EVALUATING ACUPUNCTURE USE IN ALLEVIATION OF CANCER-RELATED SYMPTOMS THROUGH THE NEUROTROPHIC PATHWAY: A SYSTEMATIC REVIEW OF HUMAN STUDIES

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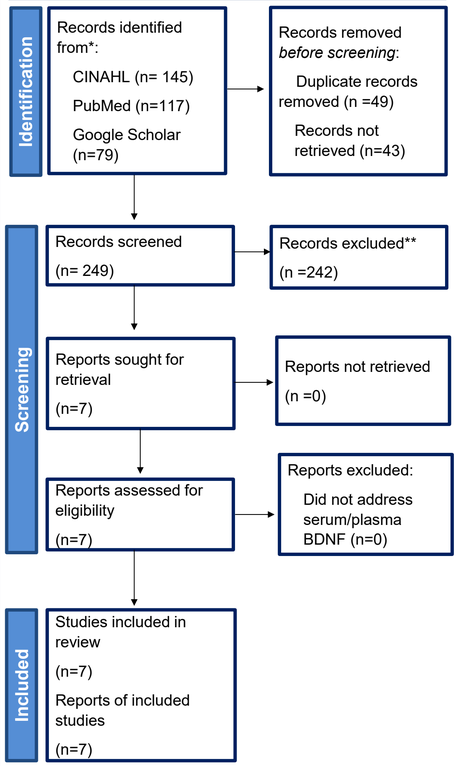
Introduction

- Acupuncture is widely used to manage cancer-related symptoms, yet its underlying mechanisms remain unclear.
- Brain-derived neurotrophic factor (BDNF) supports neuronal health and may be disrupted by chemotherapy.
- Emerging evidence suggests acupuncture may influence BDNF levels, pointing to a possible role in neuroprotection through the neurotrophic pathway.
- **Study Objective:** This systematic review investigates whether acupuncture influences brain-derived neurotrophic factor (BDNF) levels in cancer patients. Given BDNF's role in protecting the brain from chemotherapy-related neurotoxicity, we aim to determine if acupuncture's symptom-relieving effects are linked to modulation of the neurotrophic pathway.

Methods

- **Study Design:** A comprehensive literature search was conducted using **PubMed**, **Google Scholar**, and **CINAHL**, including studies published in **English** and **Chinese**.
- **Inclusion Criteria:** Human clinical trials evaluating acupuncture for cancer-related symptoms—including **insomnia, pain, neuropathy, cognitive impairment, fatigue, depression, anxiety,** and **physical function**—that also reported **BDNF biomarker levels**.
- **Data Extraction:** cancer type, intervention details, targeted symptoms, symptom assessment methods, and associations between BDNF changes and symptom outcomes. **PRISMA 2020 guidelines** were followed to ensure methodological transparency, reproducibility, and completeness.
- **Analysis:** A **meta-analysis** was conducted using **Cochrane's RevMan** online platform to statistically synthesize the relationship between acupuncture, BDNF levels, and symptom improvement, aiming to identify consistent trends and assess the overall strength of the evidence.

Figure 1: PRISMA Diagram



Results

- Seven out of 249 articles met the inclusion criteria, including 539 participants in total. Most studies **(71.4%)** were double-arm trials with 50 or more participants. They used both subjective and objective tools to assess symptoms, with nearly half **(42.9%)** including patients with multiple cancer types, and 71.4% measured serum BDNF levels. **(Table 1)**
- Four studies **(57.1%)** reported increased BDNF levels after acupuncture, and six **(85.7%)** showed improvements in cancer-related symptoms. Only one study (14.3%) found a statistically significant link between BDNF increase and cognitive improvement **($p < 0.05$). (Table 1)**
- Acupuncture improved symptoms such as insomnia, neuropathy, cognitive impairment, and cerebral dysfunction in **85.7%** of studies, with improvements supported by both subjective and objective evaluations. **(Table 2)**
- BDNF increases were mainly observed in patients with insomnia and cognitive symptoms, with only Tong et al. (2018) showing a significant correlation between BDNF levels and symptom relief **($p<0.05$). (Table 2)**
- A meta-analysis of three double-arm studies (131 experimental, 118 control) found no significant difference in BDNF levels between groups **(SMD = 0.34; 95% CI: -0.31 to 0.98). (Figure 2)**
- High heterogeneity was present **($I^2 = 84\%$, $p < 0.01$)**, though **Tong et al. (2018)** showed a strong and significant effect **(Cohen's $d > 0.8$)**, suggesting a meaningful BDNF increase in the treatment group.**(Figure 2)**

Table 1: Characteristics of eligible studies

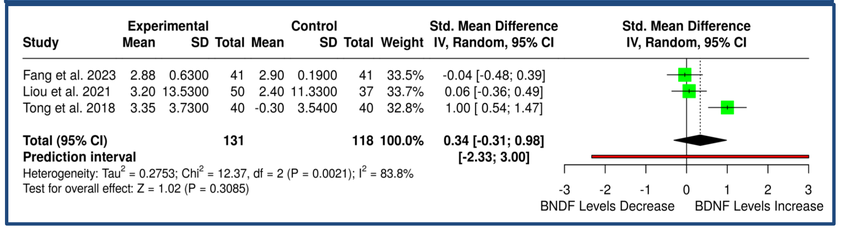
Characteristics	Number of Studies, n (%)
Total	7 (100)
Study Design	
Single Arm	2 (28.6)
Double-Arm	**5 (71.4)**
Control Group	2 (28.6)
Other Intervention[a]	3 (42.9)
Sample Size	
<50	2 (28.6)
≥50	**5 (71.4)**
Cancer Types	
Multiple Cancer Types[b]	**3 (42.9)**
Breast	2 (28.6)
Cerebral Glioma	1 (14.3)
Multiple Melanoma	1 (14.3)
Intervention	
Acupuncture	2 (28.6)
Comparison[c]	**5 (71.4)**
Combined Treatment[d]	1 (14.2)
Symptoms Evaluated	
Insomnia	**3 (42.9)**
Cognition	1 (14.2)
Chemotherapy-induced peripheral neuropathy (CIPN)	2 (28.6)
Chemotherapy-related cognitive impairment (CRCI)	1 (14.3)
Limb Function	1 (14.3)
Symptoms Measurements	
Subjective	2 (28.6)
Objective	1 (14.3)
Both	**4 (57.1)**
Source of BDNF	
Serum Levels	**5 (71.4)**
Plasma Levels	1 (14.3)
Genetic Polymorphism	1 (14.3)
Intervention Effect on Symptom	
Positive	**6 (85.7)**
No effect	1 (14.3)
Intervention Effect on BDNF	
Increase	**4 (57.1)**
Decrease	0 (0)
No effect	3 (42.9)
BDNF change association with symptom	
Yes	**1 (14.3)**
No	**6 (85.7)**

a: Other interventions included Cognitive-Behavioral Therapy (CBT-I) and conventional treatment
b: multiple cancer types, looked at breast, prostate, and other cancer types included Head/Neck, Hematologic, Gynecologic, Skin, Lung, Other Gastrointestinal, Other Genitourinary, and >1 cancer type
c: acupuncture was compared to Cognitive-Behavioral Therapy (CBT-I), to a control group, either receiving no treatment, or receiving conventional treatment
d: Acupuncture was combined with conventional treatment

Table 2: Summary of Acupuncture's Effects on Cancer-Related Symptoms and BDNF Across Clinical Studies

Reference	Type of Study	Populations	Symptom(s) Evaluated	Source(s) of BDNF	Intervention effect on symptom outcome	Intervention effect on BDNF	BDNF change relation with symptom outcome
Bao et al. (2014)	**Single Arm**	Multiple myeloma (n=27)	BIPN	Serum	**Symptom:** Improved cognition (FACT-Cog) and neuropathy symptoms (NPS)	BDNF: No significant changes in BDNF levels	-
Bao et al. (2018)		Breast cancer patients (n=27)	CRCI	Plasma	**Symptom:** Neuropathy symptoms stabilized during intervention, and remained unchanged at 3-month follow-up (NPS)	BDNF: Minimal effect	-
Genovese et al. (2021)	**Double Arm**	Breast (n=41), Prostate (n=29), Colorectal (n=8), Other types (n=51), Multiple cancers (n=10)	Insomnia	Genetic polymorphism	More carriers of the COMT rs4680-A and NFKB2 rs1056890 CC genotypes responded to acupuncture; no gene-related differences were found for CBT-I response.	BDNF: No significant differences between BDNF rs6265 SNPs in treatment response	-
Liou et al. (2020)		Breast (n=31), prostate (n=19), other (n=49)	Insomnia	Serum	**Symptom:** Acupuncture improved cognition (BSRT, BADDS) and insomnia symptoms (ISI)	↑ **BDNF**	-
Liou et al. (2021)		Breast (n=27), prostate (n=20), other (n=40)	Insomnia		**Symptom:** Among those with low baseline BDNF: improved insomnia symptoms (ISI) and sleep time (CSD)	↑ **BDNF**	-
Fang et al. (2023)		Cerebral glioma patients (n=82)	Cerebral nerve function, hemorheology, cognitive, and limb function		**Symptom:** Combined treatment had improved cognition (MMSE, MoCA), motor function (FMA), and cerebral hemorheology symptoms (PSV, HSV, LSV)	↑ **BDNF**	-
Tong et al. (2018)		**Breast cancer patients (n=80)**	**CRCI**		**Symptom: Improved CRCI symptoms (AVLT3, CDT, FACT-Cog)**	↑ **BDNF**	+

Figure 2: Forest Plot of Double-Arm Studies with Pooled Effect Size



Conclusion

- This study provides important insights into the effectiveness of acupuncture in improving cancer-related symptoms and the potential role of BDNF as a neurotrophic biomarker.
- While acupuncture showed benefits for symptoms like insomnia and neuropathy, the overall effect on BDNF levels remains inconclusive. Further research is needed to better understand the mechanisms and optimize the use of acupuncture in supportive care for cancer patients worldwide.