Dinesh Chandra Agrawal
Muralikrishnan Dhanasekaran *Editors*

Medicinal Herbs and Fungi

Neurotoxicity vs. Neuroprotection

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Editor Professor Agrawal dedicates this book to his beloved spouse
Manju
and
Editor Professor Dhanasekaran dedicates this book to his beloved spouse
Madhumalini M. Nadar

Preface

This book is the continuation of Professor Agrawal's previous Springer books: *Medicinal Plants—Recent Advances in Research and Development* (Springer link: http://www.springer. com/in/book/9789811010842); *Medicinal Plants and Fungi—Recent Advances in Research and Development* (Springer link: https://www.springer.com/gp/book/9789811059773); and *Medicinal Mushrooms—Recent Progress in Research and Development* (Springer link: https://www.springer.com/la/book/9789811363818).

The ever-rising increase in the consumption of medicinal herbs and its products and its exposure in the human population have generated concerns about the potential neurotoxicity of several new and existing botanicals. This book on "Medicinal Herbs and Fungi—Neurotoxicity and Neuroprotection" offers an accurate, relevant, and comprehensive coverage of a wide variety of medicinal herbs and fungi, which are associated with neurological diseases (central and peripheral nervous system disorders). It includes chapters (review articles) that thoroughly describe the benefits and adverse effects associated with the use of some of the most commonly used medicinal herbs and fungi, and the pathophysiological mechanisms underlying them. The rich compilation aims to deliver thorough and extensive research updates on the advances in medicinal herbs and fungi related to neurotoxicity and neuroprotection, ranging from discussions on cellular and molecular processes and pathology to clinical aspects. The chapters in the book have been contributed by the experienced and eminent academicians, researchers, and scientists working in the field across the globe.

Chapter "Mitosis Inhibitors and Medicinal Plants: Neurotoxicity and Neuroprotection" constitutes an exhaustive review on factors involved in the pathogenesis of chemotherapy-induced peripheral neuropathy (CIPN), neurotoxic mitosis inhibitors, and natural products as neuroprotective and/or neuropreventive agents. Besides, future perspectives have been manifested for the prevention or treatment of CIPN occurrence. Chapter "The Neurotrophic and Neuroprotective Potential of Macrofungi" reviews recent advances in research on the neuroprotective potential of macrofungi and perspectives for their application as neuroprotectants in biomedicine to prevent, support, or cure neurodegenerative disorders. Chapter

"Andrographolide, a Diterpene from *Andrographis paniculata*, and Its Influence on the Progression of Neurodegenerative Disorders" describes several biologically important derivatives of andrographolide and covers a comprehensive discussion on the upregulation or downregulation of specific signaling pathways targeted by andrographolide and their derivatives in the pathogenesis of important neurodegenerative diseases, including conditions such as pain and depression. Chapter "Ginseng: A Boon or a Curse to Neurodegenerative Diseases" provides a theoretical basis for the treatment of neurodegenerative diseases by ginseng and its extracts. Chapter "Insights into Mechanisms and Models for Studying Neurological Adverse Events Mediated by Pharmacokinetic Interactions Between Clinical Drugs and Illicit Substances of Herbal and Fungal Origin" discusses novel insights into the potential mechanisms of pharmacokinetics-based interactions between clinical drugs and illicit substances of herbal/fungal origin that may be responsible for neurological and related adverse events. Also, the chapter provides insights into potential experimental models that can be used in studying these pharmacokinetic interactions that lead to neurological adverse events. Chapter "Cannabis-Induced Neuroactivity: Research Trends and Commercial Prospects" deals with the concise yet broad review of chemical, medicinal (neuroprotection), and adverse psychotic aspects of cannabis. The ancient and traditional use of cannabis leaves (bhang) in India for medical as well as cultural purposes has been discussed in the scientific perspective. Further, the trends in scientific research, intellectual property (patents), and commercial prospects related to cannabis are discussed. Chapter "Neurotoxicity of Polyherbal Formulations: Challenges and Potential Solutions" focuses on potentially toxic substances present in the polyherbal products and discusses various general toxicity and neurotoxicity tests of the herbal products. Chapter "Balancing the Neuroprotective Versus Neurotoxic Effects of Cannabis" reviews the current neuropharmacological and neurotoxicological properties of cannabinoids. Chapter "Alpha-Synuclein: Biomarker for Parkinson's Disease, It's Estimation Methods, and Targeted Medicinal Therapies" provides an overview of the role of α-synuclein in Parkinson's disease, its estimation methods, and the use of phytochemicals in targetting α-synuclein for preventing the neurotoxicity. Chapter "Screening of Herbal Medicines for Neurotoxicity: Principles and Methods" reviews screening methods of herbal medicines for neurotoxicity. Chapter "Plants with Phytomolecules Recognized by Receptors in the Central Nervous System" describes the traditional, medicinal, and recreational uses of the plants, phytomolecules in these plants recognized by receptors in the Central Nervous System. Chapter "Reserpine-Induced Depression and Other Neurotoxicity: A Monoaminergic Hypothesis" summarizes depression and the monoamine depletion hypothesis, focusing on the drug reserpine and its role in establishing the hypothesis. Chapter "Traditional Medicinal Plants of Sri Lanka and Their Derivatives of Benefit to the Nervous System" describes the traditional medicinal plants of Sri Lanka and their derivatives of benefit to the nervous system. Chapter "Ameliorative Effects of Shodhana (Purification) Procedures on Neurotoxicity Caused by Ayurvedic Drugs of Mineral and Herbal Origin" discusses the ameliorative effects of shodhana (purification) procedures on

neurotoxicity caused by ayurvedic drugs of mineral and herbal origin. Chapter "St. John's Wort: A Therapeutic Herb to Be Cautioned for Its Potential Neurotoxic Effects and Major Drug Interactions" provides a brief history of St. John's Wort (SJW), a summary of its active constituents, current and potential therapeutic uses, adverse drug effects, and drug interactions that should be considered when prophylactically and/or therapeutically using SJW with prescribed medications. Chapter "Neurotoxic Potential of Alkaloids from Thorn Apple (*Datura stramonium* L.): A Commonly Used Indian Folk Medicinal Herb" describes the neurotoxic potential of alkaloids from thorn apple (*Datura stramonium* l.)—a commonly used source of folklore medicinal herb known for its mental stimulation and curative properties. It discusses the noteworthy pharmacological potential of this plant utilized by Ayurvedic practitioners in the traditional system of Indian medicine. Chapter "Medicinal Plants in Uganda as Potential Therapeutics Against Neurological Disorders" presents the complementary and alternative therapies that could potentially narrow the treatment gap in the management of neurological disorders in Uganda. Specifically, plant species from the Ugandan context are presented from ethnobotanical studies. Chapter "Ayurvedic Ideology on *Rasapanchak*-Based Cognitive Drug Intervention" explores the rationale of Ayurveda in the management of cognitive disorders. Chapter "Neurotoxic Medicinal Plants of Indian Himalayan Regions: An Overview" provides an overview of neurotoxic medicinal plants of the Indian Himalayan region and their neurotoxins, mechanism of neurotoxicity, and a few case studies explaining the adverse effects of neurotoxins. Chapter "Neuroprotective Effects of *Portulaca oleracea* and *Portulaca quadrifida* Linn" includes the important neuroprotective activity and other therapeutic benefits of two *Portulaca* species.

The editors hope that this compendium of review articles will be useful as a reference book for advanced students, researchers, academics, business houses, and all individuals concerned with medicinal herbs and fungi.

Taichung, Taiwan — Dinesh Chandra Agrawal
Auburn, AL, USA — Muralikrishnan Dhanasekaran
23 September 2020

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The editors thank all the invited authors to this book for preparing their valuable manuscripts. Without their contributions, this book would not have been possible.

The co-editor Professor Dhanasekaran wishes to place on record special appreciation and thanks to Professor Agrawal for handling the entire correspondence with the Springer and authors and dealing with the editing, reviewing, and revision process of manuscripts and managing them from start to finish. Without his untiring efforts, this book would not have become a reality.

Editor Professor Agrawal thanks Professor Tao-Ming Cheng, President of the Chaoyang University of Technology (CYUT); Professor Wen-Goang Yang, Vice-President, CYUT; Professor Sung-Chi Hsu, Dean, R&D office and Assistant Vice-President, CYUT; Professor Hsi-Hsien Yang, Dean, College of Science and Engineering, CYUT; Professor Wei-Jyun Chien, Chairperson, Department of Applied Chemistry, CYUT, Taichung, Taiwan for their constant support and encouragement during the progress of the book.

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Editors express profound gratitude towards “God, the Infinite Being” for providing strength to accomplish the arduous task of handling this book.

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Editors and Contributors

About the Editors

Dinesh Chandra Agrawal graduated in 1976 from Aligarh Muslim University (National university) and obtained his Ph.D. degree in 1982 from HNB Garhwal University (National university). Professor Agrawal has more than 38 years of research experience in plant biotechnology of diverse species, including medicinal plants and medicinal mushrooms. After serving for more than 31 years, in 2013, he superannuated as a chief scientist and professor of biological sciences at the CSIR-National Chemical Laboratory, Pune, the top-ranking institute in chemical sciences under the umbrella of the Council of Scientific and Industrial Research (CSIR), Ministry of Science and Technology, Govt. of India. Currently, he is working as a professor in the Department of Applied Chemistry, Chaoyang University of Technology (CYUT), Taiwan. While in CSIR-NCL, Prof. Agrawal worked as a coordinator and project leader of several research projects funded by the Govt. of India. He has more than 180 publications, including five books (3 by Springer Nature) to his credit on different aspects of plant biotechnology, including medicinal plants and medicinal mushrooms. More than 35 M.Tech./M.Sc. and 7 Ph.D. students have completed their thesis work under his guidance.

Professor Agrawal has been bestowed several prestigious awards and fellowships such as the Alexander von Humboldt Fellowship (Germany), DBT Overseas Associateship (USA), British Council Scholar (UK),

European Research Fellow (UK), and INSA Visiting Scientist (India). During these fellowships, he had opportunities to work in the USA, Germany, and the UK. He had a research collaboration with UMR Vigne et Vins, INRA, Centre de Recherché Colmar, France. For more than 10 years, he was a member of the executive committee of the Humboldt Academy, Pune Chapter, and held the position of treasurer. Professor Agrawal has reviewed a large number of research papers for several SCI journals on plant biotechnology and served as a member of the editorial board of *Medicinal and Aromatic Plant Abstracts*, NISCAIR, Govt. of India. Presently, he is on the editorial board of the *International Journal of Applied Science and Engineering* (Scopus), serving as associate editor in chief of the journal.

Muralikrishnan Dhanasekaran completed his Bachelor of Pharmacy from Annamalai University and Master of Pharmacy from Jadavpur University, West Bengal, India. He obtained his Ph.D. degree from the Indian Institute of Chemical Biology, Kolkata, India, under the guidance of Dr. K.P. Mohanakumar. Following which he attained his post-doctoral training from renowned scientists Dr. Manuchair Ebadi (Prof. University of North Dakota, Grand Forks, ND, and Dr. Bala Manyam (Scott & White Clinic/Texas A & M, Temple, TX). Dr. Dhanasekaran joined Auburn University in the year 2005 and currently working as a full Professor at Harrison School of Pharmacy, Auburn University, USA. Dr. Dhanasekaran's area of research and interest focuses on neuropharmacology, toxicology, dietary and natural products. Dr. Dhanasekaran completed the New Investigator Research Grant from Alzheimer's Association, several Auburn University grants, and several other research projects from a Pharmaceutical Company. He has graduated 14 students (as a mentor) and currently has 2 graduate and trained more than 50 undergraduate students in his lab. Dr. Dhanasekaran has received several teaching awards from Auburn University for teaching Pharm D. and graduate students. He has published more than 200 scientific abstracts, 85 peer-reviewed publications, a book, and several book chapters.

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Mitosis Inhibitors and Medicinal Plants: Neurotoxicity and Neuroprotection

Nadire Özenver and Thomas Efferth

Contents

Abstract Cancer is one of the devastating diseases worldwide, causing desperate outcomes and high mortality rates. Despite undeniable improvements in cancer treatment, many patients with malignancies still suffer from adverse drug reactions, among which peripheral neurotoxicity holds great importance. Peripheral neuropathy as a representation of peripheral neurotoxicity is a usual complication of chemotherapy, reducing the life quality of individuals since it can adversely induce sensory and motor dysfunctions influencing patients' life. Mitosis inhibitors are substantially administered drugs during chemotherapy. However, these drugs may induce the occurrence of chemotherapy-induced peripheral neuropathy (CIPN).

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Efficient therapy with fewer side effects specifically focusing on the eradication of malignant cells without affecting healthy cells adversely constitutes today's approach for chemotherapy. Therefore, to target the discovery of functional chemotherapeutics with minimized adverse effects is a rational approach. In this context, medicinal plants and phytochemicals may come into the focus to avoid or treat the complications of peripheral neurotoxicity, if combined with standard chemotherapy regimens, or as complementary and alternative therapy interventions. In the present chapter, we review the factors involved in the pathogenesis of CIPN, neurotoxic mitosis inhibitors, and natural products as neuroprotective and/or neuropreventive agents. Future perspectives will be further manifested for the prevention or treatment of CIPN occurrence.

Keywords Cancer · Medicinal plant · Mitosis inhibitor · Neuroprotective · Neurotoxic · Phytochemical

Abbreviations

5-FU	5-Fluorouracil
Adrs	Adverse drug reactions
AUC	Area under the curve
AUC12	Area under the curve of 12
AUC6	Area under the curve of 6
CAM	Complementary and alternative medicine
CAMKK1	Calcium/calmodulin dependent protein kinase 1CIPN
CBS	Cystathionine-β-synthase
Chıs	Chinese herb injections
CHM	Chinese herbal medicines
CIPN	Chemotherapy-induced peripheral neuropathy
CNS	Central nervous system
CRC	Colorectal cancer
Crel	Cremophor-EL
CYP	Cytochrome P450
CYP2C8	Cytochrome P450 Form 1
CYP2C9	Cytochrome P450 PB-1
DHA	Docosahexaenoic acid
DRG	Dorsal root ganglia
FDA	Food and Drug Administration
GFAP	Glial fibrillary acidic protein
HGWD	*Huangqi Guizhi Wuwu* decoction
ID3	Inhibitor of differentiation 3
LJZT	*Liu Jun Zi Tang*
LV	Leucovorin
MTD	Maximum tolerated dose
MTE	*Marsdenia tenacissima* extract

NCI	National Cancer Institute
NFATC2	Nuclear factor of activated T-cells 2
NF-κβ	Nuclear factor kappa B
OATP1B2	Organic anion–transporting polypeptide B2
OCT2	Organic cation transporter 2
OCTN2	Organic cation transporter novel 2
PN	Peripheral neuropathy
Pt	Platinum
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SNP	Single nucleotide polymorphism
TCM	Traditional Chinese Medicine
VIPN	Vincristine-induced peripheral neuropathy

1 Introduction

Cancer is a group of diseases in which cells lose their ability to control cell proliferation and gain properties to invade and metastasize distant organs of the body. Cancer is the second-leading cause of death and is predicted to induce 9.6 million deaths globally in 2018, an incidence that is steadily increasing throughout the world (WHO 2020).

Currently, the 5-year survival rate of patients receiving cancer therapy is 67%, and the number of patients is considered to reach up to 23.6 million by 2030 (Abe et al. 2016; NCI 2020). Many anticancer agents in the clinic display adverse drug reactions (ADRs) such as hematological toxicities, hepatotoxicity, nephrotoxicity, neurotoxicity, and so on (Adachi et al. 1983; King and Perry 2001; Perazella and Moeckel 2010; Yang and Moon 2013). Today's concept on chemotherapy is to perform effective treatment with fewer side effects, which means selective therapy with a specific focus on the eradication of malignant cells without affecting healthy cells adversely since ADRs are the fourth cause of mortality with 6.7% incidence in hospitalized patients (Lazarou et al. 1998). Despite their severe side effects, chemotherapeutics are unavoidable elements of cancer management, and minimizing their unwanted effects is of great importance to improve survival rates and life quality of individuals.

Peripheral neuropathy (PN), an expression of peripheral neurotoxicity, is a common complication resulting from chemotherapeutic- and anti-HIV medication-associated toxicity (Fig. 1). Although olfactory neurons and taste receptors can regenerate, many cells in the nervous system divide slowly or not at all. Therefore, neurotoxicity is quite an exciting feature of chemotherapeutics, since they generally target rapidly dividing cells. Besides, the existence of blood–brain, blood–cerebrospinal fluid, and blood–nerve barriers should theoretically prohibit the admission of antineoplastic agents to the nervous system. Recent investigations have demonstrated that chemotherapeutics may harm the nervous system through other

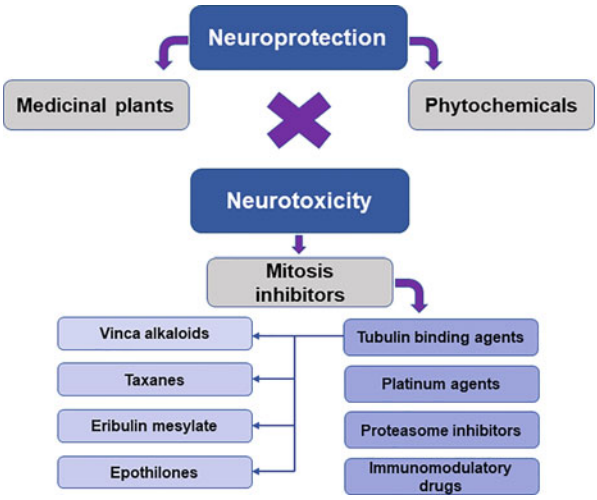

Fig. 1 Schematic representation of neurotoxic and neuroprotective agents induced by mitosis inhibitors and natural products

mechanisms (Dietrich et al. 2006). Peripheral neuropathy, usually inclined by direct involvement of peripheral nerves, is the most common complication (Magge and DeAngelis 2015). Medications may adversely affect different elements of the peripheral nervous system inclining neuropathy, which is mostly linked to axonal degeneration by a "dying back" type. Peripheral neuropathy develops weeks to months following medication exposure and may prolong even after the cessation of the drug. Commonly used sensitive electrophysiology studies have identified the existence of neuropathy, enabling early diagnosis and treatment of peripheral neurotoxicity (Peltier and Russell 2002).

Neurotoxic side effects are frequent outcomes of well-known chemotherapeutics along with bone marrow suppression and renal toxicity requiring termination of the antitumor therapy or alteration of the dose regimen. Many chemotherapeutics may even incline polyneuropathy, while only a few produce peripheral neuropathy (Quasthoff and Hartung 2002), which results in disrupted sensory and motor symptoms (Fig. 2; Table 1). Numbness, tingling, increased sensitivity to heat and cold, and pain, particularly in the hands and feet, are sensory symptoms. Motor dysfunctions include symptoms of muscle weakness and deteriorative balance (Windebank and Grisold 2008).

Chemotherapy-induced peripheral neuropathy (CIPN) is a usual long-term side effect of antineoplastic agents during or after treatment, decreasing the life quality of patients with cancer. CIPN occurrence affects oncologic treatment resultants adversely by reducing the patient's adhesion to therapy, inclining dose modifications, and therapy disruptions. Evaluations regarding demographic and clinical properties revealed that patients with neurotoxicity were usually older, not employed, and had less annual family income (Miaskowski et al. 2018). CIPN arises approximately in two-thirds (68.1%) of individuals in the first month after chemotherapy. At the same time, the prevalence of which is 60% at 3 months and 30% at 6 months or more among patients (Seretny et al. 2014). The peripheral nervous

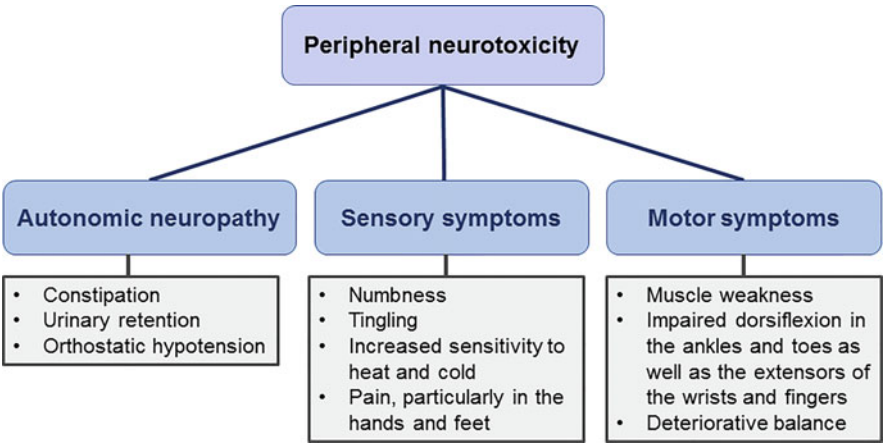

Fig. 2 Classification of the general symptoms of peripheral neurotoxicity

Table 1 Type of peripheral neurotoxicity and clinical pattern of chemotherapy-induced peripheral neuropathy (CIPN) by neurotoxic drug classification

Mitosis inhibitors	Type of peripheral neurotoxicity	Clinical pattern	References
Vincristine	Sensory, motor, and autonomic	Repression of the Achilles–tendon reflex Paraesthesia in the feet and/or hands	Bradley et al. (1970), Gomber et al. (2010), Weiss et al. (1974)
Vinorelbine	Sensory and motor	Distal paraesthesia Decrease or abolition of tendon jerks	Pace et al. (1996)
Paclitaxel	Sensory	Decline in vibration sense in the hands and feet	Hershman et al. (2011)
Docetaxel	Sensory	Tingling in hands or feet Numbness in fingers or toes	Katsumata (2003)
Eribulin mesylate	Sensory and motor	Decrease in motor activities Reduction in the sense in distal toes	Wozniak et al. (2011), Vahdat et al. (2013)
Ixabepilone	Sensory and motor	Numbness and paraesthesias	Vahdat et al. 2012
Platinum agents	Sensory	Cold-induced syndrome Reduced vibratory sensitivity	Calls et al. (2020), Velasco and Bruna (2014)
Bortezomib	Sensory and motor	Distal paraesthesias, numbness, a burning sensation, and neuropathic pain	García-Sanz et al. (2017), Thawani et al. (2015), Zajaczkowska et al. (2019)
Thalidomide	Sensory and motor	Reduction in physical activity Distal weakness in the lower limbs	García-Sanz et al. (2017), Mohty et al. (2010)

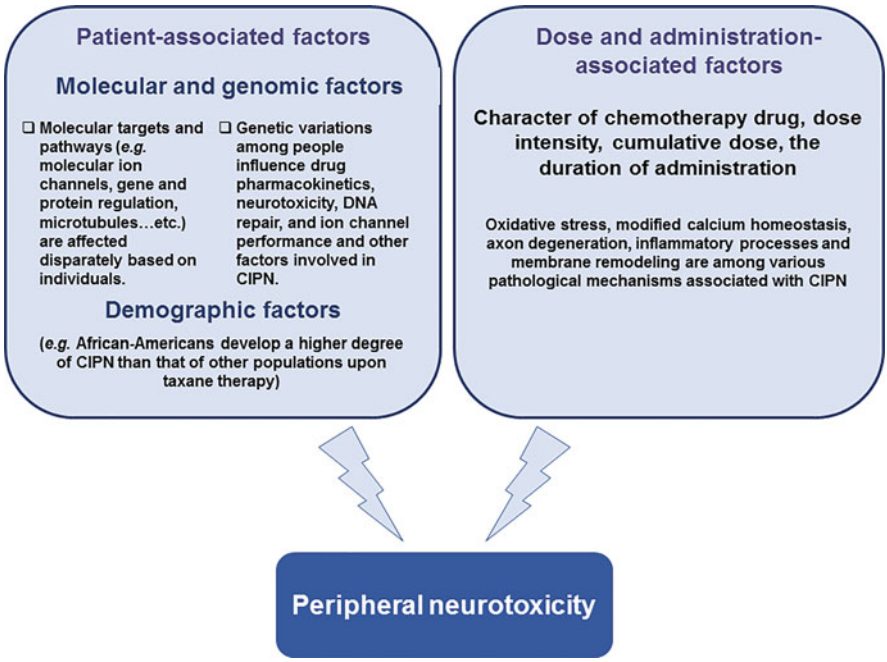

Fig. 3 Factors involved in the development of peripheral neurotoxicity

system generally can regenerate itself in response to injury. Reformation requires adequate time without damage caused by the chemotherapeutic agent. Based on the drug type and dosage, CIPN may be either reversible or irreversible, determining life quality accordingly (Quasthoff and Hartung 2002). Chemotherapeutic agents involved in the occurrence of CIPN comprise anti-tubulin drugs, platinum agents, taxanes, *Vinca* alkaloids, bortezomib, and thalidomide analogs (Cavaletti and Marmiroli 2010; Chan et al. 2019), most of which function against the dorsal root ganglia (DRG) neurons or the peripheral nerve axons due to lower efficacy of the blood–nerve barrier at these sites (Cavaletti and Marmiroli 2010).

Factors involved in the occurrence of peripheral neurotoxicity mainly consist of two groups: (1) Patient-associated factors and (2) Dose and administration-associated factors (Fig. 3).

Patient-associated factors comprise molecular, genomic, and demographic predictors of CIPN. As the response to the specific drug differs from patient to patient, CIPN development and intensity may vary based on the particular genetic variation of an individual by affecting drug pharmacokinetics, neurotoxicity, DNA repair, and ion channel performance (Chan et al. 2019). Elderly patients were at higher risk for neurotoxicity in some studies (Bulls et al. 2019; Raphael et al. 2017), while no association between age and higher CIPN incidence has been reported so far (Argyriou et al. 2006). The variance among individuals may arise from their accompanying comorbidities and demographic factors. For instance, a higher rank

of CIPN was common in diabetic patients, in contrast to the reports of patients with autoimmune diseases, which were related to the decreased odds of neuropathy (Hershman et al. 2016). Furthermore, in the case of obesity co-occurrence, the severity of CIPN symptoms may enhance reducing life quality compared to nonobese patients (Cox-Martin et al. 2017). Another example is the impact of demographic features that African Americans represented a higher degree of CIPN than that of other populations developed CIPN upon taxane therapy (Schneider et al. 2015).

Regarding dose and administration-associated factors, pathophysiology, clinical and biological predictors influenced the occurrence of CIPN. The type and intensity of peripheral neurotoxicity mainly rely on the character of chemotherapy drug, dose intensity, cumulative dose, and the duration of administration forming clinical predictors. CIPN may vary based on the type of cytotoxic drugs. Since these drugs can affect either directly sensory neurons or other cell types inducing off-target effects. Various pathological mechanisms may lead to CIPN development, including oxidative stress, modified calcium homeostasis, axon degeneration, inflammatory processes, and membrane remodeling (Argyriou et al. 2008; Mironov et al. 2005; Starobova and Vetter 2017).

The existence of genetic polymorphisms in patients may also lead up to the development of CIPN in the case of chemotherapy exposure by affecting molecular targets and pathways (Chan et al. 2019). Apart from drug type and dose, the presence of existing diseases (e.g., diabetes, alcohol neuropathy, etc.) may also increase the grade of neuropathy (Quasthoff and Hartung 2002).

CIPN is a significant adverse effect of cancer therapy, reducing life quality. In the present overview, we will review the factors involved in the pathogenesis of CIPN as a representation of neurotoxicity. Conventional mitosis inhibitors may usually act as neurotoxic chemotherapeutic agents. In contrast, medicinal plants and their phytochemical constituents mostly exhibit neuroprotective and/or neuropreventive properties (Fig. 1), which will be exemplified and discussed. Future perspectives for the prevention or treatment of CIPN occurrence will be further put forward.

2 Peripheral Neurotoxicity of Mitosis İnhibitors

2.1 Tubulin-Binding Agents

Owing to the highly dynamic character of the microtubule system of eukaryotic cells linked to cell division and cell function, it is an interesting target for drug discovery (Dumontet and Jordan 2010; Karsenti and Vernos 2001). To date, agents interfering with tubulin represent a wide range of classes of agents with significant antitumor activity. Tubulin-binding agents include both naturally occurring and semisynthetic agents, which inhibit cell division by blocking microtubule dynamics (Dumontet and Jordan 2010). The *Vinca* alkaloids, discovered more than 60 years ago (Noble et al. 1958), and the taxanes firstly identified more than 40 years ago (Wani et al. 1971) are

among the commonly administered agents in various malignancies (Minev 2011). These drugs have been usually incorporated into multi-agent chemotherapy regimens (Islam et al. 2019; Reck et al. 2020) to achieve more effective treatment outcomes.

Tubulin-binding agents are usually derived from natural sources and can bind to tubulin and/or microtubule (Dumontet and Jordan 2010). Microtubules consist of a backbone of tubulin dimers and microtubule-related proteins (Dustin 1980). Each tubulin molecule is formed by two globular subunits α- and β-tubulin and is represented by a sequence of nearly 450 amino acids and a molecular weight of 50 kD (Downing and Nogales 1998). α- and β-tubulin monomers come together as heterodimers to form a head to tail arrangement for the construction of protofilaments (Amos and Baker 1979). Microtubules are constituted by 12 or 13 protofilaments adjusted in parallel with similar polarity and have a role in intracellular transport, signaling, and mitosis (Perez 2009). Microtubule-targeting agents present highly structural diversity and structural complexity and are frequently obtained from medicinal plants or marine organisms in quite low amounts (Amador et al. 2003; Moudi et al. 2013). Taxanes, *Vinca* alkaloids, epothilones, halichondrins, maytansinoids are among the tubulin-binding agents, which influence microtubule dimerization and dynamics in different ways (Dumontet and Jordan 2010). All of these compounds are antimitotic agents, which block cell proliferation by interfering with microtubules and inhibiting microtubule dynamics during specifically the mitotic stage of the cell cycle. Mainly, the microtubule-targeted antimitotic drugs are categorized into two principal groups the microtubule-destabilizing and microtubule-stabilizing agents. Microtubule-destabilizing agents repress microtubule polymerization at high concentrations and interact with one of two domains of tubulin, which are the "*Vinca*" and "colchicine" domains. *Vinca* alkaloids, the dolastatins, eribulin, and maytansinoids are among the *Vinca*-site binders. Colchicine-site binders comprise various molecules of different origins such as podophyllotoxin, combretastatin colchicine, and its analogs (Dumontet and Jordan 2010). The microtubule-stabilizing agents increase microtubule polymerization at high drug concentrations, among which paclitaxel, docetaxel, the epothilones, and ixabepilone are well-known drugs. The stabilizing agents usually interact with the exact position of the taxoid binding site on beta-tubulin (Buey et al. 2005).

2.1.1 Vinca Alkaloids

Vinca alkaloids comprise a subset of drugs obtained from the Madagascar periwinkle plant. The substantial *Vinca* alkaloids in clinical use are either naturally occurring (vincristine and vinblastine) or semisynthetic (vindesine and vinorelbine) agents obtained from the pink periwinkle plant *Catharanthus roseus* G. Don (formerly: *Vinca rosea*) (Islam et al. 2019; Moudi et al. 2013). They bind intracellular tubulin and obstruct microtubule polymerization leading to the interruption of mitotic spindle formation and prohibiting cell division. *Vinca* alkaloids are commonly used against hematological malignancies, such as pediatric acute lymphoblastic

leukemia. Besides, they can be included in multidrug chemotherapy regimens in a wide range of cancers in adults (Islam et al. 2019; Weiss et al. 1974). *Vinca* alkaloids have usually been applied as direct intravenous injection or continuous infusion and highly metabolized and eliminated by the hepatobiliary system through cytochrome P450 3A (CYP3A) enzyme system (Saba et al. 2015).

Vincristine is the most neurotoxic one among the *Vinca* alkaloids with extensive distribution in body tissues apart from the central nervous system (CNS) due to hindering property of blood–brain barrier. However, it may lead to the development of vincristine-induced peripheral neuropathy (VIPN) even at lower cumulative dosages (Lavoie Smith et al. 2015).

Indicators of VIPN are substantially divided into three categories as sensory, motor, and autonomic neuropathy (Mora et al. 2016; Lavoie Smith et al. 2015). Numbness and tingling, neuropathic pain are common features of sensory neuropathy in the upper and lower extremities (Mora et al. 2016). Motor involvement is also a well-known disabling manifestation of vincristine neurotoxicity, impairing the dorsiflexion in the ankles and toes as well as the extensors of the wrists and fingers (Bradley et al. 1970; Casey et al. 1973). The earliest and universal indication of vincristine neurotoxicity is the repression of the Achilles–tendon reflex (Weiss et al. 1974), which can be either asymptomatic or a stage subsequently giving rise to depression of other deep tendon reflexes (Casey et al. 1973). Paraesthesia in the feet and/or hands is another subjective manifestations of VIPN, usually arises in the early weeks of therapy (Bradley et al. 1970). Hyporeflexia, a decline in deep tendon reflexes are the signs and symptoms of both sensory and motor VIPN. Indications of autonomic neuropathy mainly comprise constipation, urinary retention, and orthostatic hypotension (Gomber et al. 2010).

A number of mechanisms induce VIPN, among which axonal degeneration in peripheral nerves (Gottschalk et al. 1968) and axonal transport dysfunction (Topp et al. 2000) are of significance that axonal degeneration is a SARM1 dependent cellular process (Gerdts et al. 2016) and mice were reported to alleviate vincristine-induced neuropathy in case of its genetic deficiency (Geisler et al. 2016). Larger doses or smaller time intervals may markedly increase VIPN (Diouf et al. 2015). Vincristine is administered intravenously through bolus injections or prolonged infusions. The way of administration also affects the VIPN development and intensity that vincristine (if administered intravenously as bolus injection in comparison to prolonged infusion) caused increased VIPN occurrence in children due to reaching out high concentration in plasma (Kellie et al. 2004). Pharmacokinetic profiles and genetic factors of patients are further factors determining the risk and intensity of VIPN. The general concept about vincristine plasma clearance is that the children have higher vincristine clearance than the adults (Crom et al. 1994), representing a reduced risk of VIPN occurrence in children. Another study conducted by Egbelakin et al. (2011) unraveled that children with precursor B cell acute lymphoblastic leukemia faced less VIPN in case they had a higher CYP3A5 expression genotype than CYP3A5 non-expressers (Egbelakin et al. 2011). Many researchers have pointed out the relationship between the VIPN phenomenon and DNA single nucleotide polymorphisms (SNPs). For instance, an SNP in the

centrosome protein encoded by *CEP72* gene was involved in the VIPN development through improving the susceptibility of neuronal cells to vincristine damage (Diouf et al. 2015). Moreover, other SNPs such as CAMKK1 (calcium/calmodulin-dependent protein kinase 1), CYP2C8 (cytochrome P450 Form 1) and CYP2C9 (cytochrome P450 PB-1), NFATC2 (nuclear factor of activated T-cells 2), ID3 (inhibitor of differentiation 3), and SLC10A2 (apical sodium-dependent bile acid transporter) have been proposed to participate in vincristine-induced neuropathy (Johnson et al. 2011). Newly developed lipid-coated or liposomal vincristine has improved the pharmacokinetics and pharmacodynamics of vincristine easing its neurotoxicity (Shah et al. 2016; Silverman and Deitcher 2013).

A semisynthetic *Vinca* alkaloid vinorelbine (5′-nor-anhydro-vinblastine) is used as a single agent or in combination with other drugs against breast cancer, non-small cell lung carcinoma and other malignancies (Furuse et al. 1996; Toso and Lindley 1995). Similar to other *Vinca* alkaloids, vinorelbine blocks axonal transport but at higher concentrations compared to vincristine and vinblastine. Besides, it has a higher selective affinity for tubulin and lower activity on axonal microtubules, leading to less neurotoxicity than other *Vinca* alkaloids (Pace et al. 1996; Toso and Lindley 1995). A randomized study of vinorelbine versus vindesine showed that the peripheral neurotoxic effects of vinorelbine were milder than that of vindesine (Furuse et al. 1996). Despite vinorelbine itself did not exert clinically relevant neurotoxicity in many studies, the neurotoxic injury may intensify in case of a combination of which with other chemotherapeutics such as platinum compounds and paclitaxel (Pace et al. 1996).

2.1.2 Taxanes

Taxanes are spindle poisons inducing PN, which mostly include sensory or motor neuropathy based on the type of nerve fibers affected (Swain and Arezzo 2008). The common aspect of taxane-induced PN is that taxanes bind to the β-tubulin subunit of microtubules, causing the stabilization of microtubules and the disruption of microtubule function, which influences the structures and functions of neurons resulting in neuropathy (Rivera and Cianfrocca 2015). Taxanes usually gather in the soma of sensory neurons of DRG. The process contributing to the neurotoxicity is vice versa to the general proceeding that it often initiates at distal nerve endings followed with the Schwann cell, neuronal body, or axonal transport alterations (Argyriou et al. 2008; Chan et al. 2019).

The level of neuronal damage relies on various factors such as cumulative dose, duration of the agent, and the chemotherapeutic used (Guo et al. 2019; Wolf et al. 2008). The impact of agents in toxicity profiles is diverse based on their formulation. For instance, polyoxyethylated castor oil, or Cremophor® EL (recently renamed Kolliphor® EL), is used in the formulation of paclitaxel. At the same time, docetaxel is formulated with polysorbate 80 (or TWEEN® 80), and solvent-free *nab*-paclitaxel is formed with paclitaxel and human serum albumin at a concentration equivalent to the concentration of albumin in the blood (Summit 2014).

Paclitaxel, a member of taxanes, is a microtubule-stabilizing agent and efficient in the treatment of assorted tumor types including breast, lung, and ovarian cancer (Armstrong et al. 2006; Camidge et al. 2014; Tolaney et al. 2015). However, apart from its non-hematological toxicity, peripheral neurotoxicity is the substantial drawback of paclitaxel (Gornstein and Schwarz 2014; Mielke et al. 2006). The reason for axonal degeneration, secondary demyelination, nerve fiber loss, oxidative stress, and abnormalities in sphingolipids was reported to be linked to peripheral neurotoxicity (Duggett et al. 2016; Gornstein and Schwarz 2014; Kramer et al. 2015). Many investigations uncovered that paclitaxel-induced neurotoxicity is associated with SNPs in cytochrome P450 (CYP) CYP2C8 (Boora et al. 2016), ABCB1 (Abraham et al. 2014; Boora et al. 2016), and TUBB2A (Abraham et al. 2014). However, due to varying replication outcomes, their application in the clinic has not been confirmed. Many studies pointed out the correlation of paclitaxel pharmacokinetics with PN occurrence (Hertz et al. 2018; Scripture et al. 2006). A meta-analysis conducted by Guo et al. (2019) unraveled the dosage and the type of administration that may affect the severity and incidence of PN. Since solvent (Cremophor EL)-based paclitaxel-induced PN inclined lower rate of peripheral neurotoxicity in patients receiving monochemotherapy if compared with *nab*-paclitaxel (an albumin-bound formulation of paclitaxel free from Cremophor EL) (Guo et al. 2019). On the other hand, some clinical studies showed that intense neuropathy remained a long time in patients with metastatic breast cancer following the termination of paclitaxel and docetaxel therapy in comparison to *nab*-paclitaxel treatment (Cortes and Saura 2010; Gradishar et al. 2012).

Docetaxel is a member of the taxoid family obtained via a semisynthetic procedure from the needles of *Taxus baccata* (Chabner and Longo 2011). Docetaxel has been exhibited convincing in vitro and in vivo cytotoxic activity toward various tumor types such as breast, lung, and ovarian cancers (Katsumata 2003). Like paclitaxel, docetaxel functions as a spindle poison inducing the blockage of microtubule dynamics and cell cycle arrest (Ringel and Horwitz 1991). Despite having shared tubulin binding sites and identical characters, the mechanistic and pharmacological variations in between are available. To exemplify, docetaxel is a more potent promoter of tubulin polymerization in vitro with a longer intracellular half-life and exhibits better activity in several tumors (Bissery et al. 1996; Katsumata 2003; Ringel and Horwitz 1991). More effective cytotoxic profile of docetaxel ranges between 1.2- and 2.6-fold than paclitaxel and more than 1000-fold than cisplatin or etoposide in ovarian carcinoma cells were reported previously (Engblom et al. 1997; Kelland and Abel 1992). Likewise, docetaxel and paclitaxel have mainly different toxicity profiles. Noteworthy, docetaxel is associated with minimalized neurotoxicity and suggested as an alternative therapy to paclitaxel for the combination therapy with platinum-based regimens against advanced ovarian cancer (Katsumata 2003; Vasey 2002).

The incidence and intensity of taxane-associated neurotoxicity depend on dose levels, the cumulative dose, and probably the use of paclitaxel with other chemotherapeutics such as cisplatin. Furthermore, predisposing factors such as preexisting PNs contribute to the emergence of neurotoxicity (Mielke et al. 2006). Mielke et al.

(2003) performed research to contrast weekly 1 h infusion of paclitaxel to 3 h infusion in patients with progressive cancer of different origin (substantially breast and lung) placing neurotoxicity to the forefront. A high rate of peripheral neurotoxicity with a significant difference was noted in both infusions, suggesting the occurrence of a strong cumulative property of peripheral neurotoxicity (Mielke et al. 2003). A dose-escalation study to determine pharmacodynamics of non-break weekly paclitaxel and pharmacokinetics of the vehicle Cremophor-EL (CrEL) demonstrated that clinically significant PN usually occurs at around 1500 mg/m^2 cumulative dosage at the weekly interval and CrEL levels do not significantly accumulate at doses up to 90 mg/m^2 (Briasoulis et al. 2002).

A phase III trial study to determine the optimal duration of chemotherapy showed that later courses of therapy were associated with persistent neuropathy that patients with advanced non-small cell lung cancer receiving first-line paclitaxel plus carboplatin exhibited higher grades of peripheral neuropathy from cycle 4 (20%) to cycle 8 (43%) (Socinski et al. 2002). In another randomized trial, comparative pharmacokinetics of unbound paclitaxel during 1- and 3-h infusions were evaluated. The attenuation in the infusion duration time from 3 to 1 h decreased in the area under the curve (AUC) for unbound paclitaxel in contrast to the AUC of CrEL increased. The study pointed out shorter infusion regimes may be attributable to the occurrence of less severe paclitaxel-associated peripheral neurotoxicity but potential CrEL-related adverse effects, suggesting a challenge to foresee which infusion model (1 or 3 h) is beneficial due to the characters of both paclitaxel and CrEL inducing PN (Gelderblom et al. 2002). Still, the outcomes of many studies mostly reached an agreement about the fact that exposure to paclitaxel might be intimately related to the peripheral neurotoxicity development rather than CrEL. Since, peripheral neurotoxicity developed in patients with advanced malignancies in case of the administration of two CrEL-free formulations including ABI-007 (a novel CrEL-free, protein-stabilized, a nanoparticle formulation of paclitaxel) and Genexol-PM (a polymeric micelle formulated paclitaxel free of CrEL) (Ibrahim et al. 2002; Kim et al. 2004). Surprisingly, in another clinical study, docosahexaenoic acid (DHA)-paclitaxel, a conjugate produced by covalently binding of the natural fatty acid DHA to paclitaxel containing CrEL introduced no cases of severe PNP, which was probably due to extended exposure to very low concentrations of paclitaxel (Wolff et al. 2003). Long-term complications of taxane-associated peripheral neuropathy also differ among patients based on the time after drug exposure discontinuation. For instance, paclitaxel and docetaxel-related PN appeared in 64% of patients who were in 1–13 years post-taxane therapy after the end of the last cure and ceased 14% of them despite the symptoms, which were well-tolerated (Osmani et al. 2012). In another study, among patients receiving 6 months to 2 years of post-taxane therapy, 81% demonstrated symptoms of PN. Among these patients, 27% exhibited severe symptoms in their hands in addition to 25% in their feet (Hershman et al. 2011).

The impact of taxane-induced neuropathy may vary among other chemotherapeutics targeting tubulin. Eribulin mesylate, a microtubule-targeting antineoplastic agent presented relatively lower neuropathy in mice than paclitaxel or ixabepilone at the equivalent maximum tolerated dose (MTD)-based doses. Notable loss of caudal