limited plant distribution (available in a few Asian countries only). The leaf paste of *N. herpeticum* is also known for its medicinal properties against inflammation and pain-associated conditions, including backache [21], cuts and wounds [22], and headache [23]. Additionally, literature suggests *N. herpeticum* to possess antioxidant property [24]. Despite this, the phytochemical constituents and plausible medicinal properties of *N. herpeticum* are yet to be investigated. Nonetheless, though the plant is being consumed as a wild edible herb by various communities in different regions, the dearth of information on the toxicity profile and possible pharmacological activities persuaded us to undertake this study to fill the knowledge gap.