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A Literary review on Chemotherapy Induced Peripheral Neuropathy (CIPN) - An Ayurveda approach

Review Article

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Abstract

Cancer is a leading cause of mortality worldwide; however advanced medical diagnostic techniques and medical interventions reduced the mortality considerably. But adverse effects due to chemotherapy decreased the quality of life, Chemotherapy induced peripheral neuropathy (CIPN) is such entity as till now no established treatment protocol is not available. Hence, alternative methods of preventing or treating CIPN are necessary. Many studies found that herbal medicines showed potentially beneficial effects on CIPN. Treatment modalities in ayurvedic science should be given to the CIPN and to assess the effectiveness of herbal medicines for CIPN, a systematic review and study is essential in ayurveda to treat Chemotherapy Induced Peripheral Neuropathy. CIPN most commonly presents as a pure sensory neuropathy with symmetric symptoms typically including numbness, loss of proprioception sense, tingling, pins and needles sensation, hyperalgesia or allodynia in the hands or feet in a stocking-glove distribution. Occasionally there can be damage to motor fibers resulting in a motor neuropathy. Autonomic neuropathy can be associated with orthostatic hypotension, severe constipation, and erectile dysfunction. In ayurveda symptomatology it can be corelated to *Aganthuja vata-pitta vikara* having *alpa-bala-ojokshaya* condition. In cancer there is much reduced *Oja*, and *bala* chemotherapy having properties of *visha guna* and *vata-pitta* vitiation causes *dhatu*, *upadhatu*, *mala* and *indiriya pradoshaja vikara* with predominance of *vata* nature like *Gatrasuptata* (~numbness), *Spandanam* (~twitching sensation), *Bheda* (~splitting pain), *Toda* (~excruciating pain) and *Pitta* nature like *Daha* (~burning sensation), *osha* (~heat feel), *Plosha* (~scorching), *Dhoomaka* (~feeling as smoke being eliminated from mouth/face). Moreover, these symptoms are described in *vataja nanatmaja* and *pittaja nanatmaja vikaras.*

Key Words: Chemotherapy, Peripheral Neuropathy*, Vata-Pitta Vikara, Dushi Visha,* Cancer.

Introduction

Cancer is currently a leading cause of mortality worldwide. However, thanks to advances in medicine and modern technology, the availability of sensitive tests and diagnostic methods to detect cancer at an early stage and the use of increasingly effective treatments, including chemotherapeutic agents, the number of cancer survivors is rising. Although these survivors may have beaten cancer, many of them have poor outcomes due to several syndromes that reduce the quality of life because of cancer treatment, including pain, which they often experience for a long time after completing their cancer treatment. Unfortunately, these drugs also affect normal cells and structures of the body, causing various deleterious and sometimes even devastating side effects (e.g., anemia, diarrhea, nausea, vomiting, infections, neurological changes, fatigue, hair loss, infertility, pain, and peripheral neuropathy) which may necessitate the tapering of chemotherapy regimens or even their cessation, thereby limiting the efficacy of cancer treatment (1)

Peripheral neuropathies in cancer patients are most often due to neurotoxic chemotherapeutic agents, the so-called chemotherapy-induced peripheral neuropathy (CIPN); less frequently they occur as paraneoplastic, immune-mediated, or neoplastic neuropathies. CIPN is often a painful, dose-limiting side-effect that likely will increase in prevalence due to the progress made in cancer survival. CIPN is a common clinical problem; approximately 30–40% of patients receiving neurotoxic chemotherapy will suffer from this condition and it significantly increases the annual costs of healthcare. Several classical chemotherapeutics (platinum, vinca alkaloids, taxanes) are well-established causes of CIPN. Newer agents also induce this side-effect despite different modes of more targeted cellular action Clinically, CIPN manifests itself as deficits in sensory, motor and/or autonomic functions of a varying intensity. CIPN is a mostly sensory neuropathy that may be accompanied by motor and autonomic changes of varying intensity and duration.

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Due to its high prevalence among cancer patients, CIPN constitutes a major problem for both cancer patients and survivors as well as for their health care providers, especially because, at the moment, there is no single effective method of preventing CIPN; moreover, the possibilities of treating this syndrome are very limited. In severe cases, CIPN can lead to paresis, complete patient immobilization and severe disability. Sensory disorders occur more frequently than autonomic symptoms, which usually involve orthostatic hypotension, constipation and altered sexual or urinary function. Therefore, patients may be cancer-free but may suffer from debilitating neuropathy induced by cancer treatment.

For the present treatment of CIPN relies on reducing or discontinuing the offending agent and multiple drugs have been used to intervene in CIPN, and their effects have been evaluated over the past several decades and effective treatment protocol is not present. The therapeutic potentials of these drugs are limited by unexpected adverse effects and contradictory results, although these drugs have shown benefits in preventing CIPN. Still, no approach has sufficient evidence for recommending use in CIPN treatment. Hence, alternative methods of preventing or treating CIPN are necessary. Many studies found that herbal medicines showed potentially beneficial effects on CIPN (2). Treatment modalities in ayurvedic science should be given to the CIPN and to assess the effectiveness of herbal medicines for CIPN, a systematic review and study is essential in ayurveda to treat Chemotherapy Induced Peripheral Neuropathy (CIPN).

Materials and Methods

The source for this study is collected from the classical Ayurvedic books and commentaries, Modern medical science textbooks and different articles from PubMed, DHARA, Google scholar etc.

Results

In Ayurvedic literature, there is no direct references for Cancer(malignancy), Peripheral neuropathy, and Chemotherapeutic agents. But for the treatment and further development of medical intervention of these pathologies, ayurvedic ideologies and management principles is essential. The symptomatology corresponding to the clinical presentation of Peripheral Neuropathy is scattered in *Purvarupa* (~premonitory symptoms), *Lakshana* (~symptoms) and *Upadrava* (~complications) of *Prameha* and *Vatavyadhi*. After chemotherapy along with other adverse effects there is damage to the peripheral nerves caused by exposure to a neurotoxic chemotherapeutic agent leading to peripheral neuropathy which includes motor, sensory and autonomic symptoms. It is a common serious non hematologic adverse effect of chemotherapy.

Different symptoms of neuropathy can be attributed to involvement of sensory fibers, motor fibers, and autonomic fibers within the peripheral nerves. Trophic changes are believed to be related to a variety of factors, including loss of neurotrophic factors. Many neuropathies result in dysfunction of all types of fibers, but some conditions can result in greater involvement of one subset over others.

Positive symptoms may result from uninhibited or abnormal spontaneous nerve activity, and these may include pain, cramps, and twitching. The type of pain can be quite variable. Neuropathic pain is described as burning, sharp, electric shock-like, but it can also be reported as deep aching pain. It is often useful to ask the patients to localize the pain whether it is on the surface or deep seated. In most length dependent neuropathies, the patients may initially complain that their feet feel as if they are wrapped in stockings. The pain of neuropathy is often more noticeable at rest and during night.

Negative symptoms reflect reduced nerve activity and result in loss of sensation, weakness, ataxia, and atrophy. Patients with distal sensory loss may complain about delayed wound healing and tendency to lose balance after closing eyes or in dark surroundings.

The patients with distal weakness may develop hammer toes and complain of reduced grip strength. When the weakness spreads more proximally, they may report difficulty getting out of low chairs and problems climbing stairs. Recurrent tripping while stepping off curbs may reflect partial foot drop. More chronic conditions can result in deformities such as pes cavus.

Patients with mononeuropathy such as median neuropathy at wrist or carpal tunnel syndrome will complain about pain and nocturnal paresthesia in the affected hand. The symptoms of ulnar neuropathy may include tingling along the inner aspect of forearm and fourth and fifth fingers with numbness of those fingers. These symptoms may be triggered by elbow movements. A patient with radial nerve palsy may wake up with a wrist drop. Peroneal or fibular neuropathy can result in a foot drop but the patient may report slapping gait or tendency for the ankle to “turn” easily(3).

Six main agent groups cause damage to the peripheral sensory, motor, and autonomic neurons, resulting in CIPN development: platinum-based antineoplastics (particularly oxaliplatin and cisplatin), vinca alkaloids (particularly vincristine and vinblastine), epothilones (ixabepilone), taxanes (paclitaxel, docetaxel), proteasome inhibitors (bortezomib) and immunomodulatory drugs (thalidomide)

The taxanes, platinum drugs, vinca alkaloids, thalidomide and bortezomib, all have a high likelihood of inducing CIPN. For some other drugs (such as cyclophosphamide or methotrexate) the likelihood is low with only single cases reported in the literature. It is important to consider the route of drug administration. Methotrexate is rarely associated with neurological toxicity except when administered intrathecally. Bortezomib neurotoxicity decreases with subcutaneous administration. Symptoms of CIPN typically begin during the first two months of treatment, progress while chemotherapy continues, and then stabilize soon after treatment is completed. While most CIPN occurs in a

dose dependent fashion, other drug-specific features may be present such as the acute neurotoxicity of paclitaxel and oxaliplatin, or the worsening of neuropathy after discontinuation of cisplatin (coasting). It would be unexpected for CIPN to appear weeks or months after the last dose of neurotoxic chemotherapy treatment (4).

Chemotherapy-induced peripheral neuropathy most commonly presents as a pure sensory neuropathy with symmetric symptoms typically including numbness, loss of proprioception sense, tingling, pins and needles sensation, hyperalgesia or allodynia in the hands or feet in a stocking-glove distribution. Occasionally there can be damage to motor fibers resulting in a motor neuropathy, which occurs more commonly with paclitaxel and vincristine. Autonomic neuropathy is seen most commonly with vinca alkaloids and can be associated with orthostatic hypotension, severe constipation and erectile dysfunction.

Table 1: Summarizes typical symptoms and signs of CIPN caused by different neurotoxic chemotherapeutic agents (5)

Drug	Touch, thermal, pain sensation impairment	Vibration, position, sensation, impairment, ataxia	Neuropathic pain	Motor impairment	Autonomic symptoms
Cisplatin	++	+++	++	-	+
Carboplatin	+	++	-	-	-/+
Oxaliplatin	++	+++	+	-	+/-
Paclitaxel	++	++	+	++	+/-
Docetaxel	++	+	+	+	+/-
Vincristine	++	+	++	++	+++
Bortezomib	+++	+	+++	+	+/-
Thalidomide	++	+	+	+	-

In Ayurvedic symptomatology, sign and symptoms of CIPN are scattered in *vata pitta vikara* and *vataja* and *pittaja nanatmaja vikara* (Table No.2) After chemotherapy there is damage to the peripheral nerves caused by exposure to a neurotoxic chemotherapeutic agent leading to peripheral neuropathy which includes *Vata* symptoms like *Gatrasuptata* (~numbness), *Spandanam* (~twitching sensation), *Bheda* (~splitting pain), *Toda* (~excruciating pain) and *Pitta* symptoms like *Daha* (~burning sensation in whole body), *osha* (~heat feel), *Plosha* (~scorching), *Dhoomaka* (~feeling as smoke being eliminated from mouth/face). Moreover, these symptoms are described in *vataja nanatmaja* and *pittaja nanatmaja vikaras*(6),(7),(8).

With cancer and their treatment effect, there is considerable *Oja kshaya* in the subject. In cancer patients post-chemo, post-radiation, *Sharira balam* (physical strength) and *Satva balam* (mental strength) will be much reduced (9). *Agni* (the digestive strength and metabolic rate of the body tissues) along with *Ojas* (an extremely subtle substance produced in healthy body which gives strength and vigor par excellence and protect from onslaughts) is responsible factor for the vitality of the body. CT agents and other interventions causes imbalanced *Agni* and *Vata Pitta dosha* (10), eventually causing *ama* (represents impurities and toxins in the body) formation, decreased *dhatu Agni*, *Dhathukshayam* (*Dhatus* are the body tissues & *Dhatu agni* is the metabolic rate of the *dhatus*.) and finally *Ojokshaya* (Figure 1).

Cancer and post therapeutic cancer condition is an *Oja Kshaya-Alpa Bala-Dhatu Kshaya* condition and there will be inappropriate metabolism where the function of *Agni* is impaired.

Ayurveda and Vedic doctrines lay emphasis on the concept of *Ojas* its role in human immune-resistance in maintaining integrity of the body. The *Vishas* (substances having poisonous property) are regarded as endangering substances having properties opposing *Ojas*(11). Cancer immunoediting from immune and harboring then can slowly expose the body elements to immune-related diseases including cancer. Cancer patients show extremely low *Ojas* evident in clinical examination of documented cases which supports the immune-compromised status explained in modern oncology (12).

Discussion

Acharya Chakrapani in Charaka Samhita described *Aushadha Dravya* classification according to potency (Veerya) of Aushadha Dravya that is (a)*Mridu Virya,* (b)*Madhyam Virya,* (c)*Tikshna Virya* (13).

Chemotherapy agents for cancer therapy can be classified under *tikshna veerya aushadha* and possess properties like high potency, action at cellular, microcellular, gene level, DNA level, highly penetrating, selective toxicity etc. On basis of those characteristics, an attempt has been made to correlate/ compare the characteristics of chemotherapeutic agents.

Characteristics of chemotherapeutic agents can be understood considering concept of vishadrayas. As perAyurveda the properties of the *Visha dravyas* are *Ruksha* (*guna*-dry), *Ushna* (*veerya*-hot), *Tikshna* (penetrating), *Sukshma* (entering in to minute pores), *Ashu* (quick acting), *Vyavayi* (spreading all over the body), *Vikasi* (debilitate the tissues), *Vishada* (non-unctuous), *Laghu* (light) and *Apaki* (indigestible). Due to its *Rukshata* it aggravates *Vata*; by its *Ushnavirya* it aggravates *Pitta* and *Rakta*; by its *Tikshna* property causes delusion of the mind and breaks the binding of the vital organs; by its *Sukshmata* it enters in to all organs and causes abnormalities in them; by its *Ashu guna* it destroys the tissues quickly; by its quality of *Vyavayi* it spreads to the whole body; by its *Vikasi guna*

Table 2: Showing Sensory, Motor, Autonomic signs & symptoms of Peripheral Neuropathy in terms of *Vata* & *Pitta Vikara*

	Sensory manifestations	Motor manifestations	Autonomic manifestations
Vata	• *Svapa/supti*(~numbness) • *Suchibi nistoda*(~pins & needles) • *Pipeelika sanchara eva*(~tingling sensation) • *Spandanam* (~twitching sensation) • *Bheda* (~splitting pain) • *Toda & shula* (~excruciating pain) • *Sparsha vaigunya*, (~abnormal tactile perception) • *Twak shosha* (~dryness of skin) • *Padashula (pain in foot),* • *Padasuptata(numbness of foot)*	• *Mamsopachaya shosha* (~wasting) • *Dourbalyam & Angasada*(~weakness) • *Padabhramsha* (~foot drop) • *Vatakhuddata* (~club foot) • *Gulphagraha* (~stiff ankle) • *Bahusosha* (~atrophy of arm) • *Kampa/vepadu* (~involuntary movement) • *Pindikodweshtana* (~cramps in calf) • *Greevastambha*, *Manyastambha* (cramps in neck)	• *Shiroruk (*~headache*)* • *Shankabheda*(~severe headache) • *Akshishula* (~pain in eyes) • *Udavarta* (~mis peristalsis) • *Vidbheda* (~diarrhoea) • *Asvapna* (~sleeplessness) • *Hrinmoha* (~bradycardia) • *Hridrava* (~tachycardia) • *Bhrama, Tama* • (~Postural dizziness and syncope)
Pitta	• *Daha* (~burning sensation) • *Osha* (~heat feel) • *Plosha* (~scorching) • *Dhoomaka* (~ feeling as smoke being eliminated from mouth/face) • *Davadhu*(~boiling) • *Vidaha*(~pyrosis) • *Twak daha*(~burning -sensation of skin)		• *Tamapravesha*(~fainting) • *Atisveda &Asveda* (~abnormal sweating pattern) • *Ushmadikya* (~feeling of excessive temperature) • *Atripti* (~non satisfaction) • *Angavadarana*, *rakthamandala, raktakotha*, etc(~changes in skin color)
Kapha	**Sensory neuropathic signs & symptoms** • Numbness or loss of sensation • Pain, tingling, burning feet • Allodynia • Hyperalgesia • Paresthesia: tingling, crawling sensation • Unsteady gait and falls • Glove and stocking sensory loss • Sensory ataxia • Positive Romberg sign • Reduced or absent reflexes • Pseudoathetosis	**Motor neuropathic signs & symptoms** • Weakness: difficulty gripping objects, tendency to trip easily • Loss of muscle mass • Muscle twitching • Muscle cramps • Distal weakness • Atrophy and fasciculations in some cases • Reduced or absent reflexes	**Autonomic neuropathic signs & symptoms** • Postural dizziness and syncope • Sexual dysfunction: erectile dysfunction, retrograde ejaculation • Bladder involvement • Easy satiety, constipation, or diarrhea • Dryness of mouth, eyes, and skin • Orthostatic hypotension • Skin changes • Abnormal sweating patterns • Hyperemia or pallor

it loosens the *Dosa*, *Dhatu* and *Mala* and destroys them; by its *Vishada guna* it does not adhere to any place; by its *Laghu guna*, it is difficult to cure and by its *Apaki* nature it is difficult to expel it out and have creates trouble in the body for long time(14). Similarly, CT agents also cause manifestations as like that of *visha dravyas* and causes *vata-pitta-raktha kopa*, moreover the adverse effects of chemotherapeutic agents shows *vata-pitta kopa*.

More characteristics of chemotherapeutic agents can be understood particularly under the concept of *dushivisha* and *garavisha*.

Krutrim	Indicates artificial/manmade i.e., CT agents
Dehatsesham	Impaired excretion of CT agents
Swabhavato	Pharmacodynamics
Viryam Alpam	Selective toxicity
Varsaganubandhi	Delayed Toxicity

Acharya Susruta and *Vagbhata* described *Dushi visha* as any kind of poison originating from inanimate or animate sources or any artificial poison (*Kritrima visha*) retained in the body after partial expulsion or which has provisionally undergone detoxification, by the anti-poisonous drugs, forest fire, the wind or the sun is termed latent poison (*Dushi visha*)(15). Any poison that is devoid of the natural ten properties of *visha*, incapable of producing acute symptoms of poisoning can also be designated *Dushi visha*. A poison, which is having fewer properties, which means less than ten classical properties that actually a poison should have, or either the poison, which is having lesser potency of all the ten properties, attains a latent or hidden stage in the body called Latent poison (*Dushi visha*). Low potency of all the ten qualities is said to be responsible for the delayed action and cumulative toxicity on the body (16). Because of the low potency of the poison, it usually will not cause sudden death. Because of the enveloping (*Avarana*) action by humor *Kapha*, these low potency poisons are retained in the body for a long period without producing any grave or fatal symptoms.

The action of chemotherapeutic agents on normal tissues of body can be categorized as Abheshaja which is of two types(17) - A) *Badhan* – Acute toxicity &) *Sanubadhan* – Delayed Toxicity

CIPN may be *badhana* & *sanubadhana* variety more often in *sanubadhana* category. Neuropathic symptoms may start days after the first dose. They are dose dependent and tend to improve after stopping the treatment. In some patients, symptoms can continue up to 1–3 years after completion of the therapy and can sometimes last lifelong (18).

These *Visha Dravyas* or CT Agents are modified cytotoxic agents which are used to destroy cancer cells but these agents works as two edged sword and destroy healthy normal fast growing cells like gastro-intestinal tract, mucous membrane, skin, hair roots etc. In Ayurveda, various poisonous drugs have been used for welfare of human kind. However, Ayurveda has adopted a special technique called *Shodhana Karmas* to neutralize or reduce the unwanted qualities of *Visha Dravyas*, so that least damage to the body is done. Many a times Ayurveda has tried to transform the poisonous drugs in a fully beneficial form which is called as *Amritikarana*. Though in modern medicine, lot of research is going on in reducing the toxic effects of modern chemotherapeutics drugs still these drugs are producing unwanted symptoms

Pathophysiology of CIPN in ayurveda

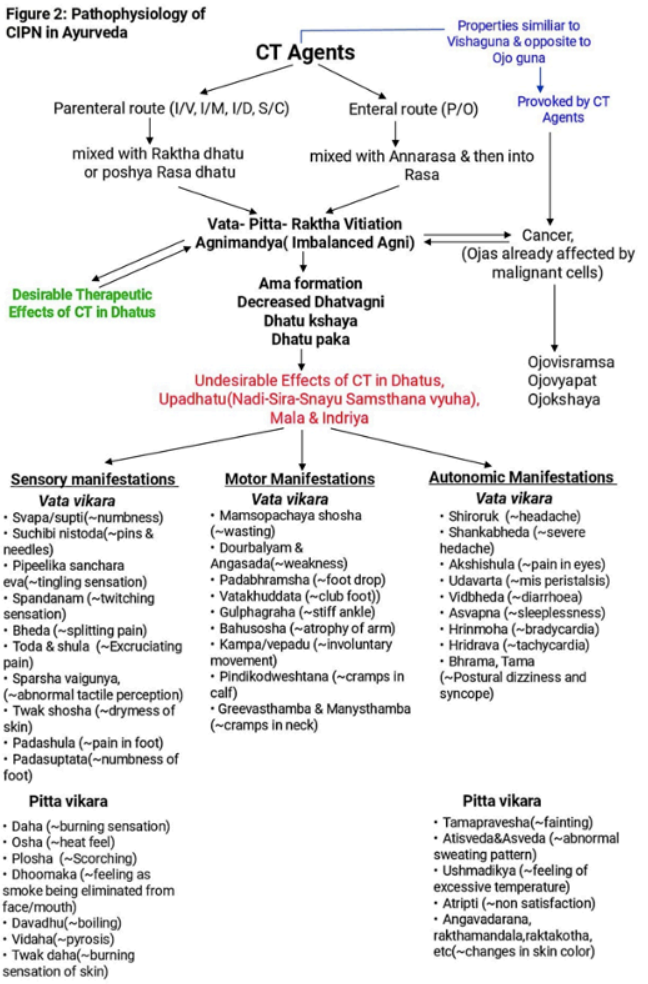
The CT agents administered parenterally mixes with *raktha dhatu* or *poshya rasadhatu* while with enteral route assimilates into *annarasa* and then into *rasa*, CT agents has properties similar to *visha* and causes *vata-pitta-raktha* vitiation which results into desirable and undesirable effects. *Vata-pitta(raktha kopa*) leads to ama formation, decreased *dhatvagni*, *dhatukshaya* and *dhatu paka* resulting to *vata pitta vikara* in *dhatu*, *upadhatus* especially in *sira-snayu-nadi samsthanavyuha*, *mala* and *indriya* as showed in figure 2.

Table No.3

Chemotherapy Induced Adverse Events	Dhatu Involved
Nausea	*Rasa*
Vomiting	*Rasa*
Anorexia	*Rasa*
Mucositis	*Rasa, Rakta*
Febrile neutropenia	*Rasa, Rakta, Majja*
Skin reactions	*Rakta*
Cachexia	*Sapta dhatus*
Malaise	*Mamsa*
Alopecia	*Rasa, Asthi*

CT induced *Vata Pitta Kopa* causes respective *dhatu dushti* and *dhatu vikara* (Table 3) like *hrillasa* and *chardi* in rasa dhatu may be corelated to Chemotherapy induced vomiting and nausea, *raktha dhatu* vitiation resulting into *asyapaka, mukapaka*, can be depicted as Chemotherapy induced stomatitis.

Figure 2: Pathophysiology of CIPN in Ayurveda



Present study is concise to CT Induced *Vata-Pitta Kopa* causing peripheral neuropathy.

In cancer patients there is considerable *Ojokshaya*, this is again provoked by CT agents resulting into advanced effects of *Ojovikriti* viz *Oja visramsa* - *Sandhi vislesha* (looseness of joints), *Gatra sadan*a (numbness of limbs) and *Dosha chyavana* (dislodgement of the deranged humour from their respective receptacles) and *Kriya sannirodha* (immobility), *Ojovyapat* - *Sthabdaguru gatrata* (stiffness and feeling of heaviness of the body), *Vatashopha* (oedema), *Varnabheda* (discoloration, *Glani* (exhaustion), *Tantra* (stupor) *Nidra* (more of sleep). *Ojakshaya* - *Murcha* (Fainting), *Mamsakshaya* (loss or decrease of muscles), *Moha* (delerium), *Maranam* (death) (19) are very much identical to that of moderate and severe stages of cancer of any type.

The Patho-mechanism by which chemo-therapeutics damage the nervous system structures and cause CIPN is multifactorial and involves microtubule disruption, oxidative stress, and mitochondrial damage, altered ion channel activity, myelin sheath damage, DNA damage, immunological processes and neuroinflammation.

Chemotherapy Induced Peripheral Neuropathy (CIPN) can be corelated to as *Aganthuja Vata Pitta Janya Roga* having *ojokshaya-albabala-dhatukshaya* condition. Chemotherapy agents have the properties similar to visha guna particularly that of dushi visha.

In CIPN If the complications appear by affecting various systems, this is possibly because of the vatic

character of the disease or predominance of vata in the disease along with the vitiation of *Oja*. Gradual loss of *vyadhi kshamatva* or defensive mechanism of the body and in consequence the disease process affects different srotas or system and various complications are manifested. *Apara oja* is related with 8 drops of *para oja*, the site of which is *hridaya* is also the *chetana sthana*; that is why at extreme stage of the disease, *para oja* is vitiated and the patient under goes *bhrama* and *murchha* (Autonomic manifestations) Various supportive and empirical intervention have been reported for the prevention and treatment of CIPN.

Conclusion

Chemotherapy induced adverse events in cancer patients results in depriving effects on quality of life. CIPN is one of the most common delayed effects of chemotherapy agents. Standardized protocols for CIPN management are not available till now. CIPN Promising results have been reported from phase I and phase II trials with these interventions but no definite conclusions can be drawn regarding this approaches because all clinical trials that have been performed were underpowered for their endpoints, utilized unvalidated endpoint assessments or employed non-randomized and/or and uncontrolled trial designs none of these empirical or investigational approaches has become a standard of care or as otherwise documented evidence of benefit in the prevention, mitigation or treatment of CIPN nor has any agent been approved specifically for the treatment of CIPN by the FDA. Symptomatology and pathophysiology of CIPN is understood through ayurvedic literature. Chemotherapy Induced Peripheral Neuropathy (CIPN) can be corelated to as *Aganthuja Vata-Pitta Janya Roga* having *ojokshaya-albabala-dhatukshaya* condition. However; there is still a need to develop a herbal formulation for the management of CIPN that is equivalent or non-inferior to the standard treatment available, and that can be manufactured in a cost effective manner and having minimal side effects and also which is more efficacious than the products known.

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