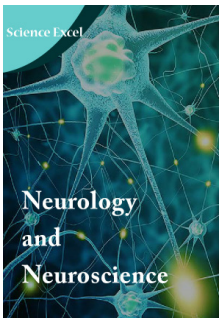
Neurology & Neuroscience

Original Article



Measurements, mechanisms and potential therapy for preventing chemotherapy-induced cognitive impairment

Jie Yin[1], Yuan-Yuan Han[2], Dong-Dong Shi[3]*

[1]*Shandong University of Traditional Chinese Medicine, Jinan, China*

[2]*Liaocheng People's Hospital, Liaocheng, Shangdong, China*

[3]*Shanghai Mental Health Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, China*

*Correspondence

Dong-Dong Shi

Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, 600 Wan Ping Nan Road, Shanghai, China

E-mail: laural.dong.shi@gmail.com

Keywords: chemobrain, neuroimaging, synaptic repair therapy, stem cells transplantation, Traditional Chinese medicine, acupuncture

- Received Date: 17 Aug 2021
- Accepted Date: 26 Aug 2021
- Publication Date: 02 Sep 2021

Abstract

Cognitive impairment following chemotherapy, also called chemobrain, is reducing the life quality of millions of cancer patients. It is urgent to discover therapeutic methods against chemobrain. In fact, neither measurements nor mechanisms are yet to be defined. To discover efficient treatment on chemobrain, in this review, we firstly focus on applications of objective and accurate methods to study the measurement of chemobrain, such as Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Furthermore, we highlight the potential mechanism of chemobrain including neuroinflammation, cell apoptosis and synaptic degeneration. Chemotherapy can induce neuroinflammation and cell apoptosis in brain. Synaptic plasticity also decreased in chemo-agent treated mice. Based on other cognitive impairment diseased, we also engaged in looking for effective treatment on cognitive impairment after chemotherapy in cancer patients. Synaptic repair, stem cell transplantation, Chinese medicine and psychological rehabilitation are all powerful candidates for treating chemobrain.

Why this study?

With the development of medical technology, the survivor rate of cancer patients is dramatically increasing nowadays [1]. Cancer survivorship is an emerging field in research. Better chemo-therapeutic regimens are discovered to contribute to human beings. However, there are many side-effects of adjuvant chemotherapy. Studies have suggested that cognitive function degeneration following chemotherapy such as amnesia, attention and learning difficulties, problems with visual and verbal memory influence the quality of cancer patients' lives greatly [2,3]. Animal studies also have shown that frequently using chemo-agents can induce cognitive impairment (chemobrain). CMF (cyclophosphamide, methothrexate, and 5-Fluorouracil) treated on rats reduced the rat's ability of learning and memory [3]. Cyclophosphamide- and doxorubicin-treated rats showed significantly impaired performance on the novel place recognition task and the contextual fear conditioning task compared with untreated controls [4]. An increasing number of reports on cancer patients treated with chemotherapy have been published in the last decade [5]. More and more patients endure the effects of cognitive dysfunction. However, there are still no accurate and common methods to measure chemobrain and no effective drugs or methods to alleviate this disease. The objective of this review article is to elucidate the advanced and objective neuroimaging using on chemobrain measurement and to find the potential methods treating on cognitive impairment caused by chemotherapy in cancer patients, such as synaptic repair therapy, stem cell transplantation, active traditional Chinese medicine, acupuncture and psychological rehabilitation.

In what follows, we first provide existing measurement methodologies about chemobrain and other cognitive impairment diseases. Advanced neuroimaging was introduced majorly, for that it's more objective and accurate than questionnaire assessment. Among all neuroimaging technologies, functional MRI and PET has been used commonly in neuroscience. Then several candidate therapies are listed in this review.

Synaptic repair therapy is based on the hypothesis that synapses is degenerated after chemotherapy. Once drugs being used to improve the synaptic transmission, synaptic plasticity or synaptic growth, cognitive functions might be ameliorated [6]. Stem cells

Citation: Yin J, Han YY, Shi DD. Measurements, mechanisms and potential therapy for preventing chemotherapy-induced cognitive impairment. Neurol Neurosci. 2021; 2(2):1-8.

transplantation is a novel methodology for treating cognitive impairment following chemotherapy. Neural stem cells will migrate towards the injured areas and engraft to the targeted place. What's more, its capacity of self-renewal and differentiation could contribute to replacing damaged tissues and repairing the injured cells and tissues [7-10]. Therefore, stem cell engrafted may be a useful therapy for treating chemobrain. Herb medicine, such as *Ginkgo biloba, Ginseng,* or *Melissa officinalis*, have been commonly used as memory or cognition enhancers. The effects of these enhancers have been demonstrated scientifically [11]. The standardized *Ginkgo biloba* extract is one of the most widely used herbal remedies for dementia and cognitive impairment [12]. Studies shows that *Warm-supplementing kidney yang* (WSKY), an herbal prescription used in Traditional Chinese Medicine has potential therapeutic implications for cognitive impairment of schizophrenia [13]. *Acori graminei rhizoma* (AGR) have a protective effect against ischemia-induced neuronal loss and learning and memory damage [14]. *Radix Polygalae* (RP) extract has some repairing effects on the memory and behavioral disorders in rats [15], has neuro-protective effects and memory-enhancing effects [16], could enhance some cognitive functions including memory [17]. *Radix Rehmanniae* could improve the ability of memory [18]. With the development of medicine and technique, nowadays the concept of acupuncture becomes broader, which is a therapeutic technique in which sharp, thin needles are inserted into specific points on the body with mechanical, electrical, or other physical stimulation [19]. Increasing clinical observations and studies show that acupuncture plays an important role in treating neuropsychiatric disorders. There are randomized clinical trials showing that compared to drug therapy, acupuncture exert a better effect on mild cognitive impairment [20]. Even though many traditional Chinese herbs and acupuncture have the ability to enhance the memory or have protective effect against cognitive impairment, no exact herbs or acupoint are proved to protect cancer patients from the cognitive impairment of chemo-agents. The mechanism of chemobrain has, however, yet to be investigated, which enhanced the difficulties of protecting patients from chemobrain.

Methodology to measure chemobrain

Chemobrain is difficulty to study, one reason is the lack of accurate and uniform methodology to measure it. In clinical, neuropsychological assessments will be first used for cancer patients. The design of assessments should be involved a large number of cognitive domains and followed the standard of the International Cognition and Cancer Task Force (ICCTF) [21]. Besides, participants should complete questionnaires about their quality of lives [22]. These messages all obtained from cancer patients themselves, which are subjective and unfaithful. More objective diagnoses are need to measure the performance of chemobrain.

With the development of technologies in neuroimaging, it is possible for researchers finding an objective and exact methodology to measure cognitive impairment following chemotherapy in cancer patients. Nowadays, functional magnetic resonance imaging (fMRI) has been used in brain tumors, mild traumatic brain injury, prostate cancer, bilateral Meniere's disease, insomnia, Alzheimer's disease and so on [23-27]. Functional MRI measures the cerebral blood flow via the blood oxygen level-dependent contrast (BOLD contrast) due to the presence of deoxyhemoglobin in the blood [28]. It is said that the cerebral blood flow was linked with the neural activity directly, which means increasing blood flows would be detected about the area of the brain responsible for the specific neural activity [29]. If less blood flows in the specific regions in the brain is detected, it can be speculated that chemo-agents has damaged the areas. According to this assumption, chembrain can be measured using fMRI. And fMRI will also contribute to the study of mechanism of chemobrain, for which regions being injured by chemo-agents will be observed based on the technique of fMRI.

Positron Emission Tomography (PET) is a nuclear medicine; a positron-emitting radionuclide will be introduced into the body of human or animal and then detected by the system [29]. Fluorodeoxyglucose (FDG), an analogue of glucose, is a commonly used radionuclide. Once FDG injected into bodies, the higher concentrations of it means that the tissue metabolic activity is more active, for it related to the regional glucose uptake. It can be concluded that FDG injected into the cancer patients who have been receiving chemotherapy, regions in the brain which are responsible for the cognitive activities will be detected less imaging than other regions. If the difference is found in the PET scan, chembrain can be confirmed and damaged areas of brain also be discovered. Besides, both fMRI and FDG-PET can be used either in resting state or active state. Studies showed that both fMRI and FDG-PET should be used in confirming a disease, for they reflected the different process of neurodegeneration [30].

Advanced neuroimaging techniques may lead to the early detection of cognitive impairment of chemotherapy, as well as to an improvement in our understanding of the underlying mechanisms of chemobrain.

Understanding the pathophysiology of chemobrain

The quality of life of cancer survivors who experience chemotherapy seriously affected [31]. No evidence-based treatment or preventative intervention for chemobrain exists, since the underlying mechanisms have not been understood [32]. Many researchers engaged to study the mechanisms of chemobrain in order to find the useful anti-drug to prevent cognitive impairment. It is demonstrated that majority chemical agents could not cross the blood–brain barrier (BBB), but can modulate endogenous levels of cytokines such as tumor necrosis factor (TNF) alpha for example adriamycin could improve TNF-α dramatically [33,34]. It is known that TNF-α will be induced the neuronal damage through affect the function of mitochondria [35]. Studies showed that TNF-α induced mitochondrial dysfunction leading to further increases in oxidative stress in the brain. This process might be responsible for the cognitive dysfunction [36]. Reports also suggested that nitric oxide (NO) plays an important role in the cognition dysfunction [37]. For breast cancer cells in vitro, Adriamycin treatment can induce an increase of NO, which is cytotoxic to the cells in vivo [38,39]. NO can inhibit the electron transport of mitochondria and inactive the iron-sulfur-containing enzymes [40,41], which indicate that nitric oxide is a mediator coupling the effect of Adriamycin with cytokine production in the brain [37]. The level of protein oxidation and lipid peroxidation in brain tissues were significantly increases since i.p. injection of Adriamycin [42]. It is hypothesized that TNF-α accumulated after Adriamycin administration, which induce mitochondria damaged and cell apoptosis in brain. The sequence as below:[32]

The mainly pathway it causing apoptosis shows in figure1.

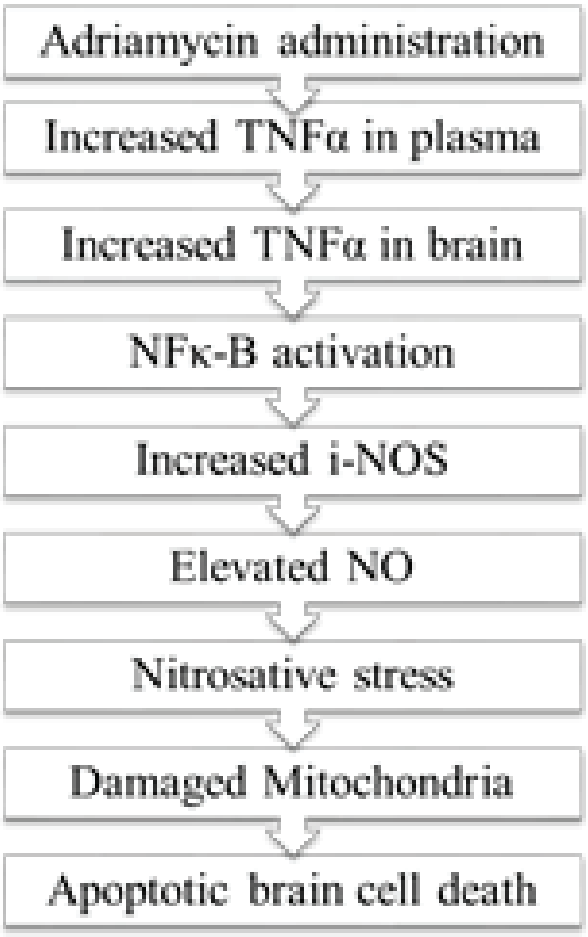


Figure 1. *TNF-α considered one of major contributes for cell apoptosis.*

There are studies to demonstrate that DNA damage induce cognition impairment. Neurotoxicity is associated with increased free radical damage to nuclear DNA. Nuclear DNA codes for many cellular and mitochondria proteins, oxidative damage to nuclear DNA, which could result in formation of dysfunction cytosolic or mitochondria proteins [43]. It is known that mitochondria dysfunction could lead to severe failure of energy metabolism and cell apoptosis [35].

Tanimukai et al reported that Paclitaxel (Px) directly causes neuronal apoptosis through endoplasmic reticulum (ER) stress responses [44]. Study shows that endoplasmic reticulum (ER) stress is involved in various human neurological diseases and cause cognitive dysfunctions [45]. When ER stress is very severe, cells induce and/or activate C/EBP homologous protein (CHOP), the c-Jun NH2-terminal kinase (JNK) pathway, and caspase 4, thus leading to apoptosis. Animal studies also have revealed that chemotherapy-induced cognitive impairment is associated with decreased cell proliferation in hippocampal neural progenitor cells which play a crucial role in short-term learning and memory process [3].

Since both clinical and animal studies have found that memory, learning and thinking abilities of patients and animals receiving chemotherapy be destroyed, brain-derived neurotrophic factor (BDNF) might play critical role in chemobrain. BNDF is indispensable for the survival of existing neurons and the growth and differentiation of new neurons [46]. The functions of BDNF include that enhance synaptic transmission, facilitate synaptic plasticity and promote synaptic growth [6], which confirmed the importance of BDNF for cognitive functions. Besides, BDNF actives in the brain areas, such as cortex, hippocampus and basal forebrain which are responsible for the cognitive functions [47]. Researchers have confirmed that the number of neural cells were decreased after treating with chemotherapy. It is calculated that chemo-agents reduced the expression of BDNF, then affected the synaptic transmission, facilitate synaptic plasticity. With the lower brain-derived neurotrophic factor, BDNF/TRKB signaling cannot work as normal, which would affect the survival of existing neural cells and differentiation/producing of novel neural cells in the brain areas especially in the hippocampus, cortex and basal forebrain.

Besides, researchers also discovered that neuroinflammation plays a critical role in chemobrain. The dysfunction of anti-inflammatory and pro-inflammatory cytokines in blood and brain tissues were found in mice treated with chemotherapy. And astrocyte and microglia were activated by chemo-agent treatment. What's more, it is showed that there was a positive relationship between pro-inflammatory cytokine, such as IL-6 and TNF-α, and cognitive impairment performance. While, a negative correlation between anti-inflammatory and cognitive decline in mice [48].

Thus, a therapy which have neurotrophic, anti-inflammation and/or anti-apoptosis effects may prevent cognitive impairment from chemotherapy.

Potential therapies about chemobrain

Synaptic repair therapy

Evidence shows that the progression of mild cognitive impairment is associated with synapse degeneration [6]. Synapse is an essential part of neuronal connections and stabilized neuronal connections are the basis on cognitive functions, especially memory [49]. It is said that synapse dysfunction and synapse loss are reversible, so that synapse loss can be repaired and new synapse can be established [6]. According to the synaptic characteristics, improving synaptic transmission and synaptic growth are benefit for the modulation of synapses. Cholinesterase inhibitors such as donepezil and rivastigmine block the metabolism of choline, which increase the transmission of cholinergic synapses [50]. Synaptic growth, including strengthen existing dendritic spines and promote new synaptic terminals, can rescue the synaptic connections causing by cognitive impairment. Studies describe brain-derived neurotrophic factor (BDNF) is a candidate for promoting synaptic growth [6]. Synaptic repair therapy might be powerful ways to achieve our goals.

Stem cells transplantation

Neural stem cells (NSCs), which play an indispensable role in neural cell differentiation and growth, are inevitable for the functions of memory and learning. Both cognitive and motor functions can be improved dramatically by NSCs transplantation through a BDNF-dependent mechanism in a transgenic model of dementia [51]. NSCs having the ability to improve the memory and learning functions mostly contributes to the neurotrophic support. The enormous increase of activated microglia cells were observed in the chemotherapy group, however, activated microglia cells were decreased dramatically

in the stem cell grafted group, which means stem cell grafting could reduce neuro-inflammation in hippocampus significantly. Morphological experiment showed that arborization of the apical and basal dendritic trees of CA1 pyramidal cells improved substantially in the group of stem cells transplantation after chemotherapy [52]. All the results show that NSCs transplantation can alleviate the neurotoxicity of chemotherapy, however the mechanisms of it stills indistinct.

The mesenchymal stem cells (MSCs) also be used in preventing the deleterious effects of chemobrain associated with Doxorubicin in albino rat [53]. MSCs, low immunogenicity, fewer immune cells, high proliferative rate, and could be differentiate into neuron-like cells [54,55], has the potential to be one kind of therapies for the chemobrain. It is said that MSCs administration could ameliorate brain injuries including stroke and other neurodegenerative disorders and improve metabolic viability and neuronal cell densities [56,57]. MSCs could activate endogenous stem cells, release growth factors and enhance immunoregulation capability, which contribute to the ability of neuroprotection [58].

Potential Traditional Chinese Medicine treated on chemobrain

A host of products from plant species and derivatives have neuro-protective effects in vitro and in vivo. Besides neuroprotection, natural products also demonstrate biological effects that target biochemical pathways underlying associated symptoms of neurodegenerative disorders that include cognitive impairments, energy/fatigue, mood, and anxiety [59].

Chinese herbs

Polygala tenuifolia Willd

The roots of *Polygala tenuifolia Willd*, which is known as "yuanzhi" in China, has been prescribed for hundreds of years to treat psychotic illnesses such as dementia and cognitive dysfunctions [60-62]. *Polygala tenuifolia Willd* extract has some repairing effects on the memory and behavioral disorders [15]. Studies shows that BT11, which is the extract of the root of *Polygala tenuifolia Willd*, plays an important role in enhancing the memory of human beings [16]. Its memory improvement has also been reported in various animal models. In morrion water maze tests (MWM), the impaired spatial memory of the mice was partly reversed by the crud extract of the roots of *Polygala tenuifolia* as compared with the control mice. It is shown that it also generated antioxidant effect via the endogenous enzymatic system [16,17,63].

Gardenia jasminoides

Gardenia jasminoides, as a traditional Chinese medicine, has been recorded in Chinese Pharmacopoeia and used for treating diuretic, cholagogue, anti-inflammatory and antipyretic effects [64]. Since in eastern countries it has been used for hundreds of years, the safety and efficacy of this herbal medicine has been reviewed.

Geniposide, an iridoid glucoside isolated from gardenia (the fruit of *Gardenia jasminoides*) and also a major component of Huang-Lian-Jie-Du Decoction, has been proven to have good therapeutic effects on cognition impairment both in clinical practice and pharmacological experiments. It is indicated that geniposide treatment could suppress the production of tumor mecrosis factor-a (TNF-α) [65]. Besides, geniposide has been demonstrated can cross the BBB [66]. Geniposide Rg1 is a major component existing in various ginseng products which have been widely used in the treatment of chemotherapy-induced side effects in cancer patients [67], including breast cancer patients [68], a study using Rg1 treated chemobrain provides compelling evidence in support of the use of ginseng products as chemopreventive agents. An effective dose of 10 mg/kg/day of Rg1 used in mice of this study was equivalent to 6 mg/day used for humans. Ginseng is safe and tolerable at the recommended dose of 1–2 g of dry ginseng root or 200–600 mg of standardized ginseng extracts per day [69].

Ginkgo Biloba

It is reported that the extract of *Ginkgo Biloba* has neuro-protective effects against various neurological disorders, such as Alzhemer's disease, depression and ischemia [70,71]. Many studies shows that the effective constituent of *Ginkgo Biloba* is Bilobalide (BB) [72]. The result of Water Maze Test demonstrated that BB significantly protected rats against cognitive deficits through alleviating neuronal apoptosis and to reduce the expression of tumor necrosis factors-α (TNF-α) in the brain cortex and the hippocampal [73]. These effects might be related to the antioxidant and antiapoptotic activities of BB.

Rehmannia glutinosa

Researches have been demonstrated that *Rehmannia glutinosa* could use to treat amnesia or dementia and memory impairment in mice [74]. Catalpol is an iridoid glycoside isolated from the *Rehmannia glutinosa*. Once injected with catapol, the mice treated with D-galactose showed greatly improved learning and memory ability in Morris water maze test comparted with control (treated with D-galactose) [75]. As catalpol administration could elevate memory function, these results implied that catalpol may be used in the therapy of cognitive impairment like AD or chemobrain [76].

Acupuncture

Increasing evidence confirms that acupuncture plays an important role in reducing anti-cancer treatment caused side effects, such as anxiety, fatigue, depression, sleep disturbance, pain and so on. Numerous studies also indicate that acupuncture exerts greatly effects in treating mild cognitive impairment [77-83].

The mechanism of mild cognitive impairment caused by chemo-therapy is complex, but apoptosis has been suggested to be one of the key elements in brain injury following chemo-agents [32,36,37,84,85]. Therefore, suppressing the apoptosis pathway may be a promising approach to prevent mild cognitive impairment induced by chemo-therapy. Apoptosis is highly regulated by complex factors. Research shows that the levels of pro-apoptotic proteins p53 and Bax and Bcl-xl increased, which induced the apoptosis of cells in brain. Electro-acupuncture at the *Baihui* and *Shenting* acupoints ameliorate wild cognitive impairment in cerebral I/R injured rats for electro-acupuncture significantly reduce the Bax expression [81]. This may be a potential therapy for the treatment of chemobrain.

It is said that *Baihui* is one of the most important acupoints to treat the neuro-degenerative disorders and cognitive impairment in acupuncture treatment. Study shows that acupuncture stimulation at *Baihui* significantly ameliorated memory deficits, which may be due to the recovery of the Ach system and the alleviation of BDNF and CREB expression [86]. The results may be another potential therapy for the treatment of chemobrain.

Neuropsychological rehabilitationy

It is reported that psychological stress such as depression, anxiety, sleep disturbances and self-body image perception may be aggregated after chemotherapy in cancer patients [87]. Cognitive performance can be affected by psychological distress directly and indirectly [88]. It is implicated that anxiety and depression may be aggravate cognitive impairment following chemotherapy. Increasing evidence has been indicated that psychological stress be related with the function of attention and memory [89-91]. Psychological stress can affected the system of immune, kinds of cytokines such as IL-6 and TNF-alpha be related with the cognitive pathway. According to these studies, it can be calculated that neuropsychological care and rehabilitation may be one of effective approaches for cognitive impairment after chemotherapy.

Based on the application of neuropsychological care and rehabilitation strategies from other cognitive impairment such as traumatic brain injury and schizophrenia, the approaches about cognitive improvement could be cognitive enhancement therapy (CET), compensatory training, environment change, meditation and physical exercise [92]. Persisting complaints, training in use of a memory notebook and training the abilities of problem solving could increase coping behaviors and reduce stress [93]. Nowadays, the specific computer software to enhance the corresponding cognitive functions has been developed [94]. It is reported that meditation can ameliorate cognitive impairment caused by chemotherapy in cancer patients [95]. Meditation is associated with reducing depression, anxiety and improving sleep quality, besides, it can stimulate the immune system response [95,96]. It is well known that physical exercise can improve the blood flow and oxygen to the brain, which may help the cell proliferation associated with cognitive functions in the brain. Qigong also be used to ameliorate cognitive impairment in cancer patients, positive effects were observed in this study [97], which may contribute to its reducing anxiety and improving immune response. Additionally, the application of yoga between cancer patients also plays an active influence [98].

Overview

It is known that cognitive impairment caused by chemotherapy affected the life quality dramatically. In order to find effective approaches ameliorate cognitive impairment after chemotherapy in cancer patients, objective and accurate measurement methodologies should be applied. Compare with the traditional questionnaire assessment and self-report method, neuroimaging is more acceptable and precise. The difference of brain structure and area can be seen directly in the imaging using functional MRI and regions in the brain having lower metabolism also be detected combined with PET, which contribute to the mechanism study of chemobrain.

About the mechanism of chemobrain, the mainly statements are, neuroinflammation, cell apoptosis and synapses degeneration. A large number of factors can cause apoptosis, thus further studies should be done to define it. BDNF reduction might be one explain for synapses degeneration. Potential therapies were listed in this review. Synaptic repair therapy is based on the assumption synapses and dendritic spines degeneration. Stem cells transplantation promote the neural cells and repair existing neural cells. Thanks to the broad and profound of Chinese medicine, it can be a powerful treatment in treating chemobrain. Besides, neuropsychological rehabilitation is convenient and safe for patients. In essence, a great deal of collaboration and methodologies will need to promote chemobrain therapies.

Conflict of interest statement

All authors have no conflicts of interest with this work.

References

1. Marín AP, Sánchez AR, Arranz EE. Nasal septum perforation in a breast cancer patient treated with bevacizumab. Ann Oncol. 2009;20(11):1901-1902.
2. Asher A. Cognitive dysfunction among cancer survivors. Am J Phys Med Rehabil. 2011;90(5 Suppl 1):S16-26.
3. Briones TL, Woods J. Chemotherapy-induced cognitive impairment is associated with decreases in cell proliferation and histone modifications. BMC Neurosci. 2011;12:124.
4. Christie LA, Acharya MM, Parihar VK, Nguyen A, Martirosian V, Limoli CL. Impaired cognitive function and hippocampal neurogenesis following cancer chemotherapy. Clin Cancer Res. 2012;18(7):1954-1965.
5. Andreis F, Ferri M, Mazzocchi M, et al. Lack of a chemobrain effect for adjuvant FOLFOX chemotherapy in colon cancer patients. A pilot study. Support Care Cancer. 2013;21(2):583-590.
6. Lu B, Nagappan G, Guan X, Nathan PJ, Wren P. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. Nat Rev Neurosci. 2013;14(6):401-416.
7. Lee IS, Jung K, Kim IS, et al. Human neural stem cells alleviate Alzheimer-like pathology in a mouse model. Mol Neurodegener. 2015;10:38.
8. Mine Y, Tatarishvili J, Oki K, Monni E, Kokaia Z, Lindvall O. Grafted human neural stem cells enhance several steps of endogenous neurogenesis and improve behavioral recovery after middle cerebral artery occlusion in rats. Neurobiol Dis. 2013;52:191-203.
9. Pluchino S, Gritti A, Blezer E, et al. Human neural stem cells ameliorate autoimmune encephalomyelitis in non-human primates. Ann Neurol. 2009;66(3):343-354.
10. Tamaki SJ, Jacobs Y, Dohse M, et al. Neuroprotection of host cells by human central nervous system stem cells in a mouse model of infantile neuronal ceroid lipofuscinosis. Cell Stem Cell. 2009;5(3):310-319.
11. Jung EY, Lee MS, Ahn CJ, Cho SH, Bae H, Shim I. The neuroprotective effect of gugijihwang-tang on trimethyltin-induced memory dysfunction in the rat. Evid Based Complement Alternat Med. 2013;2013:542081.
12. DeFeudis FV, Drieu K. Ginkgo biloba extract (EGb 761) and CNS functions: basic studies and clinical applications. Curr Drug Targets. 2000;1(1):25-58.
13. Guo X, Chen ZH, Wang HL, et al. WSKY, a traditional Chinese decoction, rescues cognitive impairment associated with NMDA receptor antagonism by enhancing BDNF/ERK/CREB signaling. Mol Med Rep. 2015; 11(4):2927-34.
14. Lee B, Choi Y, Kim H, et al. Protective effects of methanol extract of Acori graminei rhizoma and Uncariae Ramulus et Uncus on ischemia-induced neuronal death and cognitive impairments in the rat. Life Sci. 2003;74(4):435-450.
15. Chen YL, Hsieh CL, Wu PH, Lin JG. Effect of Polygala tenuifolia root on behavioral disorders by lesioning nucleus basalis magnocellularis in rat. J Ethnopharmacol. 2004;95(1):47-55.
16. Lee JY, Kim KY, Shin KY, Won BY, Jung HY, Suh YH. Effects of BT-11 on memory in healthy humans. Neurosci Lett. 2009;454(2):111-114.
17. Shin KY, Lee JY, Won BY, et al. BT-11 is effective for enhancing cognitive functions in the elderly humans. Neurosci Lett. 2009;465(2):157-159.
18. Shen H, Jiang Z. Effects of Ginsonoside Rb3 on NMDA current and KA current in rat cultured hippocampal neurons. Zhong Yao

Cai. 2011;27(5):16-21.

19. Zhang ZJ, Wang XM, McAlonan GM. Neural acupuncture unit: a new concept for interpreting effects and mechanisms of acupuncture. Evid Based Complement Alternat Med. 2012;2012:429412.
20. Cheng H, Yu J, Jiang Z, et al. Acupuncture improves cognitive deficits and regulates the brain cell proliferation of SAMP8 mice. Neurosci Lett. 2008;432(2):111-116.
21. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 2011;12(7):703-708.
22. Dwek MR, Rixon L, Simon A, Hurt C, Newman S. Examining the effects of adjuvant chemotherapy on cognition and the impact of any cognitive impairment on quality of life in colorectal cancer patients: study protocol. BMC Psychol. 2015;3:43.
23. Brommelhoff JA, Sultzer DL. Brain structure and function related to depression in Alzheimer's disease: contributions from neuroimaging research. J Alzheimers Dis. 2015;45(3):689-703.
24. Gu X, Fang ZM, Liu Y, Huang ZW, Zhang R, Chen X. Diagnostic advantages of intratympanically gadolinium contrast-enhanced magnetic resonance imaging in patients with bilateral Meniere's disease. Am J Otolaryngol. 2015;36(1):67-73.
25. Mayer AR, Bellgowan PS, Hanlon FM. Functional magnetic resonance imaging of mild traumatic brain injury. Neurosci Biobehav Rev. 2015;49:8-18.
26. Ouzzane A, Renard-Penna R, Marliere F, et al. Magnetic Resonance Imaging Targeted Biopsy Improves Selection of Patients Considered for Active Surveillance for Clinically Low Risk Prostate Cancer Based on Systematic Biopsies. J Urol. 2015;194(2):350-356.
27. Ravn S, Holmberg M, Sørensen P, Frokjaer JB, Carl J. Presurgical functional magnetic resonance imaging in patients with brain tumors. Acta Radiol. 2016;57(1):82-89.
28. Koerte IK, Lin AP, Willems A, et al. A review of neuroimaging findings in repetitive brain trauma. Brain Pathol. 2015;25(3):318-349.
29. McDonald BC, Saykin AJ, McAllister TW. Functional MRI of mild traumatic brain injury (mTBI): progress and perspectives from the first decade of studies. Brain Imaging Behav. 2012;6(2):193-207.
30. Besson FL, La Joie R, Doeuvre L, et al. Cognitive and Brain Profiles Associated with Current Neuroimaging Biomarkers of Preclinical Alzheimer's Disease. J Neurosci. 2015;35(29):10402-10411.
31. Ganz PA, Kwan L, Castellon SA, et al. Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. J Natl Cancer Inst. 2013;105(11):791-801.
32. Butterfield DA. The 2013 SFRBM discovery award: selected discoveries from the butterfield laboratory of oxidative stress and its sequela in brain in cognitive disorders exemplified by Alzheimer disease and chemotherapy induced cognitive impairment. Free Radic Biol Med. 2014;74:157-174.
33. Bigotte L, Arvidson B, Olsson Y. Cytofluorescence localization of adriamycin in the nervous system. I. Distribution of the drug in the central nervous system of normal adult mice after intravenous injection. Acta Neuropathol. 1982;57(2-3):121-129.
34. Usta Y, Ismailoglu UB, Bakkaloglu A, et al. Effects of pentoxifylline in adriamycin-induced renal disease in rats. Pediatr Nephrol. 2004;19(8):840-843.
35. Goossens V, Grooten J, De Vos K, Fiers W. Direct evidence for tumor necrosis factor-induced mitochondrial reactive oxygen intermediates and their involvement in cytotoxicity. Proc Natl Acad Sci U S A. 1995;92(18):8115-8119.
36. Tangpong J, Cole MP, Sultana R, et al. Adriamycin-induced, TNF-alpha-mediated central nervous system toxicity. Neurobiol Dis. 2006;23(1):127-139.
37. Tangpong J, Cole MP, Sultana R, et al. Adriamycin-mediated nitration of manganese superoxide dismutase in the central nervous system: insight into the mechanism of chemobrain. J Neurochem. 2007;100(1):191-201.
38. Győrffy B, Serra V, Jürchott K, et al. Prediction of doxorubicin sensitivity in breast tumors based on gene expression profiles of drug-resistant cell lines correlates with patient survival. Oncogene. 2005;24(51):7542-7551.
39. Ozen S, Usta Y, Sahin-Erdemli I, et al. Association of nitric oxide production and apoptosis in a model of experimental nephropathy. Nephrol Dial Transplant. 2001; 16(1):32-38.
40. MacMillan-Crow LA, Crow JP, Kerby JD, Beckman JS, Thompson JA. Nitration and inactivation of manganese superoxide dismutase in chronic rejection of human renal allografts. Proc Natl Acad Sci U S A. 1996;93(21):11853-11858.
41. Radi R. Nitric oxide, oxidants, and protein tyrosine nitration. Proc Natl Acad Sci U S A. 2004;101(12):4003-4008.
42. Joshi G, Sultana R, Tangpong J, et al. Free radical mediated oxidative stress and toxic side effects in brain induced by the anti cancer drug adriamycin: insight into chemobrain. Free Radic Res. 2005;39(11):1147-1154.
43. Gabbita SP, Lovell MA, Markesbery WR. Increased nuclear DNA oxidation in the brain in Alzheimer's disease. J Neurochem. 1998;71(5):2034-2040.
44. Tanimukai H, Kanayama D, Omi T, Takeda M, Kudo T. Paclitaxel induces neurotoxicity through endoplasmic reticulum stress. Biochem Biophys Res Commun. 2013;437(1):151-155.
45. Sakagami Y, Kudo T, Tanimukai H, et al. Involvement of endoplasmic reticulum stress in tauopathy. Biochem Biophys Res Commun. 2013;430(2):500-504.
46. Acheson A, Conover JC, Fandl JP, et al. A BDNF autocrine loop in adult sensory neurons prevents cell death. Nature. 1995;374(6521):450-453.
47. Yamada K, Nabeshima T. Brain-derived neurotrophic factor/TrkB signaling in memory processes. J Pharmacol Sci. 2003;91(4):267-270.
48. Shi DD, Huang YH, Lai CSW, et al. Chemotherapy-Induced Cognitive Impairment Is Associated with Cytokine Dysregulation and Disruptions in Neuroplasticity. Mol Neurobiol. 2019;56(3):2234-2243.
49. Xu T, Yu X, Perlik AJ, et al. Rapid formation and selective stabilization of synapses for enduring motor memories. Nature. 2009;462(7275):915-919.
50. Rodda J, Morgan S, Walker Z. Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. Int Psychogeriatr. 2009;21(5):813-824.
51. Goldberg NRS, Caesar J, Park A, et al. Neural Stem Cells Rescue Cognitive and Motor Dysfunction in a Transgenic Model of Dementia with Lewy Bodies through a BDNF-Dependent Mechanism. Stem Cell Reports. 2015;5(5):791-804.
52. Acharya MM, Martirosian V, Chmielewski NN, et al. Stem cell transplantation reverses chemotherapy-induced cognitive dysfunction. Cancer Res. 2015;75(4):676-686.
53. Williams LM, Debattista C, Duchemin AM, Schatzberg AF, Nemeroff CB. Childhood trauma predicts antidepressant response in adults with major depression: data from the randomized international study to predict optimized treatment for depression. Transl Psychiatry. 2016;6(5):e799.
54. Yan M, Sun M, Zhou Y, et al. Conversion of human umbilical cord mesenchymal stem cells in Wharton's jelly to dopamine

neurons mediated by the Lmx1a and neurturin in vitro: potential therapeutic application for Parkinson's disease in a rhesus monkey model [retracted in: PLoS One. 2020 Nov 2;15(11):e0242032]. PLoS One. 2013;8(5):e64000.

55. Zemel'ko VI, Kozhukharova IB, Alekseenko LL, et al. Neurogenic potential of human mesenchymal stem cells isolated from bone marrow, adipose tissue and endometrium: a comparative study. Tsitologiia. 2013;55(2):101-110.
56. Lim JY, Jeong CH, Jun JA, et al. Therapeutic effects of human umbilical cord blood-derived mesenchymal stem cells after intrathecal administration by lumbar puncture in a rat model of cerebral ischemia. Stem Cell Res Ther. 2011;2(5):38.
57. Ribeiro CA, Fraga JS, Grãos M, et al. The secretome of stem cells isolated from the adipose tissue and Wharton jelly acts differently on central nervous system derived cell populations. Stem Cell Res Ther. 2012;3(3):18.
58. Phillips AW, Johnston MV, Fatemi A. The potential for cell-based therapy in perinatal brain injuries. Transl Stroke Res. 2013;4(2):137-148.
59. da Rocha MD, Viegas FP, Campos HC, et al. The role of natural products in the discovery of new drug candidates for the treatment of neurodegenerative disorders II: Alzheimer's disease. CNS Neurol Disord Drug Targets. 2011;10(2):251-270.
60. Chen Y, Huang X, Chen W, Wang N, Li L. Tenuigenin promotes proliferation and differentiation of hippocampal neural stem cells. Neurochem Res. 2012;37(4):771-777.
61. Chung IW, Moore NA, Oh WK, et al. Behavioural pharmacology of polygalasaponins indicates potential antipsychotic efficacy. Pharmacol Biochem Behav. 2002;71(1-2):191-195.
62. Park CH, Choi SH, Koo JW, et al. Novel cognitive improving and neuroprotective activities of Polygala tenuifolia Willdenow extract, BT-11. J Neurosci Res. 2002;70(3):484-492.
63. Li Z, Liu Y, Wang L, et al. Memory-Enhancing Effects of the Crude Extract of Polygala tenuifolia on Aged Mice. Evid Based Complement Alternat Med. 2014;2014:392324.
64. He Y, Yu Z, Giegling I, et al. Schizophrenia shows a unique metabolomics signature in plasma. Transl Psychiatry. 2012;2(8):e149.
65. Lv C, Wang L, Liu X, et al. Multi-faced neuroprotective effects of geniposide depending on the RAGE-mediated signaling in an Alzheimer mouse model. Neuropharmacology. 2015;89:175-184.
66. Lv C, Wang L, Liu X, et al. Geniposide attenuates oligomeric Aβ(1-42)-induced inflammatory response by targeting RAGE-dependent signaling in BV2 cells. Curr Alzheimer Res. 2014;11(5):430-440.
67. Chen S, Wang Z, Huang Y, et al. Ginseng and anticancer drug combination to improve cancer chemotherapy: a critical review. Evid Based Complement Alternat Med. 2014;2014:168940.
68. Cui Y, Shu XO, Gao YT, Cai H, Tao MH, Zheng W. Association of ginseng use with survival and quality of life among breast cancer patients. Am J Epidemiol. 2006;163(7):645-653.
69. Helms S. Cancer prevention and therapeutics: Panax ginseng. Altern Med Rev. 2004;9(3):259-274.
70. Chandrasekaran K, Mehrabian Z, Spinnewyn B, Chinopoulos C, Drieu K, Fiskum G. Neuroprotective effects of bilobalide, a component of Ginkgo biloba extract (EGb 761) in global brain ischemia and in excitotoxicity-induced neuronal death. Pharmacopsychiatry. 2003;36 Suppl 1:S89-S94.
71. Tanaka Y, Marumo T, Omura T, Yoshida S. Serum S100B indicates successful combination treatment with recombinant tissue plasminogen activator and MK-801 in a rat model of embolic stroke Brain Res 2007; 1154: 194-9.
72. Rossi R, Basilico F, Rossoni G, Riva A, Morazzoni P, Mauri PL. Liquid chromatography/atmospheric pressure chemical ionization ion trap mass spectrometry of bilobalide in plasma and brain of rats after oral administration of its phospholipidic complex. J Pharm Biomed Anal. 2009;50(2):224-227.
73. Li WZ, Wu WY, Huang H, Wu YY, Yin YY. Protective effect of bilobalide on learning and memory impairment in rats with vascular dementia. Mol Med Rep. 2013;8(3):935-941.
74. Cai M, Shin BY, Kim DH, et al. Neuroprotective effects of a traditional herbal prescription on transient cerebral global ischemia in gerbils. J Ethnopharmacol. 2011;138(3):723-730.
75. Zhang XL, Jiang B, Li ZB, Hao S, An LJ. Catalpol ameliorates cognition deficits and attenuates oxidative damage in the brain of senescent mice induced by D-galactose. Pharmacol Biochem Behav. 2007;88(1):64-72.
76. Zhang XL, An LJ, Bao YM, Wang JY, Jiang B. d-galactose administration induces memory loss and energy metabolism disturbance in mice: protective effects of catalpol. Food Chem Toxicol. 2008;46(8):2888-2894.
77. Bai L, Zhang M, Chen S, et al. Characterizing acupuncture de qi in mild cognitive impairment: relations with small-world efficiency of functional brain networks. Evid Based Complement Alternat Med. 2013;2013:304804.
78. Cao H, Wang Y, Chang D, Zhou L, Liu J. Acupuncture for vascular mild cognitive impairment: a systematic review of randomised controlled trials. Acupunct Med. 2013;31(4):368-374.
79. Chen S, Bai L, Xu M, et al. Multivariate granger causality analysis of acupuncture effects in mild cognitive impairment patients: an FMRI study. Evid Based Complement Alternat Med. 2013;2013:127271.
80. Chu H, Li MH, Huang YC, Lee SY. Simultaneous transcutaneous electrical nerve stimulation mitigates simulator sickness symptoms in healthy adults: a crossover study. BMC Complement Altern Med. 2013;13:84.
81. Feng X, Yang S, Liu J, et al. Electroacupuncture ameliorates cognitive impairment through inhibition of NF-κB-mediated neuronal cell apoptosis in cerebral ischemia-reperfusion injured rats. Mol Med Rep. 2013;7(5):1516-1522.
82. Jittiwat J, Wattanathorn J. Ginger pharmacopuncture improves cognitive impairment and oxidative stress following cerebral ischemia. J Acupunct Meridian Stud. 2012;5(6):295-300.
83. Johnston MF, Hays RD, Subramanian SK, et al. Patient education integrated with acupuncture for relief of cancer-related fatigue randomized controlled feasibility study. BMC Complement Altern Med. 2011;11:49.
84. Tangpong J, Miriyala S, Noel T, Sinthupibulyakit C, Jungsuwadee P, St Clair DK. Doxorubicin-induced central nervous system toxicity and protection by xanthone derivative of Garcinia mangostana. Neuroscience. 2011;175:292-299.
85. Yang M, Kim J, Kim JS, et al. Hippocampal dysfunctions in tumor-bearing mice. Brain Behav Immun. 2014;36:147-155.
86. Lee B, Sur B, Shim J, Hahm DH, Lee H. Acupuncture stimulation improves scopolamine-induced cognitive impairment via activation of cholinergic system and regulation of BDNF and CREB expressions in rats. BMC Complement Altern Med. 2014;14:338.
87. Saini A, Berruti A, Cracco C, et al. Psychological distress in men with prostate cancer receiving adjuvant androgen-deprivation therapy. Urol Oncol. 2013;31(3):352-358.
88. Kerestes R, Ladouceur CD, Meda S, et al. Abnormal prefrontal activity subserving attentional control of emotion in remitted depressed patients during a working memory task with emotional distracters. Psychol Med. 2012;42(1):29-40.
89. Balash Y, Mordechovich M, Shabtai H, Giladi N, Gurevich T, Korczyn AD. Subjective memory complaints in elders: depression, anxiety, or cognitive decline?. Acta Neurol Scand. 2013;127(5):344-350.
90. Kizilbash AH, Vanderploeg RD, Curtiss G. The effects of depression

and anxiety on memory performance. Arch Clin Neuropsychol. 2002;17(1):57-67.

91. Lisiecka DM, Carballedo A, Fagan AJ, Ferguson Y, Meaney J, Frodl T. Recruitment of the left hemispheric emotional attention neural network in risk for and protection from depression. J Psychiatry Neurosci. 2013;38(2):117-128.
92. Jean-Pierre P, Johnson-Greene D, Burish TG. Neuropsychological care and rehabilitation of cancer patients with chemobrain: strategies for evaluation and intervention development. Support Care Cancer. 2014;22(8):2251-2260.
93. Tiersky LA, Anselmi V, Johnston MV, et al. A trial of neuropsychologic rehabilitation in mild-spectrum traumatic brain injury. Arch Phys Med Rehabil. 2005;86(8):1565-1574.
94. Maschio M, Dinapoli L, Fabi A, Giannarelli D, Cantelmi T. Cognitive rehabilitation training in patients with brain tumor-related epilepsy and cognitive deficits: a pilot study. J Neurooncol. 2015;125(2):419-426.
95. Biegler KA, Chaoul MA, Cohen L. Cancer, cognitive impairment, and meditation. Acta Oncol. 2009;48(1):18-26.
96. Carlson LE, Speca M, Faris P, Patel KD. One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. Brain Behav Immun. 2007;21(8):1038-1049.
97. Oh B, Butow PN, Mullan BA, et al. Effect of medical Qigong on cognitive function, quality of life, and a biomarker of inflammation in cancer patients: a randomized controlled trial. Support Care Cancer. 2012;20(6):1235-1242.
98. Culos-Reed SN, Carlson LE, Daroux LM, Hately-Aldous S. A pilot study of yoga for breast cancer survivors: physical and psychological benefits. Psychooncology. 2006;15(10):891-897.