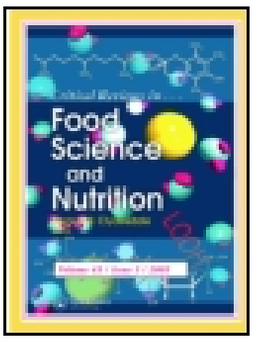

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Herbal Medicines and Chemotherapy Induced Peripheral Neuropathy (CIPN): a Critical Literature Review.

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Abstract

Background: Chemotherapy-induced peripheral neuropathy [CIPN] is a common significant and debilitating side-effect resulting from the administration of neurotoxic chemotherapeutic agents. These pharmaco–chemotherapeutics can include taxanes, vinca alkaloids, platinum analogues and others. Moderate to severe CIPN significantly decreases the quality of life and physical abilities of cancer patients and current pharmacotherapy for CIPN e.g. Amifostine, and antidepressants have had limited efficacy and may themselves induce adverse side-effects.

Methods: To determine the potential use of herbal medicines as adjuvants in cancer treatments a critical literature review was conducted by electronic and manual search on nine databases. These include PubMed, the Cochrane Library, Science Direct, Scopus, EMBASE, MEDLINE, Google Scholar and two Chinese databases CNKI and CINAHL. Thirty-four studies were selected from 5614 studies assessed and comprised of animal studies, case reports, retrospective studies and minimal randomized clinical trials investigating the anti-CIPN effect of herbal medicines as the adjuvant intervention in patients administered chemotherapy. The thirty-four studies were assessed on methodological quality and limitations identified.

Results: Studies were mixed in their recommendations for herbal medicines as an adjuvant treatment for CIPN.

Conclusion: Currently no agent has shown solid beneficial evidence to be recommended for the treatment or prophylaxis of CIPN. Given that the number of cancer survivors is increasing, the long-term side effects of cancer treatment, is of major importance.

Key Words: Chemotherapy-induced peripheral neuropathy, herbal medicines, peripheral neuropathy, herbs

Abbreviations

AC	*Acorus calamus*
CIPN	Chemotherapy-Induced Peripheral Neuropathy
CAPEOX	Chemotherapy regime comprising of: Capecitabine and Oxaliplatin
DBRCT	Double Blind Randomised Controlled Trial
FOLFOX	Chemotherapy regime comprising of: Folinic acid (leucovorin), Fluorouracil and Oxaliplatin
GB	*Ginkgo biloba*
GJG	*Gohsajinkigan*
HIV	Human Immunodeficiency virus
IPN	Induced Peripheral Neuropathy
IV	Intravenous
MC	*Matricaria chamomilla*
NHMRC	National Health and Medical Research Council
PN	Peripheral Neuropathy
PNQ	Peripheral Neuropathy Questionnaire
RCT	Randomised Controlled Trial
SO	*Salvia officinalis*
TCM	Traditional Chinese Medicine

Herbal Medicines and CIPN

Introduction

Chemotherapy-induced peripheral neuropathy [CIPN] is major dose limiting side effect of certain chemotherapy agents including taxanes, platinum compounds, epothilones, vinca alkaloids, thalidamide and newer agents such as bortezomib and lenolidamide [Wolf et al., 2008]. The incidence of CIPN varies depending on the chemotherapy agent but can range from 20% to 75% [Caveletti et al., 2011]. The symptoms of CIPN can be numbness, tingling, burning, decreased touch sensation, decreased strength and movement and sometimes pain in the fingers, toes, hands or feet [Armstrong et al., 2005; Visovsky et al., 2008].

Mechanism of Action for CIPN

Currently, the exact mechanism of action underlying the neurotoxic activity of the chemotherapy agents that can cause CIPN is largely incomplete and data is frequently based on poorly supported assumptions. There are similarities between the cytotoxicity mechanism of action of the chemotherapy agent and their action on the peripheral nervous system cells. However, if the amount of DNA damage or cellular damage exceeds the cells ability to repair, the cell will undergo apopotosis or cell death. This damage does not explain the sensory, possible motor involvement and pain associated with CIPN [Caveletti et al., 2011]. These neoplastic agents have been found to accumulate in the peripheral nervous system and its this accumulation that is said to cause the neurotoxicity leading to CIPN however, the mechanism of action is still relatively unknown. [Bhagra et al, 2007; Cavaletti et al., 2008; Cavaletti et al, 2004; Park et al., 2008; Pirzada et al., 2000; Schiff et al., 2009].

Justification for conducting a literature review on herbal medicine and CIPN

It is estimated that one third of all patients who undergo chemotherapy experience CIPN and of those, a third can have permanent nerve damage [Bhagra et al, 2007; Cavaletti et al., 2008; Cavaletti et al., 2004]. Patients experiencing moderate to severe CIPN report a reduced quality of life [Cavaletti et al., 2008], chronic discomfort [Cavaletti et al., 2004] and disruption of physical abilities for general life activities, which can be temporary or permanent [Cavaletti et al., 2008]. Moreover, CIPN can lead to dose reduction of the chemotherapy agent or possible cessation of treatment, which may have an adverse impact on cancer treatment and disease outcomes [Bhagra et al., 2007].

Currently no pharmaceutal or neutraceutical agent has shown solid beneficial evidence to be recommended for the treatment or prophylaxis of CIPN. Given that the number of cancer survivors is increasing, the long-term side effects of cancer treatment, is of major importance. Herbal medicine may have the potential to provide prevention or treatment for CIPN. Hence, examining the current literature to assess studies conducted on herbal medicine and CIPN may provide information to its possible benefit.

Herbal treatments may offer a different aspect to assisting CIPN however the main problem with research involving herbal extracts or medicinal herbs is the understanding of the mechanism of actions and the fact that the herbs contain a number of active compounds. Moreover, Asian herbal therapies contain a combination of multiple herbs, which adds to the complexity of study

analysis, data interpretation and an assessment of benefit. Isolation of one extract which is common in scientific research is unable to be conducted with herbal medicine research in most situations as the combination of compounds or combination of herbs such as Asian herbal therapies are seen to work in synergy.

The Aetiology of CIPN

A differential diagnosis of peripheral neuropathy in patients diagnosed with cancer includes a vitamin B12 deficiency, cachexia, chemotherapy, Charcot-Marie-Tooth disease, diabetes mellitus type II, atherosclerotic ischemic disease, para-neoplastic syndrome, thyroid dysfunction and alcoholic neuropathy [Armstrong et al., 2005]. Requisites for peripheral nervous system neurotoxicity include chemotherapy agent capacity to cross the blood-nerve barrier and nervous system sensitivity to the drug. People with predisposing conditions such as type II diabetes mellitus (T2DM), HIV/AIDS, alcoholism or a vitamin B12 deficiency may be more prone to the agent's adverse effects on the peripheral nervous system thereby increasing the prevalence of CIPN [Armstrong et al., 2005].

Peripheral nerve fibres are composed of small or large fibres. Small nerve fibres are unmyelinated and are comprised primarily of microtubules. They include nerves that sense pain and temperature. Large nerve fibres are myelinated and are composed mainly of neurofilaments that act as a framework for the axon. These fibres sense position and vibration as well as motor control [Armstrong et al., 2005]. Both fibres are targeted by neurotoxic chemotherapy agents, and that may explain why patients experience a variety of symptoms.

Although each neurotoxic chemotherapy agent has a different mechanism of action on the nervous system, all induce a glove and stocking distribution. This means the point most distal from the trunk of the body is affected first (e.g. fingers and toes) and progression is then towards the trunk to hands and feet and then limbs [Armstrong et al., 2005]. Each agent has been found to affect one nerve fibre more than others e.g. cisplatin targets large fibres while paclitaxel and vincristine target small fibres [Armstrong et al., 2005].

CIPN can be a temporary side effect, which can take up to two years for full recovery. In approximately one third of cases it can be a permanent side effect of the drug's neurotoxicity action. Symptoms may occur within hours, days or weeks after the introduction of the chemotherapy agent, with cumulative doses increasing the severity and length of time the patient experiences this side effect [Armstrong et al., 2005]. Cisplatin differs to other neurotoxic agents as it can induce a delayed CIPN several months after the drug has been administered rather than a more immediate response [Cavaletti et al., 2004].

Mechanism of Action of Neurotoxic Chemotherapy Agents

The neurotoxic chemotherapy agents can be divided into four main categories, alkylating and anti-tubulin agents, thalidomide and proteasome inhibitors. A common feature of these drugs is that they are unable to cross the blood-brain barrier thereby protecting the central nervous system. The peripheral nervous system has no protective barrier making it susceptible to

neurotoxicity [Cavaletti et al., 2008] and therefore neurotoxic chemotherapy agents can accumulate and target different regions of the neuron [Ferrier et al., 2013].

Methodology

Selection Criteria

The Inclusion criteria for this review were:

1) Any type of human trial e.g. RCT, retrospective, case study;
2) Animal studies;
3) The use of a herb or combination of herbs as the main intervention and specifically investigating its effects on reducing the primary outcome i.e. CIPN; and
4) The journal article or abstract must be written in English (a number of Asian journal articles had the abstract in English but the journal article in their language i.e. Japanese or Chinese.)

Databases

The following databases were used to retrieve journal articles: PubMed, the Cochrane Library, Science Direct, Scopus, EMBASE, MEDLINE, and Google Scholar.

Chinese databases included CNKI and CINAHL.

Search Terms

Electronic databases were searched using the following search terms, “chemotherapy-induced peripheral neuropathy” OR “Cisplatin” OR “Taxanes” OR “Paclitaxel” OR “Docetaxel” OR

"Oxaliplatin" OR "Carboplatin" OR "Platinum compounds" OR "Proteasome inhibitors" AND "peripheral neuropathy" OR "CIPN" AND "herb" OR "cannabis" OR "chamomile" OR "ginkgo" OR "sweet bee venom" OR "turmeric" OR "sage" OR "hypericum" OR "herbal medicines" OR "Chinese herbal medicines" OR "ayurvedic herbal medicines".

The overall body of evidence (based on a summary of the individual studies: See Table 1 and 2) evaluated within this review was primarily assessed using a separate tool, the Australian National Health and Medical Research Council's (NHMRC) body of clinical evidence assessment matrix. This is an assessment tool that assigns a level/grade (Level I: strongest evidence to level IV: weakest evidence) based on the strength of the published study [NHMRC, 2009]. Supportive evidence was obtained from animal studies.

Risk bias assessment

The risk bias of both animal and human studies was assessed using the Cochrane Risk of Bias Assessment tool (http://handbook.cochrane.org/ , part 2, Chapter 8). All studies were reviewed by two reviewers (JS, LV).

Data Synthesis

All human clinical trial data (excluding case studies) was analysed using RevMan version 5.2.7 to quantify and compare the efficacy outcomes of the intervention versus control.

Results

A total of 5614 journal articles were identified. These were retrieved through electronic search and examination of references in reviews. Dissemination of the articles and abstracts decreased the total of articles from 5614 to 34 relevant journal articles. These results found 6 single herbs [Abad et al., 2011a, 2011b; Al Moundhri et al., 2013; Cakil, 2012; Huang et al., 2007; Lim et al., 2013; Marshall et al., 2004; Muthuraman A et al., 2011; Ozturk et al., 2004; Park et al., 2011; Xu O, et al., 2004; Yoon et al., 2012;], one extract [Xu F, et al., 2011], one receptor agonist [Rahn et al., 2007; Rahn et al., 2008] and 8 combinations of herbs [Bahar et al., 2013; Deng and Zou, 2007; Fujii et al., 2004; Hashimoto et al., 2004, 2006; Hidaka et al., 2009; Hosokawa et al., 2012; Kaku et al., 2012; Kono et al., 2011, 2013; Nishioka et al., 2011; Pan et al., 2012; Shindo et al., 2008; Sima et al., 2009; Sun et al., 2008; Tatsumi et al., 2009; Ushio et al., 2012; Yamada et al., 2012; Yamamoto et al., 2009;].

All studies included in this review were analysed for common scientific characteristics however lower levels of evidence was used as rigorous randomised clinical trials were limited. The flow chart of study selection can be seen on figure 1. Of the journal articles identified n=18 were animal studies (see table 1) with human clinical studies consisting of one multi-centre, randomised double-blind placebo-controlled trial, six randomised trials, six retrospective studies, one uncontrolled study and three case reports found, [n=17] (see Table 2).

Animal Studies (*See table 1)*

Single Herbal Medicines in Animal Studies and CIPN

1. *Acorus calamus rhizome*

Acorus calamus (AC) is an Ayurvedic herb traditionally used to treat or manage pain and inflammation. This study investigated if AC had protective effects for vincristine-induced painful neuropathy in rats. *Acorus calamus* was compared to pregabalin (Lyrica) and was found to be comparable as both attenuated the vincristine-induced painful neuropathy [Muthuraman et al., 2011].

2. *Curcumin longa*

Curcumin, an extract from turmeric has been reported to have strong anti-inflammatory, anti-cancer and antioxidant activity [Al Moundhri et al., 2013]. This study looked at curcumin's potential protective effect on cisplatin and oxaliplatin induced behavioural, biochemical and histopathological changes in rats. Rats were randomly divided into five groups (six rats per group): 1) IV glucose and distilled water; 2) IV oxaliplatin and distilled water; 3) IV oxaliplatin and curcumin in water; 4) IV cisplatin and distilled water; 5) IV cisplatin and curcumin in water. Results found that oral curcumin reversed the alterations in the plasma neurotensin and sciatic nerve platinum concentrations and markedly improved sciatic nerve histology. This study doesn't provide complete evidence for neuroprotection however it does give evidence warranting further research.

3. *Ginkgo biloba (EGb 761)*

Ginkgo biloba (GB) has been found in in-vivo and in-vitro studies to have potential as a neuroprotective agent [Mills, 1991]. Four studies on animals have been conducted to test GB as a neuroprotective agent against cisplatin-induced peripheral neuropathy particularly focusing on ototoxicity [Cakil et al., 2012; Huang et al., 2007; Ozturk et al., 2004; Xu O, et al., 2004].

Cakil B, et al (2012) tested twenty rats with normal hearing to cisplatin exposure with one group receiving 100mg/kg of GB for 10 days. Results indicated that ginkgo could protect against inner ear cisplatin-induced ototoxicity. Huang X, et al. (2007) also tested GB on rats to investigate its protective effect for ototoxicity by cisplatin administration. Results from this investigation also found GB to be protective against cisplatin-induced ototoxicity.

Xu O, et al. (2004) investigated the combination of GB and deferoxamin (DFO, a chelating agent) on guinea pigs again focusing on the ototoxicity induced by cisplatin. They concluded that the combined use of GB and DFO reduced cisplatin-induced ototoxicity and that the combination was better than using just GB alone. The fourth animal study was conducted on mice by Ozturk G, et al. (2004) who investigated the neuroprotective effects of GB for cisplatin-PN, not just ototoxicity. They evaluated the neuropathy by conducing nerve conduction velocity (NCV) tests on the mice. Results indicated that GB was effective in preventing some functional and morphological peripheral nerve deteriorations induced by cisplatin administration.

4. *Matricaria chamomilla (chamomile)*

Matricaria chamomilla (MC) is traditionally used for sedation, pain management, spasms, inflammation and wound healing [Berry, 1995; Hosokawa et al., 2012]. This study's aim was to investigate the effects of MC hydro-alcoholic extract on cisplatin-induced peripheral neuropathy compared to morphine in mice. Mice were divided into 6 groups which received: 1) normal saline; 2) MC hydro-alcoholic extract; 3) cisplatin; 4) MC hydro-alcoholic extract and cisplatin; 5) morphine; 6) morphine and cisplatin. The results found that cisplatin caused significant pain ($P<0.05$) and that MC given before cisplatin decreased the pain response significantly ($P<0.05$) in the first and second phase. In comparison to morphine, morphine had analgesic effects in the first phase while MC had anti-inflammatory effects in the second phase [Abad et al., 2011a].

5. *Salvia officinalis*

Salvia officinalis (SO) or sage is a traditional culinary herb that has been found to have analgesic and anti-inflammatory activity [Howes et al., 2003, Wang et al., 2001]. One study investigated an SO hydro-alcoholic extract on vincristine-induced peripheral neuropathy in mice compared to morphine [Abad et al., 2011b]. Sixty mice were divided into six groups similar to the chamomile study [Abad et al., 2011a]. Results found that SO could be effective as a treatment for vincristine-induced peripheral neuropathy [Abad et al., 2011b].

6. *Sweet bee venom (pharmacopuncture)*

Sweet bee venom treatment is a part of a normal oriental medical practice in Korea for the treatment of various pain and neurological symptoms [Yoon et al., 2012]. Pharmacopuncture is a treatment by which pharmaceuticals and acupuncture are joined by injecting pharmaceutical

derivatives into acupuncture points chosen for each patient's diagnosis and symptoms based on TCM [Yoon et al., 2012].

A recent article looked at bee venom acupuncture for cold allodynia induced from oxaliplatin in rat [Lim et al., 2013]. It found that it was effective in alleviating the oxaliplatin-induced cold allodynia in rats which was partly due to the activation of the noradrenergic system.

Herbal Medicine Extracts in Animal Studies and CIPN

1. *Verticinone (Extract from Bulbus Fritillaria*)

Verticinone is an isosteroidal alkaloid, which has been extracted from the *Bulbus* Fritillaria [Xu F, et al., 2011]. It has been used in China for more than 2000 years as an antitussive, expectorant and anti-asthmatic [Lee et al., 2006]. Recently, verticinone has demonstrated in pharmacological studies more diverse bioactivities such as inhibiting angiotensin I converting enzyme [Li et al., 2006], antagonizing M-receptor (the muscarinic acetylcholine receptor) activity and significantly elevating cAMP concentrations in HEK cells [Oh et al., 2003].

This study aimed to investigate verticinone's effect on paclitaxel induced neuropathic pain compared to morphine. The authors concluded that verticinone seemed to exert good analgesic effects for the inflammatory pain and the CIPN pain. The hypothesised this could be through both the central and peripheral nervous system and that further studies are warranted [Xu F et al., 2011].

Herbal Medicines with Receptor Agonist Activity in Animal Studies and CIPN

1. *Cannabis (Cannabis sativa L.)*

Cannabinoids have been tested for nerve suppression and two studies have examined the cannabinoids suppression potential for CIPN from vincristine [Rhan et al., 2007] and paclitaxel [Rahn et al., 2008] in rats. The two main cannabinoids tested include 1) CB1/CB2 receptor agonist WIN55,212-2 and; 2) receptor-inactive enantiomer WIN55,212-3, a CB2-selective agonist (R,S)-AM1241 [Rahn et al., 2007].

For the vincristine experiment, WIN55,212-2 was administered intrathecally (in the spine) or locally into the hind paw of rats. Results found that WIN55,212-2 not WIN55,212-3 suppressed vincristine evoked mechanical allodynia. The authors concluded that cannabinoids can suppress the maintenance of vincristine-induced mechanical allodynia through the activation of CB1 and CB2 receptors and this was mediated partly at the spinal cord level [Rahn et al., 2007]. For the paclitaxel experiment, they concluded that cannabinoid CB(2) receptors maybe a potential treatment for paclitaxel CIPN [Rahn et al., 2008].

Combination Herbal Medicines in Animal Studies and CIPN

1. *Geramii herba plus Aconiti radix*

The combination of *Geramii herba* and *Aconiti radix* herbs was used as an external application in a rat model of oxaliplatin CIPN. The results showed that mechanical allodynia and thermal

hyperalgesia were alleviated, nerve growth factor (NGF) was increased and substance P was decreased in the treated rat group compared to oxaliplatin alone [Sima et al., 2009].

2. *Goshajinkigan (Japan), Niu Che Sen Qi Wan (Chinese), Pilula renales plantaginis et achyranthis (Lat.)*

Nine trials on both animals and humans have been conducted on this formula [Bahar et al., 2013; Hashimoto et al., 2004, 2006; Kaku et al., 2012; Kono et al., 2011, 2013; Nishioka et al., 2011; Shindo et al., 2008; Ushio et al., 2012; Yamamoto et al., 2009]. This formula contains ten herbs: *Rehmannia viride radix, Achyranthis bidentatae radix, Corni fructus, Dioscorea opposite rhizome, Plantaginis semen, Alismatis rhizome, Moutan cortex, Cinnamomi cortex, Aconiti lateralis praeparata tuber,* and *Poria alba* [Japan Society of Oriental Medicine, 2005]. A rat study tested this formula (GJG) on paclitaxel-IPN in three different studies.

The first trial found no neuroregeneration in histological examination [Hashimoto et al., 2004] however the second trial found that it showed a positive effect on cold allodynia [Hashimoto et al., 2006]. A recent trial on mice found that GJG was effective for mechanical allodynia from paclitaxel but not for tumour allodynia [Akbar Bahar et al., 2013]. Another rat study tested GJG on oxaliplatin-IPN and found that it prevented cold hyperalgesia but not mechanical allodynia or axonal degeneration in rat sciatic nerves. However, after CIPN had developed, a single administration of GJG reduced both cold hyperalgesia and mechanical allodynia [Ushio et al., 2012].

3. *Shakuyakukanzoto (Japanese), Shao Yao Gan Cao Tang (Chinese), Formula glycyrrhizae et paeonia (Lat), Peony and Licorice Decoction (English)*

This herbal formula is a combination of Peony and Licorice in a decoction. Three studies have been conducted on this herbal combination, one mouse study [Hidaka et al., 2009], a retrospective case analysis [Fujii et al., 2004] and a retrospective clinical trial comparison [Hosokawa et al., 2012]. The mouse study invested paclitaxel-IPN and found that this combination significantly relieved the allodynia and hyperalgesia induced by paclitaxel [Hidaka et al., 2009].

Human Studies on CIPN and Herbal Medicine *(see Table 2)*

Single Herbal Medicines on Human Studies and CIPN

1. *Ginkgo biloba (EGb 761)*

One retrospective study has been conducted on human beings administered oxaliplatin [Marshall et al. 2004]. The retrospective analysis was conducted on 17 colorectal patients who were being treated with either FOLFOX or CAPEOX chemotherapy regimes for either adjuvant or metastatic treatment [Marshall et al., 2004]. GB 120mg b.i.d was given orally either after cycle 1 or 2 of treatment. They concluded that GB appeared to decrease the intensity and duration of the acute dysethesias caused by oxaliplatin and have initiated a phase II RCT to confirm results. To

date, no results have been published from this phase II trial which apparently started in 2004. [Marshall et al., 2004]

2. Sweet bee venom (pharmacopuncture)

Two journal articles outlining case studies using sweet bee venom for CIPN have been found with the agent used being identified as melittin, an extracted active ingredient from the bee venom that has the allergens removed such as phospholipase A_2 (PLA_2), hyaluronidase and histamine. Melittin is a low molecular weight peptide and is reported to have analgesic, anti-inflammatory and anti-cancer effects [Choi et al., 2006; Kwon et al., 2006; Wang et al., 2001]. The first article outlined 5 case reports receiving a one week course of treatment with sweet bee venom pharmacopuncture. No side effects were experienced and results indicated clinical improvement of CIPN [Park et al., 2011]. Another case series on 11 patients were treated for three weeks with six sweet bee venom pharmacopuncture treatments. Results showed a reduction in the WHO CIPN grade and PNQ score indicating a reduction in CIPN [Yoon et al., 2012]. Further studies are required to confirm their findings.

Combination Herbal Studies on Human Studies and CIPN

1. Bu Yang Huan Wu (Chinese)

This formula consists of *Astragulus membranaceus radix, Angelica sinesis radix, Prunus persicae semen, Paeoniae rubra radix, Ligustici chuanxiong rhizome, Lumbricus terrestris, Spatholobi caulis, Curcuma radix, Chaenomeles lagenaria fructus* and *Achyranthes bidentatae*

radix. In traditional Chinese medicine (TCM) it is said to tonify the yang and restore the five-tenths decoction [Zhou et al., 2006]. This decoction was used in an RCT of 84 participants (intervention n=44, control n=40) for the treatment of CIPN after oxaliplatin administration. Results indicated that Bu Yang Huan Wu reduced the development of CIPN in the treatment group tested by standardized clinical tests [Sun et al., 2008].

2. *Modified Bu yang Huan Wu (Chinese)*

The modified formula used was *Bu Yang Huan Wu* plus *Liuwei Di Huang* which contains the herbs: *Astragulus membranaceus radix, Ligustrum lucidum fructus, Paeoniae rubra radix, Lumbricus terrestris, Prunus persicae semen, Rehmanniae viride radix, Corni officinalis fructus, Dioscorea opposite radix, Alismatis rhizome, Poria alba, Spatholobi caulis, Scolopendra, Mori fructus, Glycyrrhizae radix, Dipsaci fructus, Lycii fructus, Coicis semen, Atractylodis Rhizome, Phellodendri cortex, Scorpio, Moi ramulus* and *Cyathula officinalis.* A RCT was conducted using this decoction on 32 patients with existing CIPN from various chemotherapy agents. The treatment was compared to 32 patients who were treated daily with 2500µg of vitamin B1 orally in addition to intramuscular injections of 100mg of vitamin B1. The Chinese herbal formula was found to be significantly more effective compared to the vitamin B1 treatment ($P<0.05$) [Deng et al., 2007].

3. *Modified Chai Hu Long Gu Mu Li Wan (Chinese)*

This modified Chinese oral combination of herbs consists of *Psuedostellaria heterophylla,Pinelliae rhizome, Glycyrrhizae radix, Scutellaria baicalensis radix, Bupleuri*

radix, Fossiliaossis mastoid, Ostreae concha, Rubia cordifolia radix, Scutellariae barbatae herba and *Fritillariae thunbergia bulbi.* This combination was used in a RCT of 48 patients with ovarian cancer undergoing paclitaxel administration. They were divided into a control group of paclitaxel only or a treatment group of paclitaxel plus a combination of the oral Chinese herbal decoction and an external washing of the feet with Chinese herbs (*Astragulus membranaceus radix, Angelica sinensis radix, Paeoniae radix, lumbricus terrestris, Ligustici chuanxiong Rhizome, Prunus persicae semen* and *Carthami flos*.) Results indicated that the incidence rate of CIPN in the treatment group was nearly half compared to the paclitaxel only group. Therefore this Chinese formula may help in preventing paclitaxel CIPN [Pan et al., 2012].

4. Geramii herba plus Aconiti radix

A RCT was conducted on 58 patients experiencing CIPN from oxalipatin, taxol or capecitabine. 30 patients were assigned to the treatment group and 28 to the control group. After one week of treatment, the external application of the two herbs was found to reduce pain, paraesthesia and swelling. The authors concluded that *Geramii herba* plus *Aconiti radix* may relieve neuropathy and improve quality of life. No species of these two herbs were mentioned in the abstract [Sima et al., 2009].*Goshajinkigan (Japan), Niu Che Sen Qi Wan (Chinese), Pilula renales plantaginis et achyranthis (Lat.)*

Six human trials have been conducted on Goshajinkigan [GJG].. Firstly, GJG was invested in a non-controlled trail on 14 patients receiving oxaliplatin. GJG was administered every day after the first oxaliplatin infusion and results indicated that it seemed to prevent acute oxaliplatin-IPN [Shindo et al., 2008]. Two retrospective studies were conducted on FOLFOX (oxaliplatin) and GJG [Kono et al., 2011; Nishioka et al., 2011]. The first trial was conducted on 45 patients with

22 patients receiving GJG with their FOLFOX regime compared to 23 who did not receive GJG. They found that the incidence of grade 3 CIPN in the GJG group was significantly lower than in the control group ($P<0.01$, log-rank test) [Nishioka et al., 2011].

The second study investigated 90 patients undergoing FOLFOX for metastatic colorectal cancer. There were four groups: 1) FOLFOX plus GJG; 2) FOLFOX plus GJG plus Ca^{2+}/Mg^{2+}; 3) FOLFOX plus Ca^{2+}/Mg^{2+}; 4) FOLFOX only. Results included the incidence rate for each group which were 91% for FOLFOX only, 100% in FOLFOX plus Ca^{2+}/Mg^{2+}, 79% in FOLFOX plus GJG plus Ca^{2+}/Mg^{2+} and 50% in FOLFOX plus GJG. The authors concluded that GJG reduced the neurotoxicity of oxaliplatin without affecting the response rate [Kono et al., 2011].

In another retrospective trial, GJG was investigated for paclitaxel-IPN in 82 breast and gynaecological cancer patients. The investigators concluded that GJG was possibly effective for the treatment and the prevention of paclitaxel-IPN was seemed more effective if administered at the beginning of chemotherapy treatment [Yamamoto et al., 2009]. Another human trial on GJG involved a prospective RCT on paclitaxel/carboplatin treatment for 29 ovarian or endometrial cancer patients. They were divided into two groups; 1) 14 patients received vitamin B12; 2) 15 patients received vitamin B12 and GJG and were given treatment for six weeks. Grade 3 CIPN was observed in 2/14 patients receiving vitamin B12 compared to 0/15 receiving vitamin B12/GJG. It was concluded that GJG inhibits the progression of CIPN but further trials are warranted [Kaku et al., 2012].

A recent phase II multi-centre, randomised, double-blind, placebo-controlled trial was conducted and published on GJG and oxaliplatin-induced PN [Kono et al., 2013]. In this trial, patients undergoing FOLFOX for colorectal cancer was randomised to either receive oral GJG (7.5g) or matching placebo daily. The severity of CIPN was assessed using the common toxicity criteria for adverse events every two weeks until the 8^{th} cycle, and then every 4 weeks thereafter. The primary endpoint was the incidence of grade 2 CIPN or greater before the 8^{th} cycle. The incidence of grade 2 or greater CIPN was 39% in the GJG arm and 51% in the placebo arm. The authors concluded that GJG shows promise in delaying the onset of grade 2 or greater CIPN without impairing FOLFOX efficacy [Kono et al., 2013].

5. *Keishikajutsubuto (Jananese), Gui Zhi Jia Shu Fu Tang (Chinese), Decoctum ramulorum cassia cum atractylodis macrocephae et aconite (Lat)*

This oriental formula contains *Cinamomi cortex, Aconiti lateralis praeparata tuber, Zingiberis rhizome, Jujubae fructus, Glycyrrhizae radix* and *Atracylodis macrocephalae rhizome.* A non-controlled trial was conducted investigating this herbal formula on 11 patients with metastatic colorectal cancer undergoing FOLFOX administration. A reduction of CIPN was observed in 5 cases (45.5%) after cessation of chemotherapy [Yamada et al., 2012].

6. *Ogikeishigomotsuto (Japanese), Huang Qi Wu Wu Tang (Chinese), Decotum quinque medicamentorum cum astragalo (Lat.), Astragulus and Cinnamon Five herb combination (English)*

This oriental herbal combination contains *Astragalus membranaceus radix, cinnamomi cortex, Paeonia alba radix, Jujubae fructus* and *Zingiberis 23hizome*. A single case study was published using this formula for neuropathic pain induced by oxaliplatin. It showed a positive effect in reducing the pain and the patient was allowed to continue chemotherapy treatment with oxaliplatin [Tatsumi et al., 2009].

7. *Shakuyakukanzoto (Japanese), Shao Yao Gan Cao Tang (Chinese), Formula glycyrrhizae et paeonia (Lat), Peony and Licorice Decoction (English)*

Two studies human studies have been conducted on this formula, a retrospective case analysis [Fujii et al., 2004] and a retrospective clinical trial comparison [Hosokawa et al., 2012].

The retrospective case analysis investigated 23 patients with paclitaxel-IPN and observed that this combination had a positive effect on the neuropathic pain experienced by these ovarian cancer patients [Fujii et al. 2004]. Lastly the retrospective clinical trial compared Shakuyakukanzoto (peony and licorice) to Goshajinkigan (GJG). This was a preventive study and investigated 20 metastatic colorectal cancer patients administered Shakuyakukanzoto in conjunction with FOLFOX compared to 24 patients administered GJG. The Shakuyakukanzoto group was found to prevent 65% CIPN compared to 50% in the GJG group. It was concluded that both formulas may prevent oxaliplatin-IPN [Hosokawa et al., 2012].

Discussion

Current improvements in detection and treatment strongly correlate with increases survival rates of those patients diagnosed with cancer [Coleman et al., 2011]. With an increased survival rate, long-term side effects from chemotherapy and other medical treatments has raised significant awareness as it can affect quality of life and clinical outcomes [Bhagra et al., 2007; Cavaletti et al., 2008; Takenaka et al., 2012]. CIPN is an important side effect that can affect quality of life and can be a permanent consequence of treatment [Bhagra et al., 2007; Caveletti et al., 2004, 2008]. Currently, there are no standard recommended treatments or prophylactic options that employ pharmacological, nutraceutical or herbal medicines. Agents that have shown promise such as duloxetine [Takenaka et al., 2012; Smith et al., 2013], vitamin E [Argyriou et al., 2005, 2011; Pace et al., 2003, 2010], omega 3 fatty acids [Ghoreishi et al., 2012], and Asian herbal medicines in particular Goshajinkigan [Bahar et al., 2013; Hashimoto et al., 2004, 2006; Kaku et al., 2012; Kono et al., 2011, 2013; Nishioka et al., 2011; Shindo et al., 2008; Ushio et al., 2012;

Yamamoto et al., 2009] require further research, however, in order to assess the strength of efficacy.

Traditional scientific research is based on a single agent or active compound; herbal medicines though can be comprised of numerous active compounds with synergistic efficacy. For example in the use of Asian herbal medicines, a combination of herbs can be employed [Kono et al., 2013]. This combination may give a multi-targeted approach that complicates the identification and elucidation of the active compound and the mechanism of action. Nevertheless warranted research on single herbal extracts and compounds through validated clinical studies can still provide useful data.

Investigations carried out with herbal medicines for CIPN found no neuroprotection or treatment when a single compound or herb was studied. Animal models provide basic research for further studies but do not guarantee that the herb or compound will be efficacious in human clinical trials. Herbal medicines such as *Ginkgo biloba* [Marshall et al., 2004] and *curcumin* [Al Moundhri et al., 2013] warrant further research as they have reported a positive clinical likelihood from animal studies.

An important and common mechanism of action within the identified medicinal herbs trialled for CIPN is their anti-inflammatory activity [Al Moundhri MS et al., 2013; Berry, 1995; Choi et al., 2006; Ghoreishi et al., 2012; Howes et al., 2003; Kwon et al., 2006; Lee et al., 2006; Mills, 1991; Muthuraman et al., 2011; Wang et al., 2001]. The anti-inflammatory activity of the herbs

may be a plausible mechanism of action that assists with the protection and treatment of CIPN. Medical treatment of peripheral neuropathy has involved non-steroidal anti-inflammatory drugs for the inflammation and pain associated with this condition [Kaley and Deangelis, 2009]. This potential mechanism of action warrants further research which may attribute to other herbal remedies, nutrients or pharmaceuticals being trialled for CIPN.

The Asian herbal combination remedies investigated for CIPN were difficult to analysis as a number of the journal articles were written in their Asian language rather than English. Therefore the information obtained for twelve out of the nineteen herbal combinations journal articles was extracted from abstracts. From these Asian herbal combinations, Goshajinkigan (GJG) is the herbal medicine that has been trialled extensively through animal and human clinical trials [Bahar et al., 2013; Hashimoto et al., 2004, 2006; Kaku et al., 2012; Kono et al., 2011, 2013; Nishioka et al., 2011; Shindo et al., 2008; Ushio et al., 2012; Yamamoto et al., 2009]. Of the clinical trials, three were retrospective studies using controls for Folfox and paclitaxel administration [Kono et al., 2011; Nishioka et al., 2011; Yamamoto et al., 2009], one RCT [Kaku et al., 2013] comparing vitamin B12 administration with the herbal combination and a recent phase II multi-centre, randomised, double-blind, placebo-controlled trial conducted as an adjuvant treatment with FOLFOX [Kono et al., 2013]. All studies concluded that this herbal combination may provide neuroprotection however, as this is a Japanese combination and has been trialled in Japan, it may be difficult to transfer into other countries depending on their National regulatory body. Another limitation with GJG is that not all details of its mechanism of

action have been clearly identified and for certain herbs, their effects are unknown [Schroder et al., 2013].

All other trials with the Asian combination herbs were animal models, case studies, retrospective studies and limited RCT's so the quality of evidence is very low. Without further randomised clinical trials that are written in English and well established, they are not recommended for use.

Two herbal treatments have been investigated for peripheral neuropathy that may be considered for use in CIPN. These include St John's wort and capsaicin cream. St John's Wort (*Hypericum perforaturn)* was selected to trial for PN as tricyclic antidepressant medication is used medically for its treatment. In a crossover DBRCT, 54 patients with or without diabetes were investigated for treatment with St John's Wort (SJW) for diabetic PN. Participants were randomly assigned to either SJW (900mcg hypericin/tablet) or placebo for five weeks. They were then crossed over to the other treatment for an additional five weeks. No statistical significant was found in pain indexes however a trend was noted for an improved overall pain score [Sindrup et al., 2001].

Capsaicin has been investigated as a topical application for diabetic [Biesbroeck et al., 1995; Chad et al., 1990; Low, et al., 1995; No authors listed, 1991; Tandan et al., 1992] and HIV peripheral neuropathy [Brown et al., 2013; Clifford et al., 2012; Simpson et al., 2103]. The majority of studies have been conducted on diabetes PN with most resulting in statistical significance [Biesbroeck et al., 1995; Chad et al., 1990; Low, et al., 1995; No authors listed, 1991; Tandan et al., 1992]. The results indicate that capsaicin cream may provide relief for

chronic, intractable pain and reduce dependence on opioids however the main side effect of burning at the site of application may be of concern [No authors listed, 1991]. It is recommended that it is not used as a monotherapy but in combination with oral medication to assist this condition.

Clinical Relevance

We have previously reported in a systematic review, that there was limited evidence for the administration of nutraceuticals in the treatment or prevention of CIPN [Schloss, et al., 2013]. Herewith we again report that the current scientific literature demonstrates that there is limited evidence for the concurrent administration of herbal remedies as adjuvants to neurotoxic agents for the prevention or treatment of CIPN. The clinical studies conducted with single or combination herbal medicines identified in this review do not provide a clear recommendation for clinical use. *Goshajinkigan* has shown the most promise in preventing severe CIPN but maybe limited in use depending on national governing body guidelines. Other herbs that may be considered after further research include *Ginkgo biloba*, curcumin and capsaicin cream.

Conclusions

Investigations into the research on herbal medicine and CIPN have not yet yielded clinical evidence to support the standard use of herbal medicine as a prevention or treatment of CIPN. However, data does suggest that herbal medicine may provide potential benefits with further research required. More extensive scientific research into the mechanism of action of not only

the herbal extracts but the neurotoxic activity of the chemotherapeutic agents may provide a key in identifying remedies that may help prevent or treat this side effect.

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Table 1: Animal Studies with Herbal Medicines for the Prevention and or Treatment of CIPN

Medicinal Herb	Study Type	Chemotherapy Agent	Results
Single Medicinal Herbs			
Acorus calamus rhizome	Rat model (Muthuraman et al., 2011)	Vincristine	Improvement in neuropathic pain
Curcumin	Mouse model (Al Moundhri et al., 2013)	Oxaliplatin and cisplatin	Possible neuroprotection
Gingko biloba	Rat model (Cakil et al., 2012)	Cisplatin	Protection of ototoxicity
	Rat model (Huang et al., 2007)	Cisplatin	Protection of ototoxicity
	Mice model (Ozturk et al., 2004)	Cisplatin	Some functional and morphological protection against CIPN
	Guinea pigs (Xu O, et al., 2004)	Cisplatin	Protection of ototoxicity
Matricaria chamomilla (chamomile)	Mouse model (Abad et al., 2011)	Cisplatin	Improvement of neuropathic pain
Salvia officinalis	Mouse model (Abad et al., 2011)	Vincristine	Improvement in neuropathic pain
Sweet Bee Venom	Rat model (Lim et al., 2013)	Oxaliplatin	Alleviated cold related pain
Extract			
Verticinone (Extract from *Fritillaria bulbus*)	Mouse and rat model (Xu F et al., 2011)	Paclitaxel	Decreased inflammation and neuropathic pain

Receptor agonist			
Cannabis-Receptor agonists	Rat model (Rahn et al., 2008)	Paclitaxel	Reduced pain and sensitivity to stimuli
	Rat model (Rahn et al., 2007)	Vincristine	Reduced pain and sensitivity to stimuli
Combination Herbal Studies			
Geramii herba plus *Aconiti radix*	Rat model (Sima et al., 2009)	Oxaliplatin, taxol or capecitabine	Reduced neuropathic pain and paraesthesia
Goshajinkigan (Japan)	Mice model (Bahar et al., 2013)	Paclitaxel	Prevents paclitaxel-IPN without interfering with the anti-cancer action of paclitaxel.
	Rat model (Hashimoto et al., 2004)	Paclitaxel	Improvement in neuropathic pain
	Rat model (Hasmimoto et al., 2006)	Paclitaxel	Improves paclitaxel-IPN without affecting anti-tumour efficacy
	Rat/mouse model (Ushio et al., 2012)	Oxaliplatin	Improvement in neuropathic pain, no neuroregeneration
Shakuyakukanzoto (Japanese)	Mouse model (Hidaka et al., 2009)	Paclitaxel	Reduced neuropathic pain and hyperalgesia

DBRCT: Double Blind Randomized Controlled Trial; SBRCT: Single Blinded Randomized Controlled Trial; RCT: Randomized Controlled Trial; NRCT: Non Randomised Clinical Trial; CS: Case Study; TNS: Total Neuropathy Score

Table 2: Human Clinical Studies with Herbal Medicines for the Treatment and or Prevention of CIPN

Medicinal Herb	Study Type	No of Pts[1]	T[2]	C[3]	NHMRC Rating	Chemotherapy Agent	Results
Single Medicinal Herbs							
Ginkgo biloba	RS (Marshall et al., 2004)	17	N/A[4]	N/A	Level IIIb	Oxaliplatin	Possible neuroprotection
Sweet bee venom (pharmacopuncture)	Case series (Park et al., 2011)	5	N/A	N/A	Level IV	Taxol, carbo/taxol[5]	Injecting into the acupoint decreased pain and neuropathy (treatment)
	Case series (Yoon et al., 2012)	11	N/A	N/A	Level IV	Taxol, carbo/taxol	Injecting into the acupoint decreased pain and neuropathy (treatment)
Combination Herbal Studies							
Bu Yang Huan Wu (Chinese)	RCT (Sun et al., 2008)	84	44	40	Level II	Oxaliplatin	Reduced development of CIPN
Modified Bu yang *Huan Wu* (Chinese)	RCT (Deng, et al, 2007)	64	32	32	Level IIIa	Different chemotherapies	Reduced development of CIPN

[1] Pts: Participants
[2] T: Treatment group
[3] C: Control group or placebo
[4] N/A: Not applicable
[5] Carbo/Taxol: Carboplatin and Paclitaxol chemotherapy combination

Modified *Chai Hu Long Gu Mu Li Wan* (Chinese)	RCT (Pan et al., 2012)	48	N/A	N/A	Level II	Paclitaxel	Possible neuroprotection
Geramii herba plus *Aconiti radix*	RCT prospective (Sima et al., 2009)	58	30	28	Level II	Oxaliplatin	Reduced neuropathic pain
Goshajinkigan (Japan)	NRCT (Shindo et al., 2008)	14	N/A	N/A	Level IIIb	Oxaliplatin	Reduced acute neurotoxicity
	RS (Nishioka et al., 2011)	45	22	23	Level IIIa	Folfox	Possible neuroprotection
	RS (Kono et al., 2011)	90	11	44	Level IIIa	Folfox	Possible neuroprotection, no change of anticancer activity
			Plus CaMg[6] = 21	CaMg = 14			
	RS (Yamamoto et al., 2009)	82	N/A	N/A	Level IIIb	Paclitaxel	Possible neuroprotection, better when administered early
	RCT prospective study (Kaku et al., 2012)	29	Vit B12 + I = 15	Vit B12 = 14	Level IIIa	Carbo/Taxol	Less severe neurotoxicity, better in combined group

[6] CaMg: Calcium and magnesium infusion

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	DBRCT (Kono et al., 2013)	89	44	45	Level II	Folfox	Acceptable safety margin and indicates a delay in onset of grade 2 or higher CIPN without impairing FOLFOX efficacy.
Keishikajutsubuto (Jananese)	Uncontrolled study (Yamada et al., 2012)	11	N/A	N/A	Level IIIb	Folfox	76.6% mean improvement
Ogikeishigomotsuto (Japanese)	Case report (Tatsumi et al., 2009)	1	N/A	N/A	Level IV	Oxaliplatin	Reduced neuropathic pain
Shakuyakukanzoto (Japanese) Peony and Licorice Decoction (English)	Retrospective case analysis (Fujii et al., 2004)	23	N/A	N/A	Level IV	Paclitaxel	Reduced neuropathic pain
	RS comparison (Hosokawa et al., 2012)	44	20 (SKK)	24 (GJG)	Level IIIa	Folfox	50% response in Shakuyu-kanzoto and 65% in Goshajinkigan on prevention of neurotoxicity.

DBRCT: Double Blind Randomized Controlled Trial; SBRCT: Single Blinded Randomized Controlled Trial; RCT: Randomized Controlled Trial; NRCT: Non Randomised Clinical Trial; CS: Case Study; TNS: Total Neuropathy Score; RS: Retrospective Study

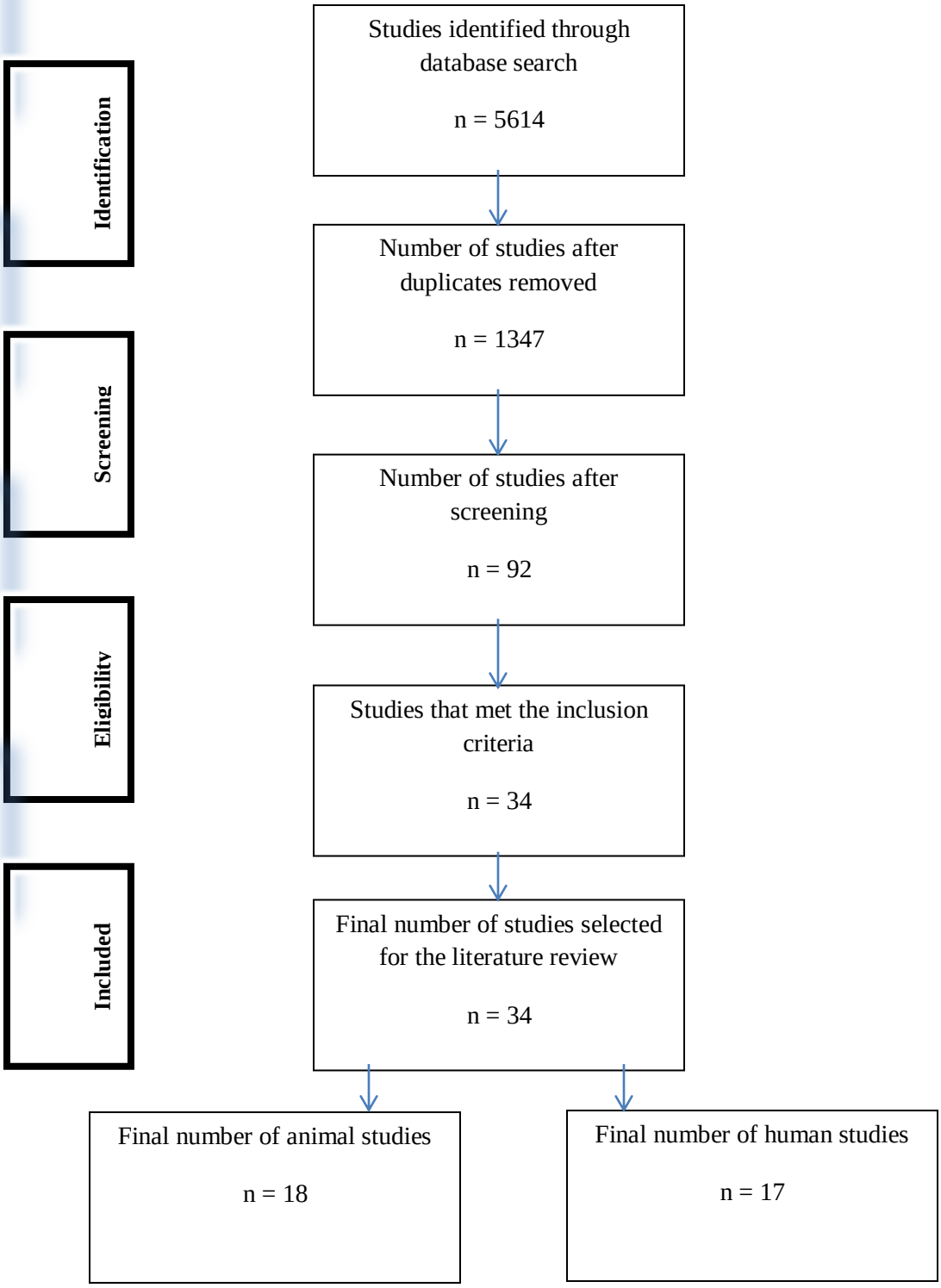

Figure 1: Flow chart of study selection

