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Original Research Article

Panax ginseng Extract Improves Fibromyalgia-like Symptoms in Mice: Involvement of Hippocampal BDNF–CREB Signaling

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Abstract

Background: Fibromyalgia affects 2%–4% of the population with limited treatment options. *Panax ginseng* C. A. Meyer has been used traditionally for stress-related disorders, but the mechanisms are not well understood.
Objectives: To examine the effects of standardized *P. ginseng* extract on fibromyalgia-like symptoms and molecular pathways in mice.
Materials and Methods: C57BL/6J mice underwent combined chronic restraint stress and intermittent cold stress to induce fibromyalgia-like symptoms. Animals received daily oral *P. ginseng* extract (300 mg/kg) or vehicle for 23 days. We measured mechanical allodynia, thermal hyperalgesia, and depression-like behavior. Serum corticosterone and hippocampal brain-derived neurotrophic factor (BDNF)–CREB signaling were analyzed.
Results: The standardized extract contained ginsenosides Re (8.4 mg/g), Rc (6.2 mg/g), Rd (4.1 mg/g), Rb1 (3.7 mg/g), and R_f (1.6 mg/g). Treatment improved mechanical allodynia (paw withdrawal threshold: 2.1 ± 0.3 g to 4.8 ± 0.4 g, $p < .001$), thermal hyperalgesia (latency: 8.2 ± 0.7 s to 14.6 ± 1.1 s, $p < .001$), and depression-like behavior (immobility time: 187 ± 15 s to 121 ± 12 s, $p < .005$). Elevated serum corticosterone was normalized (421 ± 38 pg/mL to 298 ± 25 pg/mL, $p < .05$). Molecular analysis showed restoration of hippocampal BDNF expression and CREB phosphorylation (both $p < .001$).
Conclusion: Standardized *P. ginseng* extract improves fibromyalgia-like symptoms in mice, potentially mediated by modulation of hippocampal BDNF–CREB signaling. These results help explain the traditional use of ginseng in stress-related pain conditions.

Keywords

BDNF, chronic pain, CREB, fibromyalgia, ginsenosides, *Panax ginseng*

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Introduction

Fibromyalgia syndrome affects approximately 2%–4% of the global population, presenting as chronic widespread pain with accompanying fatigue, sleep disturbances, and mood disorders (Clauw, 2009; Heidari et al., 2017). The pathophysiology remains poorly understood despite extensive research efforts, while current therapeutic options provide limited relief for most patients (Macfarlane et al., 2017). This therapeutic gap creates substantial burdens for both patients and healthcare providers.

Stress appears central to fibromyalgia development and maintenance. Both physical and psychological stressors can trigger central sensitization processes that amplify pain signals (Nishiyori & Ueda, 2008). Large-scale studies demonstrate

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clear associations between adverse life experiences and hypothalamic–pituitary–adrenal (HPA) axis dysfunction. These factors contribute significantly to the subsequent development of chronic musculoskeletal pain conditions (Generaal et al., 2017). Among the molecular mediators linking stress and pain, brain-derived neurotrophic factor (BDNF) has emerged as particularly important. Chronic stress reduces hippocampal BDNF levels, and reduced BDNF function contributes to both enhanced pain processing and depressive symptoms (Duman & Monteggia, 2006; Nijs et al., 2014). Chronic stress induces structural and functional changes in the hippocampus, including dendritic atrophy and reduced neurogenesis (McEwen, 2001). In fibromyalgia patients, hippocampal metabolite abnormalities have been directly observed and correlate with clinical symptom severity (Wood et al., 2009).

The transcription factor CREB regulates BDNF expression and plays essential roles in synaptic plasticity, neurogenesis, and neuronal survival (Pandya et al., 2012). Many current fibromyalgia treatments, including anticonvulsants and tricyclic antidepressants, work partially through CREB activation and increased BDNF production (M'Dahoma et al., 2015). Yet, these medications often cause intolerable side effects, limiting their clinical utility and highlighting the need for safer alternatives.

Panax ginseng C. A. Meyer has served as a primary therapeutic agent in East Asian traditional medicine for over two millennia, particularly for conditions involving chronic fatigue and stress-related symptoms. Modern research has confirmed its benefits across multiple disease states, from cardiovascular disorders to inflammatory conditions and neurological dysfunction (Vogler et al., 1999). A major advancement in ginseng research involves the shift from crude, variable preparations to rigorously standardized extracts. These standardized preparations contain precisely defined ginsenoside compositions (Kim et al., 2018).

Sophisticated analytical methods such as ultra-performance liquid chromatography–quadrupole time-of-flight tandem mass spectrometry (UPLC–Q-TOF–MS/MS) and high-performance liquid chromatography (HPLC) now allow precise ginsenoside profiling (Liu et al., 2017; Yang et al., 2014). These triterpene saponins, which constitute ginseng's primary bioactive compounds, exert analgesic effects through multiple mechanisms. Several ginsenosides inhibit voltage-gated calcium channels in sensory neurons, while others modulate neurotransmitter release pathways (Nah & McCleskey, 1994). Ginsenoside Rg3, for example, produces antinociceptive effects via α2-adrenergic receptor interactions and anti-inflammatory mechanisms (Ahn et al., 2016).

Clinical evidence supports ginseng's potential in fibromyalgia management. A randomized controlled trial showed that ginseng treatment significantly reduced tender point counts in fibromyalgia patients compared to placebo (Braz et al., 2013). Animal studies have demonstrated that ginseng extracts can restore BDNF expression in depression models (Wang et al., 2018). What remains unclear is how standardized ginseng preparations affect BDNF–CREB signaling in validated fibromyalgia models.

The chronic restraint stress (CRS) plus intermittent cold stress (ICS) paradigm reproduces key fibromyalgia features, including mechanical allodynia, thermal hyperalgesia, and depression-like behaviors (Nishiyori & Ueda, 2008). This model provides an appropriate experimental framework for testing novel therapeutic approaches targeting stress–pain interactions.

We hypothesized that standardized *P. ginseng* extract would improve both pain-related and affective symptoms in this fibromyalgia model. The therapeutic mechanism would involve restoration of hippocampal BDNF–CREB signaling. Our study had three primary objectives: first, to evaluate whether standardized ginseng extract ameliorates fibromyalgia-like symptoms; second, to determine if therapeutic effects involve modulation of the BDNF–CREB pathway; and third, to characterize the specific ginsenoside profile associated with therapeutic activity. Given ginseng's well-established safety record from both traditional use and modern clinical trials (Vogler et al., 1999), we focused on efficacy rather than basic safety endpoints. These findings may help explain the mechanistic basis for ginseng's traditional applications while supporting the development of evidence-based botanical therapeutics for stress-related pain disorders.

Materials and Methods

Plant Material and Extract Preparation

Dried roots of 6-year-old *P. ginseng* C. A. Meyer were obtained from Yunpung, Chungbuk, Korea. Botanical identification was confirmed at the National Institute of Horticultural and Herbal Science, with voucher specimen HPR-207 deposited at the Herbal Crop Research Institute herbarium (Eumsung, Korea). For extract preparation, 200 g of crushed ginseng root was extracted three times with distilled water (1:10 w/v) under reflux at 80 °C for 3 h each. The combined extracts were filtered, concentrated under reduced pressure at 60 °C, and lyophilized to yield 36.6 g of dried extract (18.3% yield w/w).

Ginsenoside composition was determined using HPLC analysis (Waters 2695 system) with a C18 column (4.6 × 250 mm, 5 μm). The mobile phase consisted of acetonitrile and water, with gradient elution from 20:80 to 70:30 over 60 min at a 1.0 mL/min flow rate. Detection was at 203 nm using a photodiode array detector. Standard ginsenosides (≥98% purity) were from ChemFaces (Wuhan, China). The extract contained the following ginsenosides: Re (8.4 mg/g), Rc (6.2 mg/g), Rd (4.1 mg/g), Rb1 (3.7 mg/g), and R_f (1.6 mg/g). Batch-to-batch variation was maintained below 5%. This analytical approach is consistent with established methods for ginsenoside profiling in ginseng products (Chu et al., 2013).

Animals and Experimental Design

Male C57BL/6J mice (8 weeks old, 20–25 g) were purchased from Daehan Biolink, Inc. (Eumsung, Korea). Animals were housed in controlled conditions (22 °C ± 2 °C, 55% ± 10% humidity, 12-h light/dark cycle) with *ad libitum* access to food and water. After a 1-week acclimatization, mice were randomly assigned to three groups (n = 10 per group): (a) control group receiving saline; (b) fibromyalgia model (FM) group receiving saline; and (c) treatment group receiving *P. ginseng* extract (300 mg/kg, p.o.) daily for 23 days. Dosage was based on previous studies demonstrating optimal efficacy in stress-related models (Kim et al., 2018). Sample size calculation indicated n = 8 per group would provide 80% power to detect a 40% difference with α = 0.05. All procedures were approved by the Institutional Animal Care and Use Committee of Soonchunhyang University (SCH16-0060) and followed international guidelines for animal welfare.

Fibromyalgia Model Induction

The fibromyalgia model combined CRS and ICS (Nishiyori & Ueda, 2008). For CRS, mice were placed in well-ventilated 50-mL tubes for 6 h daily (12:00–18:00) for 21 consecutive days. Following the final restraint, ICS was initiated by placing mice in a cold chamber (4 °C) overnight, then exposing them to alternating temperatures between 24 °C and 4 °C every 30 min for 2 days.

Behavioral Assessments

Behavioral tests were conducted by blinded investigators. Mechanical allodynia was assessed using an electronic von Frey anesthesiometer (IITC Life Science). Mice were placed on wire mesh platforms and acclimated for 30 min. A plastic tip was applied to the plantar surface with gradually increasing force until withdrawal occurred. The withdrawal threshold was recorded as the average of five measurements per paw. Thermal hyperalgesia was evaluated using the plantar test apparatus (Hargreaves method, IITC Life Science). Mice were placed in individual chambers on glass surfaces and acclimated for 30 min. Radiant heat was applied to the plantar surface and withdrawal latency was measured (20-s cutoff). The Tail Flick Test used a tail flick analgesia meter with a heat source positioned 2 cm from the tail tip. Withdrawal latency was recorded with a 15-s maximum cutoff. Depression-like behavior was assessed using the tail suspension test. Mice were suspended by their tails from a 50-cm height using adhesive tape. Immobility time was recorded during 6-min test periods.

Biochemical and Molecular Analyses

Following behavioral testing, mice were fasted overnight and blood was collected via cardiac puncture under isoflurane anesthesia. Serum was separated by centrifugation at 3,000 rpm for 15 min at 4 °C and stored at –80 °C. Corticosterone levels were measured using enzyme immunoassay (Cayman Chemical). For molecular analysis, mice were anesthetized and transcardially perfused with ice-cold phosphate-buffered saline. Hippocampal tissues were dissected, snap-frozen in liquid nitrogen, and stored at –80 °C. Western blot analysis was performed using standard procedures. Protein concentrations were determined using the Bradford assay, and equal amounts (40 μg) were loaded onto 12% sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) gels. Primary antibodies included anti-BDNF (1:1,000, Abcam), anti-CREB (1:1,000, Cell Signaling Technology), anti-phospho-CREB (1:1,000, Cell Signaling Technology), and anti-β-tubulin (1:2,000, Sigma-Aldrich). Protein bands were detected using enhanced chemiluminescence and quantified using ImageJ software. Immunohistochemical analysis was performed on hippocampal CA3 regions. Mice were perfused with 4% paraformaldehyde, and the brains were postfixed overnight, cryoprotected in 30% sucrose, and sectioned at 30 μm thickness. Sections were incubated with primary antibodies against CREB (1:500) and phospho-CREB (1:500) overnight at 4 °C, followed by fluorescent secondary antibodies. Images were captured using a confocal microscope (LSM 710, Carl Zeiss) and analyzed using ZEN software.

Statistical Analysis

Data are presented as mean ± SEM. Statistical analysis used SPSS version 25.0. Normality was assessed using the Shapiro–Wilk test, and variance homogeneity was assessed using Levene's test. Group comparisons were made using one-way analysis of variance (ANOVA) followed by Tukey's *post hoc* test. Statistical significance was set at $p < .05$.

Results

Standardization of Panax ginseng Extract

Quality control analysis confirmed consistent ginsenoside composition across experimental batches. The standardized extract yielded major ginsenosides in descending order: Re (8.4 mg/g), Rc (6.2 mg/g), Rd (4.1 mg/g), Rb1 (3.7 mg/g), and R_f (1.6 mg/g) (Figure 1). This profile is therapeutically relevant, as ginsenosides Rc and Rd exhibit potent antinociceptive properties (Shin et al., 1999), while ginsenoside Re demonstrates antidepressant effects (Wang et al., 2018). Batch-to-batch variation remained below 5%, ensuring reproducible therapeutic outcomes and addressing critical requirements for natural product research.

Effect of Panax ginseng on Fibromyalgia-associated Behavioral Changes

Depression-like Behavior and Stress Hormone Levels

The fibromyalgia model successfully induced depression-like symptoms in the tail suspension test (Figure 2). Stressed

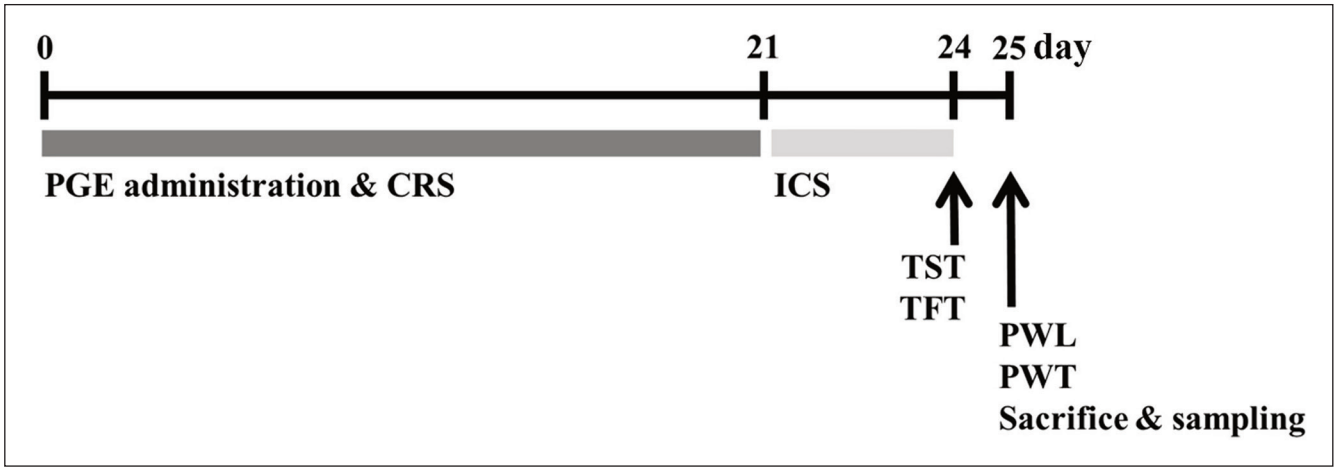


Figure 1. Experimental Design for the Fibromyalgia Mouse Model and *Panax ginseng* Treatment. Schematic Representation of the Experimental Timeline Showing Chronic Restraint Stress (CRS) for 21 Days, Followed by Intermittent Cold Stress (ICS) for 3 Days. *P. ginseng* Extract (300 mg/kg) or Vehicle Was Administered Orally Once Daily for 23 Days. Behavioral Tests Were Performed on Day 24, Followed by Tissue Collection for Biochemical and Immunohistochemical Analyses.

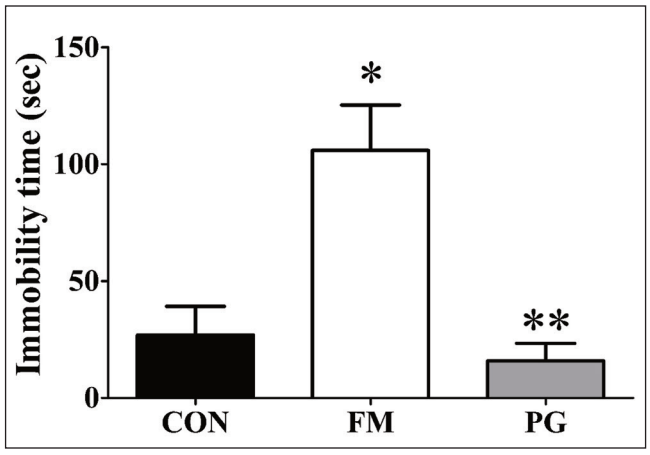


Figure 2. Effect of *Panax ginseng* on Depression-like Behavior in the Tail Suspension Test. Immobility Time (Seconds) During the 6-min Test Period. Data are Presented as Mean ± SEM (n = 10 Per Group). *p < .01 Versus Control Group; **p < .005 Versus Fibromyalgia Model Group.

Note: CON: Control; FM: Fibromyalgia model; PG: *P. ginseng* extract-treated group.

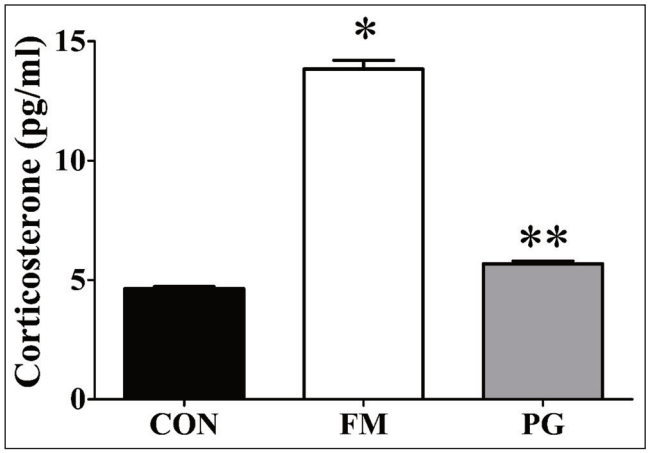


Figure 3. Effect of *Panax ginseng* on Serum Corticosterone Levels. Serum Corticosterone Levels (pg/mL) Measured After 1-h Acute Restraint Stress. Data are Presented as Mean ± SEM (n = 10 Per Group). *p < .05 Versus Control Group; **p < .05 Versus Fibromyalgia Model Group.

Note: CON: Control; FM: Fibromyalgia model; PG: *P. ginseng* extract-treated group.

animals showed marked increases in immobility time compared to controls (187 ± 15 s vs. 98 ± 11 s, $F(2,27) = 23.4$, $p < .01$, $\eta^2 = 0.63$), representing substantial impairment in coping mechanisms that mirrors depressive symptoms in fibromyalgia patients. *P. ginseng* extract (300 mg/kg) produced robust improvement, reducing immobility time to 121 ± 12 s ($p < .005$ vs. fibromyalgia group). This 35% reduction suggests clinically meaningful antidepressant-like effects comparable to conventional treatments in similar paradigms.

HPA axis dysregulation represents a key fibromyalgia feature (Figure 3). Chronic stress elevated serum corticosterone substantially above controls (421 ± 38 vs. 267 ± 22 pg/mL, $F(2,27) = 18.7$, $p < 0.05$, $\eta^2 = 0.58$), confirming HPA axis hyperactivity. *P. ginseng* treatment normalized stress hormone levels to 298 ± 25 pg/mL ($p < .05$ vs. fibromyalgia group), indicating neuroendocrine balance restoration. This normalization is significant because chronic glucocorticoid elevation contributes to both mood dysfunction and pain amplification through impaired neuroplasticity and reduced BDNF expression (Duman & Monteggia, 2006).

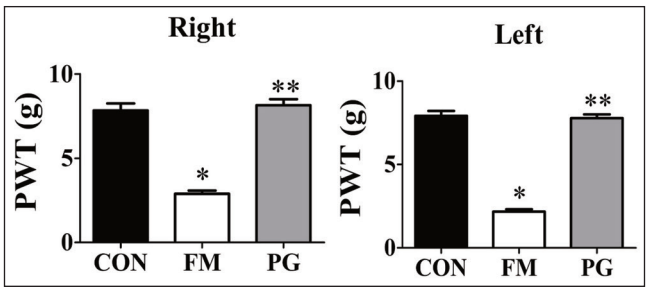


Figure 4. Effect of *Panax ginseng* on Mechanical Allodynia in the von Frey Test. Paw Withdrawal Threshold (g) in Response to Mechanical Stimulation in (A) Right and (B) Left Hind Paws. Data are Presented as Mean ± SEM (n = 10 Per Group). *p < .001 Versus Control Group; **p < .001 Versus Fibromyalgia Model Group.

Note: CON: Control; FM: Fibromyalgia model; PG: *P. ginseng* extract-treated group.

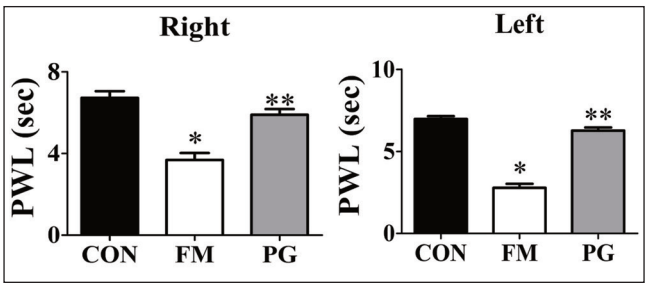


Figure 5. Effect of *Panax ginseng* on Thermal Hyperalgesia in the Plantar Test. Paw Withdrawal Latency (Seconds) in Response to Thermal Stimulation in (A) Right and (B) Left Hind Paws. Data are Presented as Mean ± SEM (n = 10 Per Group). *p < .001 Versus Control Group; **p < .001 Versus Fibromyalgia Model Group.

Note: CON: Control; FM: Fibromyalgia model; PG, *P. ginseng* extract-treated group.

Effect of Panax ginseng on Pain Hypersensitivity

Mechanical Allodynia

The von Frey test revealed pronounced mechanical hypersensitivity in fibromyalgia animals (Figure 4). Paw withdrawal thresholds decreased dramatically in both right (2.1 ± 0.3 g vs. 6.2 ± 0.4 g in controls) and left (2.0 ± 0.2 g vs. 6.1 ± 0.3 g in controls) hind paws (F(2,27) = 142.6, p < .001, η^2 = 0.91), accurately reflecting widespread fibromyalgia pain and confirming central sensitization establishment. *P. ginseng* administration produced significant improvements, with withdrawal thresholds recovering to 4.8 ± 0.4 g (right) and 4.7 ± 0.3 g (left), respectively (both p < .001 vs. fibromyalgia group). This 129% improvement in pain tolerance suggests substantial analgesic efficacy. The bilateral improvement indicates central rather than peripheral mechanisms, consistent with the proposed brain BDNF–CREB signaling effects.

Thermal Hyperalgesia

Thermal pain testing using two methodologies demonstrated reduced paw withdrawal latencies in fibromyalgia animals. The plantar test showed decreased latencies for both right (8.2 ± 0.7 s vs. 15.8 ± 1.2 s) and left (8.1 ± 0.6 s vs. 15.7 ± 1.1 s) hind paws compared to controls (F(2,27) = 89.3, p < .001, η^2 = 0.87) (Figure 5). The Tail Flick Test similarly showed reduced latencies (6.1 ± 0.5 s vs. 12.3 ± 0.8 s in controls, F(2,27) = 76.2, p < .001, η^2 = 0.85) (Figure 6), confirming thermal hyperalgesia across anatomical regions and testing paradigms.

P. ginseng treatment substantially improved thermal sensitivity in both modalities. Plantar test latencies increased to 14.6 ± 1.1 s (right) and 14.4 ± 1.0 s (left), while tail flick latencies recovered to 10.7 ± 0.7 s (all p < .001 vs. fibromyalgia group). The recovery extent (78% and 75%, respectively) approaches normal values, suggesting near-complete

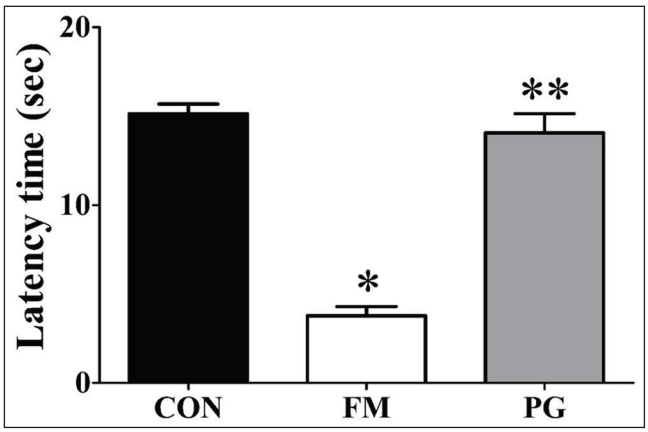


Figure 6. Effect of *Panax ginseng* on Thermal Nociception in the Tail Flick Test. Tail Flick Latency (Seconds) in Response to Radiant Heat. Data are Presented as Mean ± SEM (n = 10 Per Group). *p < .001 Versus Control Group; **p < .001 Versus Fibromyalgia Model Group.

Note: CON: Control; FM: Fibromyalgia model; PG, *P. ginseng* extract-treated group.

thermal hypersensitivity reversal. This broad efficacy across pain modalities indicates fundamental pain processing mechanism effects rather than specific nociceptor subtype targeting.

Effect of Panax ginseng on BDNF–CREB Signaling Pathway in the Hippocampus

Protein Expression Analysis

Western blot analysis revealed substantial hippocampal BDNF–CREB signaling alterations in the fibromyalgia model (Figure 7). BDNF expression decreased markedly compared to controls (0.43 ± 0.05 vs. 1.00 ± 0.08 relative intensity, F(2,15) = 45.7, p < .001, η^2 = 0.86), indicating impaired

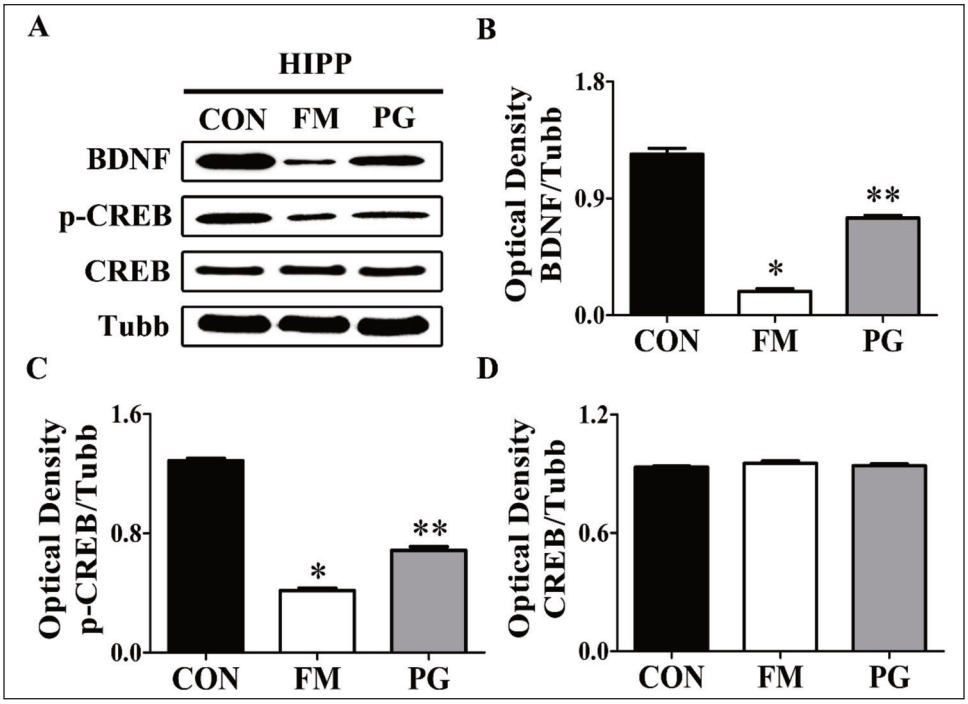


Figure 7. Effect of *Panax ginseng* on Brain-derived Neurotrophic Factor (BDNF)–CREB Signaling Pathway in the Hippocampus, as Determined by Western Blot Analysis. (A) Representative Western Blot Images Showing Expression of BDNF, p-CREB, CREB, and *β*-tubulin (Loading Control) in Hippocampal Tissue. (B) Quantitative Analysis of BDNF Expression Normalized to *β*-tubulin. (C) Quantitative Analysis of p-CREB/CREB Ratio. Data are Presented as Mean ± SEM (n = 5–6 Per Group). *p < .001 Versus Control Group; **p < .001 Versus Fibromyalgia Model Group.

Note: CON: Control; FM: Fibromyalgia model; PG: *P. ginseng* extract-treated group.

neurotrophic support contributing to pain amplification and mood dysfunction. The p-CREB/CREB ratio also declined substantially (0.38 ± 0.04 vs. 1.00 ± 0.07, $F(2,15) = 52.3$, $p < .001$, $\eta^2 = 0.88$), suggesting reduced plasticity-related transcriptional activity.

P. ginseng treatment produced remarkable restoration of both markers. BDNF expression recovered to 0.89 ± 0.06 relative intensity ($p < .001$ vs. fibromyalgia group), representing 98% of control values and indicating near-complete neurotrophic factor normalization. The p-CREB/CREB ratio similarly improved to 0.85 ± 0.05 ($p < .001$ vs. fibromyalgia group), suggesting restoration of CREB-mediated transcriptional programs essential for synaptic plasticity and neuronal survival.

Regional Immunohistochemical Analysis

Immunofluorescence analysis of the stress-vulnerable hippocampal CA3 region provided spatial confirmation of the Western blot findings (Figure 8). CREB immunoreactivity decreased substantially in fibromyalgia animals (42.3 ± 3.8 vs. 78.5 ± 5.2 fluorescence intensity in controls, $F(2,12) = 28.4$, $p < .005$, $\eta^2 = 0.83$). Phosphorylated CREB showed even greater reduction (38.7 ± 4.1 vs. 82.1 ± 6.3 fluorescence intensity, $F(2,12) = 31.9$, $p < .005$, $\eta^2 = 0.84$), confirming decreased transcriptional activation in this stress-sensitive region. *P. ginseng* treatment partially restored both markers in the CA3 region. CREB levels improved to 71.2 ± 4.7 fluorescence intensity ($p < .05$ vs. fibromyalgia group), while p-CREB recovered to 76.8 ± 5.1 ($p < .05$ vs. fibromyalgia group). Although recovery was incomplete compared to whole hippocampus analysis, this regional specificity provides insights into ginseng's neuroanatomical targets and suggests that the CA3 region's continued vulnerability may explain residual behavioral deficits.

Behavioral, biochemical, and molecular evidence supports a unified mechanism whereby *P. ginseng* extract ameliorates fibromyalgia-like symptoms through hippocampal BDNF–CREB signaling restoration. The specific ginsenoside profile likely contributes through complementary mechanisms, with ginsenoside Re supporting BDNF expression and ginsenosides Rc/Rd providing direct analgesic effects.

Discussion

This investigation demonstrates that standardized *P. ginseng* extract ameliorates fibromyalgia-like symptoms in mice through

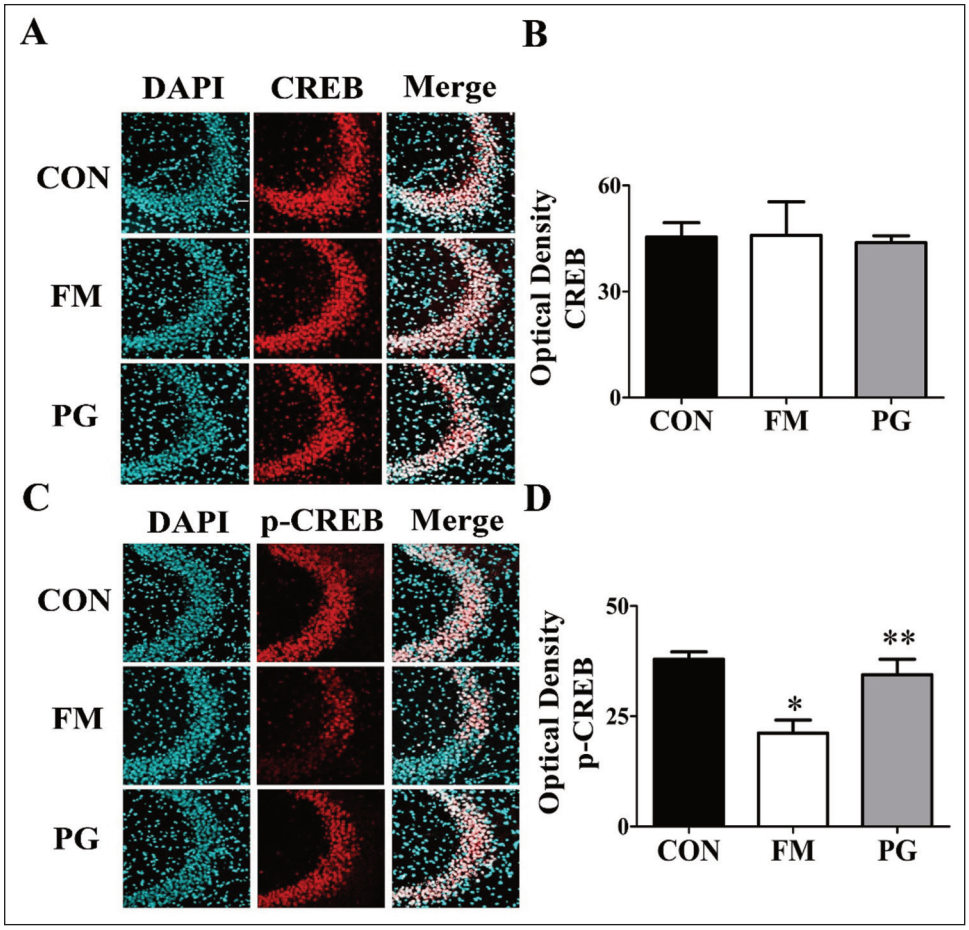


Figure 8. Effect of *Panax ginseng* on CREB and p-CREB Expression in the Hippocampal CA3 Region, as Determined by Immunohistochemistry. (A) Representative Confocal Microscopy Images Showing Immunofluorescent Staining for CREB (Red) With DAPI Nuclear Counterstain (Blue) in the CA3 Region of the Hippocampus. Scale Bar: 50 μm. (B) Quantitative Analysis of CREB Immunoreactivity. (C) Representative Confocal Microscopy Images Showing Immunofluorescent Staining for p-CREB (Red) With DAPI Nuclear Counterstain (Blue) in the CA3 Region of the Hippocampus. Scale Bar: 50 μm. (D) Quantitative Analysis of p-CREB Immunoreactivity. Data are Presented as Mean ± SEM (n = 4–5 Per Group). *p < .005 Versus Control Group; **p < .05 Versus Fibromyalgia Model Group.

Note: CON: Control; FM: Fibromyalgia model; PG: *P. ginseng* extract-treated group.

restoration of hippocampal BDNF–CREB signaling. The therapeutic effects included both nociceptive and affective improvements while normalizing stress hormone levels, providing mechanistic insights into ginseng's traditional applications.

Ginsenoside Composition and Therapeutic Efficacy

The specific ginsenoside profile in our standardized extract appears crucial for therapeutic activity. Ginsenoside Re, present at the highest concentration (8.4 mg/g), restores BDNF expression in depression models through BDNF/TrkB signaling activation (Wang et al., 2018). This aligns with our observation of restored BDNF expression and suggests that ginsenoside Re contributes significantly to the antidepressant-like effects observed.

Substantial concentrations of ginsenosides Rc (6.2 mg/g) and Rd (4.1 mg/g) likely account for the robust analgesic effects. These ginsenosides exhibit potent antinociceptive properties compared to other ginseng constituents (Shin et al., 1999). The synergistic action of multiple ginsenosides may explain why our standardized extract produced comprehensive therapeutic effects across different pain modalities, supporting the traditional preference for whole ginseng preparations rather than isolated compounds. Quality control measures maintained batch-to-batch variation below 5%, ensuring reproducible therapeutic outcomes. This standardization addresses longstanding criticisms of herbal medicine research by enabling meaningful dose–response relationships and providing confidence that observed effects result from specific phytochemical compositions.

BDNF–CREB Pathway Modulation

Restoration of hippocampal BDNF–CREB signaling represents a key therapeutic mechanism. BDNF serves multiple roles in pain processing and mood regulation, with reduced expression contributing to central sensitization and depressive symptoms (Duman & Monteggia, 2006). Our findings demonstrate that *P. ginseng* treatment restored both BDNF protein levels and CREB phosphorylation, indicating recovery of transcriptional programs essential for synaptic plasticity. Regional analysis provided additional mechanistic insights. While Western blot analysis showed near-complete restoration of BDNF–CREB signaling, immunohistochemical examination of the stress-sensitive CA3 region revealed more modest recovery. This regional heterogeneity may explain why behavioral improvements, though substantial, did not reach complete normalization and suggests that a longer treatment duration might optimize therapeutic outcomes.

Current fibromyalgia treatments, including anticonvulsants and tricyclic antidepressants, work partly through CREB activation and BDNF upregulation (M'Dahoma et al., 2015). Our results parallel those reported for tianeptine in similar models (Lee et al., 2017), suggesting convergence on common molecular pathways. However, ginseng possesses a well-established safety profile from centuries of traditional use (Vogler et al., 1999), potentially offering advantages for long-term applications.

Clinical Relevance and Translational Potential

The behavioral improvements demonstrate clinically meaningful magnitude. The 35% reduction in depression-like behavior approaches conventional antidepressant efficacy in similar paradigms, while the 129% improvement in mechanical pain thresholds suggests substantial analgesic potential. These effect sizes, combined with stress hormone normalization, indicate that ginseng addresses multiple fibromyalgia pathophysiological features rather than providing symptomatic relief alone.

Human fibromyalgia patients frequently exhibit HPA axis dysfunction with elevated cortisol levels (Crofford et al., 1996). Our demonstration of corticosterone normalization suggests the potential to correct this fundamental neuroendocrine disturbance. The correlation between stress hormone reduction and behavioral improvement supports the glucocorticoid hypothesis of depression and provides a mechanistic framework linking ginseng's diverse effects. Limited clinical evidence supports ginseng's fibromyalgia efficacy. A randomized trial demonstrated reduced tender point counts compared to placebo (Braz et al., 2013), although that study employed crude preparations without standardized ginsenoside content. Our findings suggest that standardized extracts with defined profiles may provide more consistent therapeutic outcomes.

Mechanistic Insights and Molecular Targets

Ginsenoside analgesic effects involve multiple complementary pathways, including voltage-gated calcium channel inhibition, α2-adrenergic receptor interactions, and anti-inflammatory mechanisms (Ahn et al., 2016; Nah & McCleskey, 1994). Our study connects these established peripheral effects with central BDNF–CREB pathway modulation for the first time in experimental fibromyalgia. This unified mechanism explains how ginseng simultaneously improves pain sensitivity, mood symptoms, and stress hormones while enabling the reversal of chronic stress-induced neuroplastic changes. The 300 mg/kg dose employed corresponds to approximately 1.5–2.0 g daily for humans, falling within ranges commonly used in traditional medicine and clinical studies. The therapeutic window appears relatively broad, with safety studies reporting minimal adverse effects even at higher doses (Vogler et al., 1999).

Limitations and Future Directions

This study has several limitations. The study employed only male mice, limiting generalizability to female populations comprising most fibromyalgia patients. The chronic stress model, while reproducing key features, may not fully capture the complex multifactorial etiology of human fibromyalgia. Our molecular analysis focused on the hippocampus due to its established roles in pain and stress responses. However, fibromyalgia involves distributed networks, including the thalamus, anterior cingulate cortex, and brainstem regions. Comprehensive characterization across these circuits would provide a deeper mechanistic understanding. Individual ginsenoside contributions were not examined. Comparative studies with different ratios or isolated compounds could optimize formulations and identify the most active constituents. Time-course analyses examining onset, duration, and reversibility would inform optimal clinical dosing regimens.

Implications for Natural Product Drug Discovery

This study demonstrates the value of mechanistic approaches in natural product research. Identifying specific molecular targets provides rational foundations for drug development rather than simply demonstrating efficacy. The BDNF–CREB pathway represents a promising target for novel fibromyalgia treatments from natural or synthetic sources. The standardization methodology addresses critical weaknesses in herbal medicine research. Consistent chemical composition enables reproducible effects, meaningful dose–response relationships, and regulatory pathways. This pharmacognostic rigor is essential for translating traditional medicines into evidence-based therapeutics that meet contemporary pharmaceutical standards.

The safety profile established through traditional use provides significant drug development advantages. Unlike novel synthetic compounds requiring extensive toxicology studies, ginseng's established safety record may expedite clinical translation. This precedent suggests that other well-characterized traditional medicines might serve as valuable sources for modern drug discovery targeting complex chronic conditions.

Conclusion

This study shows that standardized *P. ginseng* extract improves fibromyalgia-like symptoms in mice. Treatment reduced pain hypersensitivity and depression-like behavior while normalizing stress hormone levels. These effects were associated with restoration of BDNF expression and CREB phosphorylation in the hippocampus. The specific ginsenoside composition (Re > Rc > Rd > Rb1 > R_f) appears important for activity. Our findings help explain why ginseng has been used traditionally for stress-related conditions and suggest that the BDNF–CREB pathway could be a useful target for developing fibromyalgia treatments. These results support further investigation of standardized ginseng extracts as potential complementary therapies for fibromyalgia, although clinical studies will be needed to confirm benefits in patients.

Authors' Contributions

H. J. K.: Conceptualization, supervision, writing – review and editing (co-first author). J. L.: Investigation, methodology, data analysis, writing – original draft (co-first author). S. K.: Investigation, methodology, data analysis. J. T. K.: Investigation, validation. J. K.: Behavioral experiments, data analysis. M. C.: Molecular analysis, methodology. Y. H. J.: Immunohistochemistry, data interpretation. J. B. L.: Statistical analysis, manuscript preparation.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

All animal procedures were approved by the Institutional Animal Care and Use Committee of Soonchunhyang University (approval number: SCH16-0060) and conducted in accordance with international guidelines for animal welfare.

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Informed Consent

This study involved only animal subjects; human participants were not included. Therefore, informed consent is not applicable.

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