IMPORTANT MEDICINAL PLANTS - BHUTAN

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Contents

Summary

This chapter introduces the reader to the topic of medicinal plants in Bhutan with particular focus on plants of spiritual, health and economic significance. It also highlights recent developments and findings on drug discovery projects, identifies gaps, and offers recommendations for further research.

Since antiquity, humans have learned to use wild plants for treating various disorders. Even today, many plants that grow in gardens, homesteads, meadows and woods hold the key to the physical and mental health of the people worldwide. More than 50,000 plant species are used as medicines worldwide, and approximately 80-85% of the world's population relies on these plant-derived medicines for their primary health care needs. Additionally, medicinal plants have secured a special place in drug discovery due to their prolonged clinical use in the health care system, which ensures i) safety of the medicinal products, ii) rich chemical diversity, ii) superior biological activities, and iv) shorter routes to drug discovery. Indeed, 80% of the current plant-based drugs were discovered from medicinal plants.

Medicinal plants grow in diverse ecological zones of tropical, temperate and alpine countries. In Bhutan, the extreme differences in altitudes (ranging from 150-7500

meters above sea level) have enabled the growth and development of a rich biological diversity including medicinal plants. With 72% of the country still under forest cover, it is a home to more than 600 medicinal plant species. These medicinal plants have become an important resource for health care, trade, and drug discovery projects. The medicinal plant collection program is one of the important sustainable development initiatives of Bhutan, and it generates income for farmers, yak herders, herbal brokers and industries.

1. Introduction

"The doctor of the future will give no medicine, but will interest his patients in the care of the human frame, in food, and the cause and prevention of disease."

-Thomas A. Edison

Humans have learned to survive in a hostile environment using plants for shelter, clothing, warfare, food and medicine. For example, a tropical hardwood tree, *Tectona grandis,* is used for making long-lasting houses and high-end furniture. Another tropical plant, *Gossypium hirsutum,* is used for making various types of beautiful cotton clothing materials. *Aconitum laciniatum* is used in warfare for poisoning enemies and animals. *Oryza sativa* is one of the staple foods of Asian countries. *Artemisia annua* is used as a medicine for treating malaria.

It is likely that humans have used plants as medicine since the beginning of human race. However, the first written records regarding the Sumerians' use of medicinal plants dates back to only 5,000 years ago (Pan et al., 2014). A history of herbal medicines including European and Asian scholarly medical practices have been described elsewhere (Petrovska, 2012; Pan et al., 2014). By the 19th and 20th centuries CE, with the discovery of molecule-derived drugs from medicinal plants and the antibiotics from fungus, we lost this primal connection to the natural medicines. While biomedicine moved much of mainstream healthcare from traditional medicines to modern pharmaceutical approaches, there is a rising movement to restore ancient plant-based healing practices. In fact, even today, traditional medicines provide primary health care services to 85–90 % of the world's population, and they continue to be an important knowledge-base that guides modern drug discovery projects (Wangchuk, 2018).

One of the important scholarly traditional medical systems that caters to the health needs of many Asian countries is Himalayan *Sowa Rigpa* medicine (*gSo ba Rig pa* in Wylie transliteration). *Sowa* mean to heal, nourish or correct; and *Rigpa* mean science, knowledge, perception or erudition (Dompnier, 1998). *Sowa Rigpa* is popularly known as Tibetan medicine in the West, as this medical system originated in Tibet during the rule of King Trisong Deutsen (755–795 CE). Under his patronage, an international conference on medicine was organized at Samye in Tibet, inviting physicians from India, Nepal, Persia, Greece, China, and other neighboring countries including Bhutan. It is said that best medical practices, especially Indian Ayurvedic, Greco-Arabic, and Chinese traditional medicines were translated or compiled into a compendium of Tibetan Materia Medica. While all these three major medical traditions have influenced the way Tibetan medicine evolved for centuries, the Tibetan medicine is closest to Ayurveda in principle and in practices. For example, three primary energies or dosas

(*vata, pitta*, and *ka pha*) of Indian Ayurvedic medicine are known as three humours or *nad pa gsum* (*rlung*, *mkhris pa* and *bad kan*) in Tibetan medicine. Similarly, a popular Indian triphala formulation (prepared from *Terminalia chebula*, *Terminalia bellerica* and *Phyllanthus emblica*) is known as *Dre bu gsum* (three fruits) in Tibetan medicine.

In the 12th century, a renowned Tibetan physician, Yuthok Yonten Gonpo (the Elder) synthesized many principles and techniques of these non-indigenous medical traditions and wrote the *Four Tantras* (in Tibetan known as the *Rgyud bzhi*), which serves as the textual basis of Tibetan medicine (Roberti et al., 2011). *Rgyud bzhi* comprises *Four Tantras* or treatises: the root Tantra (*Rtsa rgyud*), explanatory Tantra (*Bshad rgyud*), oral instructional Tantra (*Man ngag rgyud*) and the subsequent Tantra (*Phyi ma rgyud*) (Gonpo, 2011a, Gonpo, 2011b, both reprint editions). While the root Tantra gives an overview of the whole treaty; the explanatory Tantra describes the human body including anatomy, embryology, and physiology. The instructional Tantra deals with the causes, symptoms and treatment of a variety of diseases, and the subsequent Tantra explains on diagnosis and pharmacology. The concluding chapters summarize the content. The fully trained physicians have to study them in-depth for 5-6 years and must know the details before becoming clinicians. A recent dataset (in the English version) published by Dhondrup et al. (2020) depicts disease classifications listed in the Four Tantras and the encyclopedic compendium "Oral Instructions Treatise" (*Man ngag rgyud*) of the Tibetan medical classics. Other important textbooks including *Khrungs dpe dri med shel gyi melong* (Dorje, 1995), and *Shel gong shel phreng* (Phuntshok, 1994; Wangyal et al., 2020) describes 2294 different single medicinal substances with illustrations including their classification, identifications, nature, potencies, collections, uses, doses and mode of administration. These medicinal substances are classified into three main categories: minerals, animal parts and medicinal plants.

Today, the Himalayan *Sowa Rigpa* medicine is practiced worldwide especially in countries including Austria, Canada, Bhutan, Germany, India, Italy, Mexico, Mongolia, Nepal, Netherlands, Poland, Russia, Switzerland, Tibet/China, United Kingdom, and United States of America (USA) (Adams and Craig 2008; Craig and Gerke 2016) (Figure 1). While the same medical textbooks are used in these countries, differences in the types of ingredients and preparation methods of polyherbal formulations are notable. Such variations are to be expected as the *Materia Medica* of this tradition has constantly been evolving in several countries with its adaptations to local vegetation, culture and foreign influences. The *Sowa Rigpa* medical system constitutes a significant economic and public health resource for these countries. The pharmaceutical industries based on this medical system is rapidly growing in size and prominence not only in Asia but also worldwide. A recent study revealed that there was a tenfold growth of the Himalayan *Sowa Rigpa* pharmaceutical industry in Asia between 2000 and 2017, and that the industry had a total sales value of 677.5 million USD (Kloos et al. 2020).

In Bhutan, the unique Himalayan biodiversity, local culture and traditions, prevailing disease types, and the government policy of integration with biomedicine greatly influenced the way *Sowa Rigpa* Medicine has evolved. For this reason, it is known as Bhutanese *Sowa Rigpa* Medicine (BSM) or Indigenous Medicine in Bhutan, as distinct from the tradition of *Sowa Rigpa* that originate in and continues in practice in Tibet and

other countries. The similarities and differences between these two systems have been previously described (Wangchuk et al., 2013a). One notable difference between the larger corpus of Tibetan Medicine and the Bhutanese *Sowa Rigpa* Medicine (BSM) is that the latter has separated the medical services, manpower training, and the production of medicines. The medical services (treatment of patients) are provided by the traditional physicians stationed at the hospitals and basic health units, which are built countrywide. The manpower training (human resource development) is provided by the Faculty of Traditional Medicine under Khesar Gyalpo University of Medical Sciences of Bhutan. The collection of medicinal plants and the manufacturing of medicines are carried out by Manjong Sorig Pharmaceuticals Corporation Limited (MSPL).

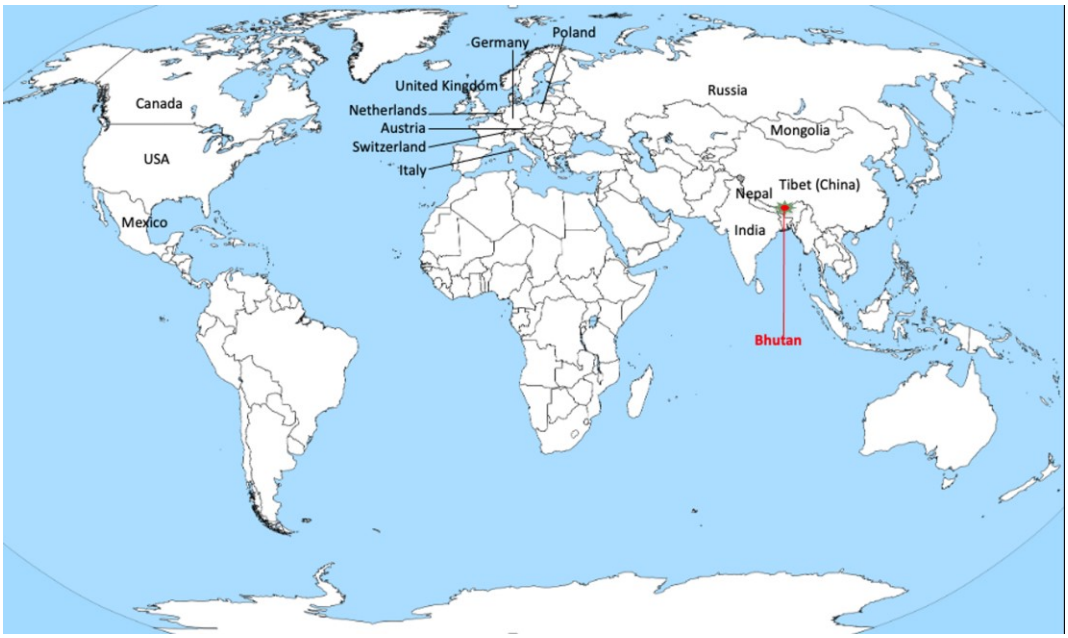

Figure 1. World map showing *Sowa Rigpa* (Tibetan medicine)-practicing countries: Austria, Canada, Bhutan, Germany, India, Italy, Mexico, Mongolia, Nepal, Netherlands, Poland, Russia, Switzerland, Tibet/China, United Kingdom, and United States of America (USA) (Adams and Craig 2008; Craig and Gerke 2016)

Other practices unique to BSM are:

1) certain procedures related to the acupressure golden needle therapy, which was innovated by a Bhutanese traditional physician, Sherab Jorden, based on the principle of a Tibetan moxibustion procedure;
2) the current formulations and the medicinal ingredients, which are based on the expertise of the local physicians and their familiarity with the locally available medicinal plants; and
3) the methods of preparation of herbal drugs, which uses modern pharmaceutical equipment and Good Manufacturing Practices.

It should be noted that the medicinal plants are never used as single plant components in the Tibetan medicine and in the BSM, but rather as a mixture of two or more active ingredients. The medicines comprise different poly-ingredient formulations, and the medicinal plants are often mixed with minerals and animal-derived components. The

theory behind using multi-ingredient compounds is that the specific mixtures of ingredients are understood to act synergistically, where necessary to neutralize the toxicities of individual ingredient(s) and enhancing the therapeutic value of the base mixture (Tidwell et al., 2019). Quite often, the individual therapeutic indication of any given herbal ingredient is altered when it is formulated as multi-ingredient products. Since the medicinal plant is just one component of such polyingredient formulations, it is important to provide the history and overview of the BSM medical system, so that the contextualization of this chapter becomes apparent.

This chapter describes the historical perspectives of the BSM, disease concepts, medicinal plant classification, current utilization and sustainability, quality control system, isolation of bioactive compounds, conservation policies, and recent developments on drug discovery projects. It identifies gaps, and offers recommendations for further research.

2. Historical Perspectives and Development of Medical Traditions in Bhutan

Historically, Bhutan was known by many synonyms such as "Dragon kingdom of bountiful medicinal sandalwood" and "Land of medicinal plants" (Wangchuk et al., 2011a). The abundance of medicinal plants has supported the development of two primary forms of traditional healing systems: the oral tradition of Folklore medicine and the scholarly tradition of the BSM. Until the advent of modern medicine in the 1960s, these two forms of traditional medical systems were the mainstream health care system in Bhutan, and they are still practiced today. The practitioners of the Folklore medicine are known as Folk Healers, and the practitioners of the BSM are known as Traditional Physicians (Bhutanese call them '*Drungtsho*') and Traditional Clinical Assistants (*Man pa*). While the Folk healers do not have a formal training, BSM practitioners undergo an intensive formal training at the Khesar Gyalpo University of Medical Sciences of Bhutan.

BSM was formally introduced as a form of monastic education system in Bhutan by Zhabdrung Ngawang Namgyal in 1616. Most traditional physicians, who obtained their medical training from the monastic institutions in Bhutan and some from Chagpori monastic medical college in Tibet, served in the royal courts of the Regional Administrator of Trongsa district (Trongsa Ponlop), Jigme Namgyal (1825-1881) and other successive rulers of the country (Dorji and Morisco 1989). For example, Drungtsho Mahaguru, who obtained his medical training from Gangtey Goenpa monastery in Bhutan, served in the royal court of second monarch, King Jigme Wangchuck. The King Jigme Dorji Wangchuck integrated the *Sowa Rigpa* medicine with the modern medical system in 1967, and the first dispensary was built at Dechencholing, Thimphu in 1968. This dispensary unit provided a three-year on-the-job training for clinical assistants in 1971. In 1978, the fourth monarch, King Jigme Singye Wangchuck, established the National Indigenous Hospital, which offered a Bachelor of Science in Traditional Medicine. The duration for the bachelor degree course was set for five years, including a one-year internship to maintain equivalence to the modern medical system of Bachelor of Medicine and Bachelor of Surgery (MBBS) courses. The first principal of this training institute, Thubten Lekpai Lodre (1978 - 1997) and his medical students formed the core group of the BSM in Bhutan. He composed many

textbooks – including a treatise on pulse reading and urinalysis – developed standard training curricula for the five-year B.Sc. program, revived the traditional methodology of the BSM teaching and learning, and established institutional norms (Wangdi and Wangdi 2007).

In 1988, the National Indigenous Hospital was renamed 'National Institute of Traditional Medicine'. *Drungtsho* Pema Dorji was appointed as the first director of this institute, and he modernized the pharmaceutical research and production activities of the BSM. The government, the World Health Organization, Italian Disarmo Sviluppo, and European Union projects provided financial support to improve quality of medicines and health care services. *Drungtsho* Pema Dorji and Dr. Paolo Morisco established the Research and Quality Control Laboratory in 1990, and provided on-the-job training to research assistants. The multi-disciplinary experts in the areas of ethnobotany, pharmacy, pharmacognosy, chemistry, pharmacology, herbalism, product development and marketing were recruited to establish research and quality control protocols, and impart training to the local students. In 1993, the BSM nomenclature, medicinal plants names, formulations and preparation of traditional drugs, and the teaching programs were standardized. The botanical identification of the medicinal plants was carried out from 1994 to 1998 (Wangchuk and Tashi 2016).

In 1998, the National Institute of Traditional Medicine was renamed 'Institute of Traditional Medicine Services' and the three subsections became more independent with self-governing organizations. The National Institute of Traditional Medicine was affiliated with the Royal University of Bhutan in 2003. It was renamed 'Faculty of Traditional Medicine' when it was transferred to a newly established University of Medical Sciences of Bhutan, which was recently renamed in 2015 as the 'Khesar Gyalpo University of Medical Sciences of Bhutan'. The Faculty of Traditional Medicine provides Bachelor of Science (5 years *Drungtsho* course, equivalent to Western medical degree course) and Diploma in Traditional Medicine (3 years *Manpa* course). The Four Root Medical Tantras (*Rgyud bzhi*), Crystal Rosary and Orb (*Shel gong Shel phreng)* and as many as 26 other Tibetan contemporary medical textbooks are used for teaching and training the students (Wangchuk et al., 2016a). The National Traditional Medicine Hospital was upgraded to the Department of Traditional Medicine, under the Ministry of Health. The Pharmaceutical and Research Unit became an autonomous organization and it was recently renamed 'Manjong Sorig Pharmaceuticals Corporation Limited'. This pharmaceutical industry collects 229 species of medicinal plants to produce 103 polyingredient formulations with different dosage forms including pills, tablets, capsules, powders, decoctions and other packaged products (Tenzin, 2007).

3. Theory, Concepts and Classification of Medicinal Plants

In the BSM practices, mainly four principles are apparent (Wangchuk et al., 2013a):
(1) the principle of five elements (*byung ba lnga*);
(2) the principle of three humors (*nad pa gsum*);
(3) the principle of astrology (rtsi); and
(4) the principle of the binary opposition of intrinsic hot-cold quality (*tsha grang byung ba*).

The five elements: earth, water, fire, air and space, take a biological manifestation as the three humors of the body, namely
'air' (*rlung*),
'bile' (*mkhris pa*), and
'phlegm' (*bad kan*).

While the 'air' is associated with the body movement and the circulatory system, the 'bile' is responsible for digestive system, and the 'phlegm' for body fluids including lymphatic system and endocrine glands. When there is a harmony and balance in these three principles, a person is said to be healthy, and any imbalances result in the pathologies or disorders. The medical classics describe 84,000 types of disorders, which are classified into 404 major pathologies, of which 79 major diseases are currently prevalent in Bhutan (Gayleg, 2005). These pathologies or diseases are treated using five main approaches:
1) dietary guidance,
2) behavior modification,
3) herbal medications,
3) physiotherapies, and
5) minor surgical procedures.

More importance is given to the modification of diet and behavior in addressing root causes of disease, than herbal medications and physiotherapies though the latter are more important once disease has substantially progressed. Before a patient is considered for treatment, a differential diagnosis of their individual disorder, and the potency and contra-indications of medicinal ingredients are carefully determined by the practicing physicians.

The five elements determine the growth of a medicinal plant and its properties including taste, smell, main constituents, potency and quality. For example, the combination of earth and water elements fosters a sweet taste for a plant, which improves the defective air and bile disorders, but may aggravate phlegm disorders if the equilibrium is not achieved in the medications. These elements determine the principle of the binary opposition of intrinsic hot-cold qualities. Medicinal plants with cold potency are used for treating illnesses with a hot nature (for example, pain or swelling). Such plants are predominantly collected from cool and shady places on the northern side of the mountains with minimum exposure to sunlight. On the other hand, medicinal plants with hot potencies that are used for treating diseases with cold natures (for example, indigestion) are collected from sunny places on the southern or eastern side of the mountains with high exposure to sunlight (Krug, 2008).

In BSM, medicinal plants are broadly classified into three main categories (Wangchuk, 2009):
1) high altitude medicinal plants (*sngo sman*),
2) low altitude medicinal plants (*khrog sman*), and
3) plant exudates (*rtsi sman*).

High altitude medicinal plants are generally considered herbaceous and tend to grow on snowy alpine mountains at an altitude range of 2000 to 5000 meters above sea level (masl) (Figure 2).

Figure 2. High altitude alpine mountains of Bhutan (Jomolhari -7326 masl and Jitchu Drake-6989 masl).

Figure 3. Low altitude sub-tropical forests of Bhutan (Royal Manas National Park - 80 masl)

Low altitude medicinal plants are mostly woody types, which grow in the temperate and sub-tropical zones at an altitude range of 150 to 1999 masl (Figure 3). Plant exudates, although considered a separate class, are generally extracted from the other two classes.

4. Naming of Medicinal Plants and the Collection Seasons

Categorizing, describing, naming, and identifying medicinal plants in the BSM was described by Yeshi and colleagues (Yeshi et al., 2019). The naming of medicinal plants is mainly based on the habitat, life form, and the morphological characteristics including smell, taste, texture, color and their resemblance to animate and inanimate objects. For examples, *Clematis acutangula* and *Meconopsis paniculata* are named after the white and yellow color of their flowers as *dbyi mong dkar po* (*dkar po* meaning white) and *aut pal serpo* (*serpo* meaning yellow), respectively. *Dactylorhiza hatagirea* and *Pedicularis flagellaris* are named as *dbang po lag pa* and *glang sna*, after their resemblances with human hand and elephant's trunk, respectively. *Polygonum macrophyllum* and *Juniperus indica* are named after the habitat types as *spang ram* (since it grows in meadows, locally known as '*spang*') and *la-shug* (mountain, locally known as '*la*'), respectively.

Habitat is considered one of the important factors in choosing the collection sites for medicinal plants. Pristine and pleasant environments especially the sacred places endowed with balanced sun, air and water elements are considered favorable for collecting medicinal plants. According to the BSM guidelines for identification and collection of medicinal plants in Bhutan (Krug 2008), medicinal plants should not be harvested from the places inhabited by humans and animals, dirty water sources, footpaths, cemetery grounds, and industrial and other polluted places. Further, it is recommended not to collect medicinal plants that are infested by insects, populated by dried and shriveled plants, and plants damaged by fire, frost, wind, hailstorms and floods.

The collection seasons depend upon the classes of medicinal plants and vary from plant to plant. Generally, each plant part must be collected at the prescribed time, and the BSM recommended collection timings are:

- Fruits should be harvested in autumn when they are mature;
- Flowers should be harvested in spring at the pollination time when the aroma is intense;
- Buds and tender shoots should be harvested in the late spring;
- Leaves and milky saps should be harvested in early summer;
- Bark, cortex and resin must be harvested in early spring;
- Root, rhizomes, branches and trunks should be harvested in late autumn;
- Purgative medicinal plants are harvested at the end of autumn; and
- Plants of emetic nature are harvested in mid or end of spring (Phuntshok, 1994).

5. Medicinal Plants Diversity, Distribution and Parts Used

Bhutan has three main eco-floristic zones, namely alpine, temperate, and sub-tropical zones, with extreme variation in altitudes that range from 100 masl in the south to as high as 7,500 masl in the north (Govil, 2000). These extreme variations in altitudes and vegetation zones have enabled the growth of the diverse range of flora and fauna. Bhutan has a total of 5,603 species of vascular plants under 220 families and 1,415 genera, out of which approximately 600 medicinal plant species have been identified as medicinal plants. Of these species, 229 medicinal plants (Table 1) are currently used in formulating 108 current multi-ingredient formulations.

Out of 229 species, 116 species were identified as the high altitude medicinal plants and 113 species as low altitude medicinal plants. The 116 species of high-altitude medicinal plants belong to 39 families and 80 genera, with Asteraceae, Gentianaceae and Ranunculaceae being the top-ranking family and genera, respectively. The most important species belong to the genera of Meconopsis, Delphinium, Gentiana and Veronica (Figure 4).

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Biographical Sketches

Dr. Phurpa Wangchuk obtained his Bachelor of Bioscience (Chemistry, Botany and Zoology as majors) from the University of Delhi, India with an 'Overall Academic Excellence Award'. He completed his M.Sc. in Medicinal Chemistry (Research) from the University of Wollongong, Australia, and Post Graduate Diploma in Research Methodology (Clinical Research) from the DBL-Centre for Health Research and Development, Copenhagen University, Denmark. He was awarded PhD with an 'Outstanding Thesis' from the University of Wollongong in 2014. Both his M.Sc. and PhD research projects on medicinal plants resulted in the discovery of five novel molecules, 15 drug lead compounds and one patent on the novel anti-malarial drug lead compound.

Currently, as a Senior Research Fellow at the Centre for Molecular Therapeutics, Australian Institute of Tropical Health and Medicine, Dr. Wangchuk works on discovering novel anti-inflammatory, anti-parasitic, and anti-malarial drugs from natural sources including Aboriginal medicinal plants, endemic mountain-top tropical plants affected by climate change, insect fungi, parasitic helminths and marine organisms. This biodiscovery projects involves using advanced technologies including HPLC, MALDI-MS, GCMS, NMR, and metabolomics platforms for isolation and characterization of small molecules, and bioactivity screening of compounds using *in vitro*, *in vivo* and *ex vivo* experimental models. He also worked in various capacities as a Research Officer, Chemist, Product Manager and as Head of the Research and Development Section of the Manjong Sorig Pharmaceuticals. As Head of the Research and Development Section, he led a team comprising a ethnobotanist, pharmacognosist, traditional physician and several external technical consultants from Europe, Japan, India and Thailand.

Dr. Wangchuk was awarded a number of prestigious fellowships and competitive grants including the Royal Government of Bhutan Scholarship (2002-2004), Danish DANIDA Research Fellowship (2006), Endeavour Postgraduate Australia Award (2010-2014), National Health and Medical Research (NHMRC) Early Career Peter Doherty - Australian Biomedical Fellowship (2015-2019), and NHMRC Ideas Grant (2020-2023). He was also Associate Investigator of a AUD 19 million-dollar NHMRC program grant,

Chief Investigator on four World Health Organisation grants, and an executive team member of a EUR three million-funded European Union Medicinal Plants Project in Bhutan.

He has published two books, five book chapters, four conference proceedings, two plant monographs and numerous journal articles in the areas of natural products, medicinal plants, helminths, biodiscovery and metabolomics. He is also an active member of professional organizations; a reviewer of journal papers, books and grant proposals; and an examiner of an HDR thesis. He has served as, and continues to serve as topic editor, guest editor and editorial board member of few national and international journals including 'Plants', 'Molecules' and 'Journal of Biologically Active Products from Nature'.