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Review Article

Efficacy of *Panax ginseng* on stress: a systematic review of clinical evidence on psychological and biomarker outcomes

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Abstract

Objective: *Panax ginseng*, particularly Korean Red Ginseng (KRG), enhances energy, influences stress responses, and provides therapeutic benefits through ginsenosides and polysaccharides. This systematic review assessed whether *P. ginseng* supplementation reduces perceived psychological stress in humans, based on its suggested neuromodulatory properties.

Materials and Methods: Following Cochrane methodology, databases (PubMed, Scopus, and Web of Science) were searched up to June 2025. Included studies measured human psychological stress. Risk of bias was assessed. Significant heterogeneity prevented meta-analysis, leading to the completion of only systematic review.

Results: Eight studies revealed varied impacts on psychological stress, with significant enhancements linked to larger doses or bioavailable formulations, not 200 mg KRG. Cognitive advantages were consistently noted, although not for depression. Physiologically, particular ginseng extracts reduced cortisol in 2 out of 3 studies, whereas effects on catecholamines and other biomarkers varied. A study indicated genomic mechanisms through the downregulation of beta-2 adrenergic receptor (ADRB2) gene expression.

Conclusion: Most studies indicate *P. ginseng* supplementation may reduce psychological stress and positively influence key stress pathways (epinephrine, autonomic nervous system, serotonin, and hypothalamic-pituitary-adrenal (HPA axis), but inconsistencies in outcomes and biomarkers, coupled with insufficient gene expression data limit current evidence. More rigorous, standardized research is needed to confirm effects and elucidate mechanisms, warranting caution in interpretation.

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Introduction

Chronic psychological stress poses a significant public health challenge, negatively impacting both mental and physical health. Perceived stress, the individual's assessment of stressors that surpass their coping capabilities, plays a crucial role in the onset and worsening of issues such as anxiety, depression, heart disease, and cognitive decline. Stress can hasten the advancement of current diseases by reducing resilience and weakening immune function. Thus, recognizing efficient approaches to reduce its adverse effects is essential for improving general health and averting illness (Alotiby 2024; Cohen et al. 2007).

Panax ginseng, especially its heat-treated variant called Korean Red Ginseng (KRG), has been used for thousands of years in East Asia as a natural solution to enhance physical and mental energy. Known for its adaptogenic characteristics, it is believed to influence the body's stress reaction and improve resilience (Zheng and Moritani 2008). Its therapeutic potential is attributed to a rich profile of bioactive compounds, including ginsenosides, polysaccharides, and polyphenols, which exert diverse effects across physiological systems (Lee and Rhee 2017).

Preclinical research has yielded important insights into the biological mechanisms responsible for the stress-regulating effects of *P. ginseng*. These processes involve the adjustment of the hypothalamic–pituitary–adrenal (HPA) axis, modulation of neurotransmitter activity (e.g. serotonin and dopamine), attenuation of oxidative stress and inflammatory responses, and promotion of neuroplasticity and neuroprotection within critical brain regions associated with stress response such as hippocampus and prefrontal cortex (Iqbal et al. 2020; Lee et al. 2012). These neuromodulatory (Zhao et al. 2014), neuroprotective (Ban et al. 2012; Jun et al. 2015; Kim et al. 2014) and anti-inflammatory properties (Li et al. 2015; Yayeh et al. 2012) provide a strong biological rationale for its clinical implication.

Recent clinical findings seem to support this premise. Several single/double-blind, randomized, placebo-controlled trials (RCTs) have indicated that *P. ginseng* may help reduce stress-related symptoms and enhance cognitive abilities like memory and concentration in those experiencing fatigue (Ellis and Reddy 2002; Mariage et al. 2020; Reay et al. 2005). These studies suggest a positive effect on stress adaptability and managing psychological stress by regulating stress responses and enhancing resilience.

Despite the increasing research interest in *P. ginseng*, the current human studies examining its effect on physiological stress have not been systematically consolidated, especially those that evaluate both subjective physiological states (using validated questionnaires) and objective biological markers (e.g. cortisol and catecholamines) in a specific population. This systematic review, therefore, aims to distinguish strong clinical effects from variable outcomes while evaluating the adaptogenic potential of *P. ginseng* in individuals with stress, examining both psychological and physiological parameters.

Methods and Materials

Data sources and search strategy

A comprehensive literature search was performed utilizing databases including PubMed, Scopus, and Web of Science up to June 1, 2025. The studies selected were randomized, double-blind, placebo-controlled trials reported in English that explored the association between ginseng administration and markers of psychological stress, including relevant blood biomarkers.

The formulation of the search methodology was undertaken in partnership with a medical librarian, using a

combination of controlled vocabulary (MeSH terms) and general search terms associated with ginseng and stress-related concepts. The search terms included: "*Panax ginseng* " OR "Ginseng" OR "Korean Red Ginseng" AND "Stress" OR "chronic stress" OR "perceived stress" OR "psychological stress" OR "eustress" OR "neurotransmitter" OR "Serotonin" OR "Dopamine" OR "Norepinephrine" OR "Cortisol" OR "Cathecholamine" OR "biomarker" OR "HPA axis".

This comprehensive review was carried out following the Cochrane methodology, concentrating on research assessing the effects of *P. Ginseng* therapy on psychological stress levels and physiological indicators linked to stress. The review was conducted according to the methodological standards outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Sterne et al. 2019). The key phases included defining a research question, establishing eligibility criteria, conducting a systematic literature search, selecting studies, collecting data, assessing the risk of bias in included studies, and synthesizing and interpreting the findings.

Study selection and eligibility criteria

The study selection process for this review adhered to the PICO framework. Based on the PICOs framework (Population, Intervention/Exposure, Comparator, Outcome, Study Design), the eligibility criteria for inclusion were as follows: (P) Individuals aged 18 years or older experiencing moderate-to-high levels of perceived stress; (I/E) Involvement or administration of ginseng; (C) A control group with placebo ; (O) Evaluation of stress levels using questionnaires or biochemical stress markers; (S) Interventional designs such as Randomized Controlled Trials. Only articles written in English were considered for the final evaluation.

Study design

In this present analysis, we included all research examining the effects of *P. ginseng* on psychological stress and stress-related blood markers such as dopamine, serotonin, cortisol, epinephrine, norepinephrine, triglycerides, and glucose levels. To be eligible, studies needed to be randomized, blinded clinical trials that featured a control group with minimal or no ginseng consumption and assessed outcomes related to psychological stress (using validated questionnaires) or stress-related physiological indicators like cortisol, catecholamines (epinephrine and norepinephrine), serotonin, dopamine, glucose, and triglycerides.

Our first investigation through the designated databases produced a sum of 826 entries. After eliminating non-relevant research papers (n=695) and duplicate files (n=26), we reviewed the titles and abstracts of 105 articles. If the relevance of an article could not be determined solely from its title and abstract, the complete text was obtained for a more detailed assessment. After the final selection of articles, the full-text versions underwent thorough scrutiny. For studies that were not readily accessible, the researchers made efforts to retrieve the necessary information by reaching out to the corresponding author via email. The PRISMA flow chart in Figure 1 visually represents the methodology employed for selecting articles in this analysis.

Data extraction

The gathered data encompassed details such as participant count, age distribution, gender proportion, study design, variety of Ginseng used, administered dosage, stress intensity, duration of treatment, evaluation methods, post-treatment stress levels, depression and cognitive outcomes following intervention, stress-associated blood biomarkers (dopamine, serotonin, cortisol, epinephrine, norepinephrine, triglycerides, and glucose concentrations), and potential adverse effects. Finally, all

the collected information was classified into the following categories: the effect of ginseng on physiological stress, the effect of ginseng on blood stress related biomarkers, and the effect of ginseng on gene expression patterns.

Quality assessment

The risk of bias was evaluated using the updated Cochrane Risk of Bias tool (RoB 2.0) (Sterne et al. 2019). This instrument assesses five areas: (1) bias stemming from the randomization process, (2) bias resulting from deviations from planned interventions, (3) bias from absent outcome data, (4) bias in outcome measurement, and (5) bias in the selection of the reported outcome. Through structured signaling questions, every domain was evaluated as possessing a 'Low', 'Some concerns (moderate) ', or 'High' risk of bias. To enhance the precision and objectivity of the evaluation, two independent reviewers (GA and SA) conducted the assessments simultaneously. Any discrepancies were handled through consensus-driven discussions or, when necessary, settled by a third party (YM).

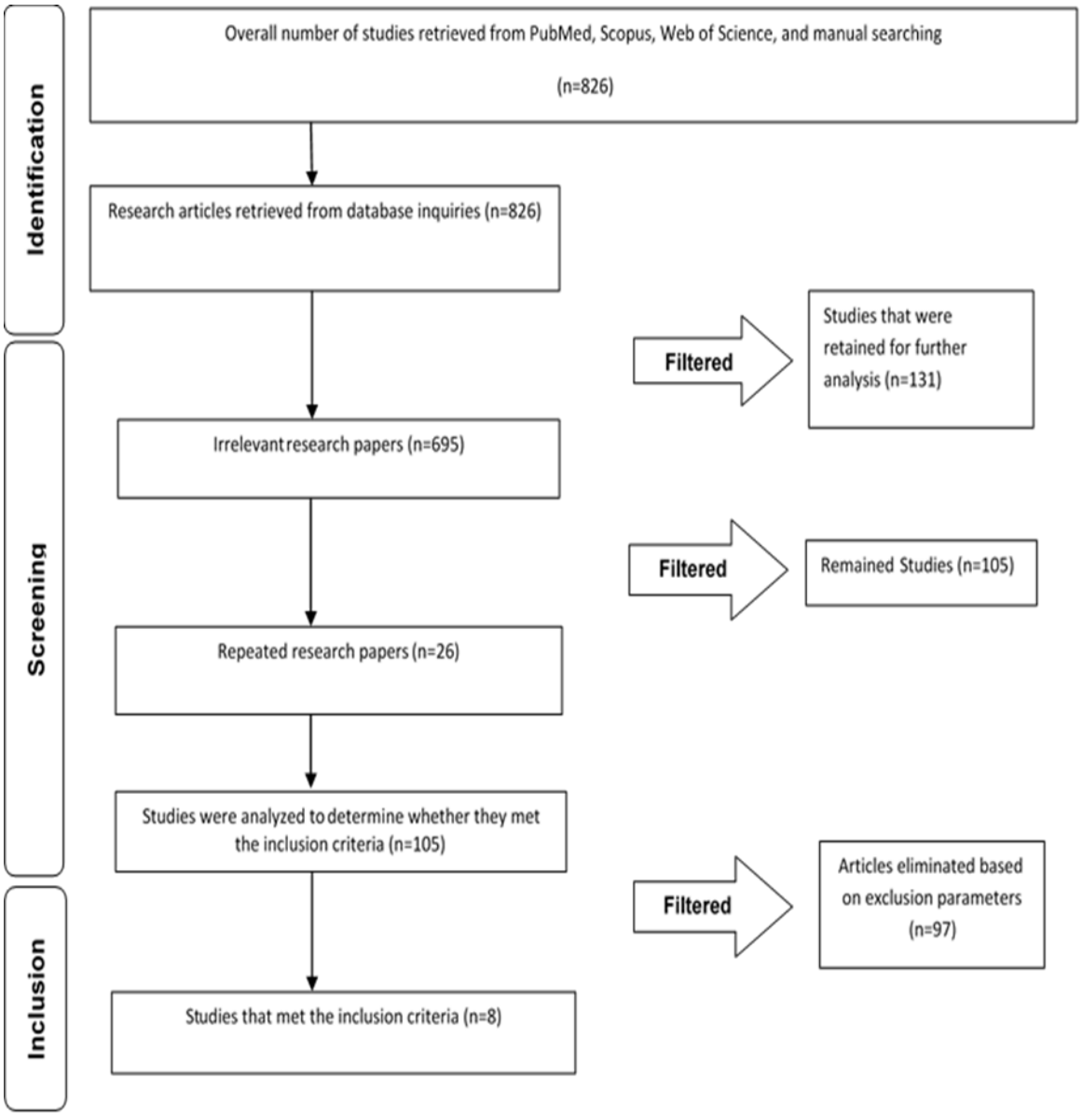

Figure 1. PRISMA diagram illustrating the study selection procedure

Data Synthesis

Owing to considerable differences in clinical (e.g. dosage, formulation), methodological (e.g. study design and outcome measures), and statistical aspects across the included studies, a quantitative meta-analysis was deemed inappropriate for the primary outcomes of perceived stress and cortisol levels. These variations arose from discrepancies in study design, demographic attributes of the population, definitions and duration of ginseng treatment, methods of supplement formulation, approaches to outcome evaluation, and adjustments for potential confounding variables. As a result, a narrative synthesis method was adopted to systematically compile and analyze the findings. The synthesis was structured according to the Synthesis Without Meta-analysis (SWiM) guideline to enhance reporting transparency (Campbell et al. 2020).

Results

Study selection

During the systematic search across three databases, a total of 826 records were discovered. Following the elimination of 26 duplicates, 800 records were screened for titles and abstracts. As a result, 695 studies were excluded because they were considered irrelevant or concentrated on mental health issues unrelated to stress (e.g. fatigue). The final 105 publications were subjected to full-text evaluation for eligibility.

At this phase, several exclusions were applied: studies not published in English (n=2), full texts that were not accessible (n=1), articles that were non-original, including reviews and qualitative analyses (n=33), laboratory and in vitro research (n=3), other experimental approaches that did not adhere to the protocol (n=4), animal research (n=48), and studies addressing outcomes outside this review's focus, such as general cognitive function, depression, anxiety, or quality of life (n=6). As a result, a total of 8 studies fulfilled all eligibility requirements and were incorporated into the final qualitative synthesis. The PRISMA flow diagram (Figure 1) outlines the process for selecting studies.

Characteristics of included studies

Table 1 provides a summary of the characteristics of the eight included single/double blind, placebo-controlled RCTs. A total of 473 participants were enrolled, with 254 assigned to receive ginseng supplementation. The average age of participants in the studies varied between 22.6 and 49.3 years. The research was varied in location, featuring three studies from East Asia including South Korea (Baek et al. 2019; Yoon et al. 2023) and Japan (Zheng and Moritani 2008), two from Belgium (Dormal et al. 2025; Mariage et al. 2020), and one from Australia (Gaffney et al. 2001), Iraq (Al-Kuraishy and Al-Gareeb 2017), and the United States (Flanagan et al. 2018). The ginseng interventions were diverse, featuring KRG (Baek et al. 2019; Dormal et al. 2025; Yoon et al. 2023), a mix of Red and White ginseng (Mariage et al. 2020), and Korean ginseng extract (Flanagan et al. 2018; Gaffney et al. 2001). Dosages varied between 160 mg and 500 mg per day, with intervention periods spanning from 14 days to 8 weeks.

Stress was evaluated through psychological scales as well as biomarkers. Four research studies utilized the Perceived Stress Scale (PSS) (Al-Kuraishy and Al-Gareeb 2017; Baek et al. 2019; Dormal et al. 2025; Mariage et al. 2020) one employed the Stress Response Inventory (SRI) (Yoon et al. 2023), and three focused solely on biomarker evaluation (Flanagan et al. 2018; Gaffney et al. 2001; Zheng and Moritani 2008). The biomarkers that were assessed comprised cortisol, catecholamines (epinephrine and norepinephrine), serotonin, and dopamine.

Table 1. Summary of data from the selected studies

Author (years) Country Reference	Sample Size	Age (y)	Male/female ratio	Type of study	Type of Ginseng	Dosage	Stress level	Treatment duration	Assessment tools		Primary outcome		Secondary outcome				Adverse effects	Key points
									Primary outcome	Secondary outcome	Stress	Depression and Cognition	Serotonin or Dopamine	Cortisol or CgA	TG or Glucose levels	Norepinephrine and Epinephrine levels		
Baek et al. (2019) Korea (Baek et al. 2019)	63 KRG: 32 P:31	KRG: 39.59 P:41.29 (20-60) (p>0.05)	KRG: 7/15 P:15/16 (p>0.05)	Double-blind, randomized, placebo-controlled trial	KRG	200 mg /day (four capsules total, taken twice daily)	High stress job	6-week	BDI/ PSS/ POMS/ SDS/ CPT	--	No significant difference between two groups	No significant difference in depression outcomes, but cognitive benefits observed	--	--	--	No change in norepinephrine, but a reduction in epinephrine (p>0.05)	No	The rise in TG is linked to a decline in epinephrine, suggesting that KRG may help regulate sympathetic nervous system activity.
Yoon et al., (2023) Korea (Yoon et al. 2023)	87 KRG: 43 P:44	KRG: 49.3±8.5 P: 48.2±8.6 (35-60)	KRG: 43/0 P:44/0	Double-blind, randomized, placebo-controlled trial	KRG	200 mg/ day (four capsules daily)	Healthy men with high stress	8-week	SRI	NTs/ NT-related gene expression/ Blood TG/ Blood Glucose	No significant difference between two groups	--	Reduction in the KRG group (p<0.05)	Cortisol lesser increase in KRG group (p<0.05)	Triglyceride and Glucose showed a smaller increase than the placebo (p<0.05)	Reduction in the KRG group (p<0.05)	No	KRG influences NT-related stress responses and modulates gene expression linked to the metabolism of choline, adrenaline, and monoamines.
Flanagan et al., (2018) USA (Flanagan et al. 2018)	19 Self-controlled study	38.7 ± 7.8	9/10	Double-blind, placebo-controlled, crossover study	KRG (GINST15)	High: 960 mg/day Low: 160 mg/day	High stress job	Three 14-day treatment cycles	--	Cortisol/ MDA	--	--	--	Reduced cortisol levels following treatment	--	--	No	GINST15 administration led to stress-responsive, dosage-related declines in circulating cortisol levels while enhancing enzymatic function and broad-spectrum antioxidant activity.
Dormal et al., (2025) Belgium (Dormal et al. 2025)	149 GS: 72 P:77	GS: 29 P:31 (p>0.05)	GS: 29/41 P:34/38 (p>0.05)	Double-blind, randomized, placebo-controlled trial	Red Panax Ginseng root	200 mg/day, (24 mg of rare ginsenosides)	Moderate levels of stress PSS scores:14 to 26	3 weeks	PSS/ BDI/ PANAS/ CANTAB/ PAL/ OTSC		An enhancement in the PSS rating was observed in the GS group (p<0.05)	Reduction in the BDI (p>0.05), negative PANAS and PAL (p<0.05) in GS group	--	--	--	--	No	The therapeutic potential of Red PG, containing high levels of rare ginsenosides, has been confirmed in alleviating stress, enhancing emotional well-being, and improving cognitive function.

Table 1.Continued

Al-Kuraishy et al. (2017) Iraq (Al-Kuraishy and Al-Gareeb 2017)	65 PG: 35 P:30	22.61±3.63	PG: 20/15 P:16/14	Single-blind, randomized, placebo-controlled trial	PG	500 mg/day	High stress job	1 month	PSS/ Psycho motor performance/ N-back working memory		PSS score and MDA were significantly lower in PG group than placebo group ($p<0.05$)	An improvement in the psychomotor performance and visual working memory accuracy ($p<0.05$)	--	--	--	--	No	The perceived stress scale showed a direct association with oxidative stress, as indicated by MDA serum concentrations, which were reduced in the PG group
Mariage et al., (2020) Belgium (Mariage et al. 2020)	50 HRG80: 17 WG: 16 P:17	37.46 (18-65)	--	Double-blinded,randomized, placebo-three-arm controlled, crossover trial,	HRG80® WG	HRG80®: 418 mg/day WG: 764 mg/day	Tired subjects Moderate stress PSS = 16.2 ± 2.2	14 days	PSS/ Memory test	--	PSS score was lower in HRG80 and WG groups than placebo group ($p<0.05$)	Mental performance and memory improved in HRG80 and WG groups than placebo group ($p<0.05$)	--	--	--	--	Diarrhea, and abdominal distention and weariness	HRG80 therapy exhibited a notably greater effectiveness than PGS and P in terms of focus, recall, and PSS evaluations following both initial and multiple administrations.
Zheng et al., (2008) Japan (Zheng and Moritani 2008)	10 Self-controlled study	27±1	10/0	Double-blind, randomized, placebo-controlled trial	Ginseng, oriental bezoar and glycyrrhiza	250 mg/day	Normal stress	--	--	CgA/ HF/ SNS Index	A decrease in mental stress in PG groups than placebo group ($p<0.05$)	--	--	CgA was lower in PG group ($p<0.05$)	Glucose level was not difference between groups	--	No	Ginseng is beneficial for alleviating psychological stress
Gaffney et al., (2001) Australia (Gaffney et al. 2001)	30 ES: 10 PG: 10 P:10	(18-40)	ES: 10/0 PG: 10/0 P: 10/0	Double blind placebo-controlled pre-test post-test trial	Ethanolic extract of PG	500 ml/day containing a 35% ethanolic extract of PG	--	6-weeks		LSN/ Cortisol/ DHEA to TES ration	No significant difference between groups	--	--	No significant difference in between groups	--	--	No	Ginseng intake did not influence stress - related physiological biomarkers

BDI: Beck Depression Inventory, CANTAB: Cambridge Neuropsychological Test Automated Battery , CgA: Salivary Chromogranin A, CPT: Visual and Auditory Controlled Continuous Performance Test, DHEA to TES: Dehydroepiandrosterone/ Testosterone ratio, ES: Eleutherococcus Senticosus, GS: Ginseng Supplementation , HRG80®: Hydroponic Red *Panax ginseng* Meyer, HF: High-Frequency Power, KGR: Korean Red Ginseng , LSN: Lymphocyte Subset Numbers, MDA: Malondialdehyde, NT: Neurotransmitter, OTSC: One Touch Stockings of Cambridge , P: Placebo, PAL: Paired Associate Learning, PANAS: Positive and Negative Affect Schedule, PG: *Panax ginseng* , POMS: Profile of Mood States, PSS: Perceived Stress Scale, SDS: Sheehan Disability Scale , SRI: Stress Response Inventory, SNS :Sympathetic Nervous System, TG : Triglyceride, WG: White *Panax ginseng*

Synthesis of results

Effects on psychological stress

Of the five studies using PSS and SRI questionnaires, a pattern related to dosage and ginseng type emerged. The two that provided 200 mg of KRG extract for a longer period (6-8 weeks) showed non-significant trends in stress reduction (Baek et al. 2019; Yoon et al. 2023). Conversely, three studies showing statistically significant benefits utilized different protocols: one administered a comparable 200 mg/day dose of KRG over a reduced 14-day span (Dormal et al. 2025), while the other two involved higher daily doses of 418 mg of a proprietary ginseng extract (G115) and 500 mg of a combination of red and white ginseng extracts over four weeks, respectively (Al-Kuraishy and Al-Gareeb 2017; Mariage et al. 2020).

Effects on cognitive function and mood

Regarding other psychological aspects, all four studies evaluating cognition—utilizing different extracts such as KRG, G115, and a red/white ginseng mixture—indicated notable advantages in areas like memory and psychomotor skills (Al-Kuraishy and Al-Gareeb 2017; Baek et al. 2019; Dormal et al. 2025; Mariage et al. 2020). Nevertheless, research on depression using 200 mg of KRG and 500 mg of the red/white ginseng mix revealed no notable differences when compared to placebo (Baek et al. 2019; Dormal et al. 2025), although one study reported an enhancement in the Positive and Negative Affect Schedule Score (Dormal et al. 2025).

Effects on stress-related biomarkers

The impact of ginseng on cortisol levels was examined in three studies. In two of them, KRG resulted in a attenuation of stress-induced cortisol increases in the KRG group compared to placebo (Flanagan et al. 2018; Yoon et al. 2023). In one study, a 400 mg dosage of a unique ginseng root extract (GINST15) was administered that resulted in a dose-dependent effect (Flanagan et al. 2018), while another study used 200 mg of Korean red ginseng in capsules (Yoon et al. 2023). Conversely, the research that reported no substantial impact employed a 500 mg ethanolic extract of *P. ginseng* (Gaffney et al. 2001).

A notable difference in the form of ginseng administration was observed between the studies. The two studies that demonstrated a significant effect of ginseng on cortisol used ginseng root administered orally in capsule form (Flanagan et al. 2018; Yoon et al. 2023). In contrast, the study that found no significant effect utilized an ethanolic extract of *P. ginseng* (Gaffney et al. 2001), suggesting that the formulation may influence efficacy.

The effect of KRG on catecholamines was evaluated in two studies that employed an identical daily dosage of 200 mg, though the treatment periods varied (Baek et al. 2019; Yoon et al. 2023). Baek et al. found no difference in norepinephrine levels but reported a decrease in epinephrine levels over a six-week period (Baek et al. 2019), while Yoon et al. observed a decrease in both norepinephrine and epinephrine levels in the KRG group compared to placebo groups in eight-week period of the study (Yoon et al. 2023). Although the results are contradictory, it is suggested that the duration of supplementation may alter the adrenergic response.

Interestingly, Yoon et al. (2023) found that KRG supplementation resulted in considerable decreases in acetylcholine, dehydroepiandrosterone (DHEA), dopamine, triglycerides, and glucose levels. Nevertheless, the result regarding glucose was contradicted by (Gaffney et al. 2001), who noted no significant variation in glucose levels when compared to the placebo. Additionally, distinct research conducted by Zheng and Moritani (2008) demonstrated that ginseng supplementation significantly lowered salivary Chromogranin A, an alternative indicator of stress. Moreover, one study with 200 mg of KRG for six weeks indicated a notable

decrease in serotonin levels, a result not investigated in the other studies included (Yoon et al. 2023).The diverse results for these secondary biomarkers, based on limited studies, prevent any conclusive determinations.

Effect of ginseng on gene expression patterns

Transcriptome investigation by Yoon et al. (2023) revealed notable changes in gene expression after KRG supplementation. The expression of the beta-2 adrenergic receptor (ADRB2) gene showed a 30% downregulation in the KRG group, a notably larger reduction compared to the 20% decline seen in the placebo group. Within the same group, KRG supplementation correlated with lower circulating epinephrine levels. Additionally, the catechol-O-methyltransferase domain-containing 1 (COMTD1) gene exhibited a 61% decrease in the KRG group, in contrast to a 42% decline in the placebo group (Yoon et al. 2023).

Safety of ginseng

In terms of safety, ginseng supplementation was typically well-tolerated. Of the eight studies included, adverse effects were noted in just one trial, in which a small percentage of participants (8%) experienced temporary diarrhea, abdominal distention, and weariness (Mariage et al. 2020). No other research reported notable negative outcomes.

Quality assessment

The Cochrane Risk of Bias tool (RoB 2.0) was utilized to evaluate the risk of bias in the eight included randomized controlled trials, focusing on seven essential domains. The total risk of bias was assessed to be low. In particular, the research indicated a minimal risk of bias related to the randomization procedure, deviations from planned interventions, absence of outcome data, outcome measurement, and selection of the reported findings. Table 2 provides a detailed assessment of each domain for all individual studies, which is visually summarized in Figure 2.

Figure 2. Evaluation of the quality assessment of the articles

Table 2. Evaluation of the methodological quality of the studies included in the review.

Author (Reference)	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the Reported Result
Baek et al. (Baek et al. 2019)	Low	Low	Low	Some Concerns	Low
Yoon et al., (Yoon et al. 2023)	Low	Low	Low	Some Concerns	Low
Flanagan et al., (Flanagan et al. 2018)	Low	Low	Low	Some Concerns	Low
Dormal et al., (Dormal et al. 2025)	Low	Low	Low	Some Concerns	Low
Al-Kuraishy et al. (Al-Kuraishy and Al-Gareeb 2017)	Low	Low	Low	Some Concerns	Low
Mariage et al., (Mariage et al. 2020)	Low	Low	Low	Some Concerns	Low
Zheng et al., (Zheng and Moritani 2008)	Some Concerns	Some Concerns	Low	Some Concerns	Some Concerns
Gaffney et al., (Gaffney et al. 2001)	Some Concerns	High	Low	High	Some Concerns

Discussion

This systematic review revealed findings from eight RCTs examining the impact of *P. ginseng* on psychological and physiological stress-related indicators in adults. The evidence showed conflicting and heterogeneous findings regarding the association of ginseng supplementation and psychological stress. The efficacy appears to be influenced by critical factors such as dosage, ginseng formulation, and treatment duration, rather than being a uniform effect. For further examination, the findings obtained from the present studies can be categorized into three categories. The effect of ginseng on psychological stress, the effect of ginseng on blood parameters associated with stress**,** and the effect of ginseng on gene expression patterns.

Effect of ginseng on psychological stress

Our synthesis suggests a potential dose-response relationship for psychological stress. The protective characteristics of ginsenosides extracted from KRG in alleviating stress have been thoroughly examined in animal trials (Jiang et al. 2022; Kim et al. 2019; Oh et al. 2017; Yu et al. 2018). Nonetheless, research involving humans in this field remains relatively scarce. Across five studies evaluating ginseng effect on psychological stress, two concluded that consuming a standard 200 mg dose of KRG showed no impact on stress levels, despite longer intervention periods (Baek et al. 2019; Yoon et al. 2023). However, factors such as excessively demanding occupations, the influence of placebo, and short treatment duration may have hindered achieving significant outcomes (Baek et al. 2019). Conversely, the other three studies documented an enhancement in PSS scores among individuals receiving ginseng compared to those in the placebo group, utilized increased daily dosages (418-500 mg) or specialized, highly absorbable formulations such as HRG80 and steamed red ginseng. (Al-Kuraishy and Al-Gareeb 2017; Dormal

et al. 2025; Mariage et al. 2020). This suggests that a minimum level of exposure to bioactive compounds might be required to produce a detectable psychometric effect, a theory backed by pharmacokinetic research on ginsenosides (Lee et al. 2024; Panossian et al. 2021). The effectiveness of certain formulations can be linked to their high levels of unique ginsenosides. Metabolites, including those present in steamed red ginseng and the HRG80 formulation, are recognized for having enhanced bioavailability and pharmacological efficacy compared to their main ginsenoside equivalents (Mariage et al. 2020, Dormal et al. 2025). The enhanced efficacy of these processed extracts highlights that the anti-stress effects of ginseng are not solely determined by the overall ginsenoside levels, but are significantly affected by the particular composition and bioavailability of its active components.

Rare ginsenosides, which are present in lower concentrations within ginseng, are metabolites of ginsenosides and represent the most biologically potent forms. The conversion of standard ginsenosides into these rare variants by altering their chemical composition can be achieved through physical processes such as steaming, chemical techniques like acidic or alkaline hydrolysis, and biotransformation via bacterial or fungal fermentation (Dormal et al. 2025). Dormal et al. incorporated red ginseng (steamed ginseng) in their research (Dormal et al. 2025).

The chemical properties of red and white ginseng vary (Lee et al. 2015). A majority of ginseng therapeutic properties are credited to a specific tetracyclic triterpenoid glucoside—saponins—particularly the ginsenosides, which exhibit diverse physiological effects such as immune modulation, anticancer properties (Chen et al. 2016), fatigue resistance, antiaging benefits (He et al. 2012), blood sugar regulation, mood-enhancing qualities (Ren et al. 2017), and neuroprotective functions (Ahmed et al. 2016). As of now, 112 different saponins have been identified as key constituents of *P. ginseng*, commonly referred to as Korean ginseng.

Effect of ginseng on stress related biomarkers

The effect of *P. ginseng* on stress biomarkers demonstrates a nuanced scenario, with effectiveness closely related to the specific biological pathway and the type of intervention used. The most reliable discovery among the analyzed studies was the modulation of the HPA axis indicated by cortisol levels. Across the reviewed studies, cortisol concentrations were assessed in three investigations. In two of them, KRG led to a more moderate rise in cortisol within the KRG group when contrasted with the placebo group (Flanagan et al. 2018; Yoon et al. 2023), However, the third study reported no substantial difference in cortisol reduction between those receiving the intervention and the placebo (Gaffney et al. 2001).

Importantly, the successful interventions—a fermented ginseng root extract (GINST15) and KRG in capsules—were distinct from the ethanolic extract that exhibited no effect (Gaffney et al., 2001). This indicates that the preparation method, affecting the bioavailability of active ginsenosides, is a key factor in HPA axis effectiveness. The dose-dependent reduction of cortisol linked to antioxidant effects demonstrated by Flanagan et al. reinforces a biologically credible, direct impact on the neuroendocrine stress response. This clinical observation is plausibly explained by preclinical evidence demonstrating that KRG has been shown to counteract stress-induced plasma corticosterone elevation by inhibiting the effect of adrenocorticotropic hormone in the adrenal gland, particularly in chronic restraint stress-induced depression models (Jiang et al. 2021).

The evidence concerning the influence on the sympathoadrenal system and catecholamines is less clear but indicative of a relationship that varies with time. Two studies administering the same 200 mg dosage of KRG yielded conflicting findings regarding epinephrine and norepinephrine (Baek et al., 2019; Yoon et al., 2023). The study with an extended duration noted a wider suppressive impact on both catecholamines, suggesting that extended supplementation might be required to significantly affect this rapid-response system. This clinical observation is backed by preclinical data indicating that ginseng saponins can inhibit cholinergically-induced catecholamine release (Jang et al. 2011), offering a mechanistic foundation for these results.

The effect on additional biomarkers such as serotonin, glucose, and triglycerides, remains uncertain because of insufficient and contradictory data. The solitary observation of a notable decrease in serotonin levels due to KRG supplementation (Yoon et al., 2023) is intriguing but lacks confirmation from additional studies. Likewise, the documented reductions in glucose and triglycerides in one study (Yoon et al., 2023) were not consistently found in other research (Gaffney et al., 2001; Zheng & Moritani, 2008), and one study even reported a rise in triglycerides that remained within the normal range (Baek et al., 2019). This clinical observation is plausibly explained by preclinical evidence demonstrating that an extract of KRG may stimulate intestinal enterochromaffin (EC) cells, thereby elevating serotonin levels in plasma (Shin et al. 2023; Yu et al. 2021).

In summary, additional validating research involving a larger patient cohort and an extended treatment duration is required to generate stronger evidence for the evaluation of ginseng influence on blood biomarkers.

Effect of ginseng on gene expression patterns

The results from the transcriptome analysis conducted by Yoon et al. (2023) provide a convincing, gene-centric viewpoint that could integrate many of the previously mentioned physiological observations. The finding that KRG supplementation notably decreases the expression of the ADRB2 gene offers a refined mechanistic rationale for the noted decrease in sympathetic tone. Instead of simply lowering epinephrine levels, KRG seems to operate at a deeper level by diminishing the responsiveness of target tissues to catecholamines. This decrease in ADRB2 is anticipated to dampen the "fight-or-flight" reaction at the cellular level, resulting in the lower physiological arousal and perceived stress noted in certain clinical studies. This exemplifies a typical adaptogenic effect: instead of diminishing the stress response, it may improve the body's capacity to handle it more effectively by regulating receptor density. This finding is supported by extensive studies on adaptogens, showing that plants such as *Rhodiola rosea* and *Schisandra chinensis* may affect the gene expression tied to the stress-response system, especially concerning the HPA axis and molecular chaperones such as Hsp70 (Panossian and Wikman 2009).

Additionally, the significant downregulation of the COMTD1 gene presents a new possible mechanism for controlling monoamine availability. Although the precise function of COMTD1 is not as clearly established as its paralog COMT, its participation in monoamine metabolic pathways implies that KRG may reduce the breakdown of important neurotransmitters such as norepinephrine, dopamine, and potentially serotonin. This aligns with the clinical and preclinical data observed, forming a unified model in which KRG lowers catecholamine-driven signal intensity (through ADRB2 downregulation) and extends

neurotransmitter availability (through COMTD1 suppression). This combined action may successfully restore balance to the sympathetic nervous system and HPA axis, encouraging increased resilience without inducing sedation (Panossian and Wikman 2009). The transcriptional control of ADRB2 and COMTD1 provides an intriguing molecular basis for ginseng adaptogenic properties by implying it modifies essential neuroendocrine pathways, though these results are still initial and need to be supported by future researches.

Strengths and limitations

This comprehensive investigation provides important perspectives on the impact of KRG on stress levels and blood biomarkers associated with stress. Notably, the review exclusively incorporated eight randomized clinical trials, providing a qualitative overview of the current evidence landscape and making the results from these studies generally credible. Moreover, this study specifically addresses both clinicopathologic features of psychological stress and stress related biomarkers in relation to ginseng supplementation. However, the limited number of studies and their considerable clinical heterogeneity—evident in the variations in ginseng dosage, formulation, treatment duration, and outcome measurement protocols—precluded a quantitative meta-analysis and limited the robustness of our conclusions.

The findings of this study on the effects of daily ginseng supplementation, ranging from 200 to 500 mg over a period of 14 days to 8 weeks, on stress and stress-related blood markers shows that *P. ginseng* has a potential but inconsistent adaptogenic effect in humans facing stress. The effectiveness seems to depend significantly on essential intervention features, especially the dosage and the specific, bioavailable form of the ginseng extract. The strongest evidence indicates a modulatory influence on the HPA axis, as shown by reduced cortisol levels, while the impacts on psychological stress and other biomarker systems were less consistent. The considerable variability and small number of strong studies prevent clear clinical guidelines. Consequently, a perceived lack exists in high-quality, large-scale RCTs employing standardized, well-defined ginseng interventions, uniform outcome measures, and extended durations to confirm these results, clarify the ideal conditions for efficacy, and solidify the role of *P. ginseng* in managing clinical stress.

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Author contribution statement

Co first author: Ghazaleh Elah Abadi and Sofia Salari: writing-original draft; Visualization, and writing - review & Editing: they do the same work. Yasamin Moeini pour: Formal analysis and writing Amirhooshang Mohammad poor and Seyed Alireza sadjadi: Conceptualization, methodology, investigation, formal analysis, and revising the manuscript

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