The Journal of Medicinal Plants and By-products

Original Article

The Therapeutic Potential of Propolis for Anxiety and Depression: A Systematic Review of Preclinical and Clinical Evidence

Hanieh Salehi-Pourmehr[1], Ali Bahadori[2], Javad Mahmoudi[3], Morteza Akbari[4], Alireza Bagherzadeh-karimi[5], Jafar Rahmani-Kahnamoei[6*] and Mojtaba Ziaee[5,1,7,8*]

[1]*Research Center for Evidence-based Medicine, Iranian EBM Centre: A JBI Centre of Excellence, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[2]*Department of Medical Microbiology, Sarab Faculty of Medical Sciences, Sarab, Iran*
[3] *Neuroscience Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[4] *Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran*
[5] *Research Center for Integrative Medicine in Aging, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran*
[6] *Department of Clinical Sciences, TaMS.C., Islamic Azad University, Tabriz, Iran*
[7]*Medical Philosophy and History Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[8] *Medicinal Plants research Center, Maragheh University of Medical Sciences, Maragheh, Iran*

*Corresponding authors: Email: rahmani@iau.ir; m.ziaee@tbzmed.ac.ir

Article History: Received 01 September 2025/Accepted in revised form 25 November 2025

ABSTRACT

Anxiety and depression are highly prevalent neuropsychiatric disorders, often comorbid with chronic physical illnesses. Given the limitations of conventional treatments, there is growing interest in natural adjunctive therapies. Propolis, a resinous bee product enriched with flavonoids and phenolic acids, has emerged as a candidate due to its reported antioxidant, anti-inflammatory, and neuroprotective properties. This systematic review synthesizes the available evidence on the efficacy of propolis for symptoms of anxiety, depression, and stress. This review was conducted in accordance with PRISMA 2020 guidelines. A comprehensive search of PubMed, EMBASE, Web of Science, Scopus, and Google Scholar was performed from inception to June 2025. We included preclinical studies and randomized controlled trials (RCTs) that assessed behavioral or clinical outcomes related to anxiety, depression, or stress following propolis administration. Fourteen studies (10 preclinical, 4 RCTs) were included. Preclinical studies (doses 10–200 mg/kg) consistently demonstrated anxiolytic, antidepressant, and anti-stress effects, associated with increased BDNF, reduced cortisol, and attenuated oxidative stress. In clinical trials (doses 500–1500 mg/day), propolis significantly reduced anxiety scores in three RCTs (e.g., a 59.8% reduction in menopausal women, $p < 0.01$) and depressive symptoms in two RCTs (e.g., a 54.2% reduction, $p < 0.01$). Stress-related outcomes were inconsistent. Proposed mechanisms include antioxidant and anti-inflammatory activities, neuroprotection, and gut-brain axis modulation. Current evidence indicates that propolis is a promising adjunctive intervention for anxiety and depression. However, clinical heterogeneity and limited data on stress outcomes necessitate further validation. Future research should prioritize standardized preparations, dose-response studies, and large-scale RCTs to firmly establish efficacy, safety, and mechanistic pathways.

Keywords: Propolis, Depression, Anxiety, Stress, Mental Health, Systematic Review

INTRODUCTION

Depressive and anxiety disorders are among the most prevalent mental health conditions globally and are frequently comorbid with chronic illnesses such as cancer, cardiovascular disease, and metabolic syndromes [1, 2]. For example, depression and anxiety affect about 20% and 10% of cancer patients, respectively, regardless of the stage of the disease or the goal of treatment [3].

While conventional pharmacological and psychological interventions are available, their limitations, including side effects, variable efficacy, and access issues, have spurred interest in novel, safer therapeutic options [4].

Propolis, a complex resinous material produced by honeybees from botanical sources, has garnered attention for its broad-spectrum biological activities, including potent anti-inflammatory, antioxidant, and neuroprotective properties [5, 6]. Its chemical composition is highly variable, influenced by geography, bee species, and local flora, but typically features pharmacologically active polyphenolics such as flavonoids, phenolic acids, and their esters [7, 8]. Despite its widespread use as a dietary supplement for general wellness [9], evidence for its effects on neuropsychiatric conditions remains fragmented. While numerous animal and human studies suggest benefits for anxiety, depression, and cognitive decline[10], other investigations report null effects, potentially due to variations in propolis formulation, dosage, and study duration.

Therefore, a systematic and critical synthesis of the existing evidence is required to evaluate the potential of propolis as a therapeutic agent for mental health. This systematic review aims to bridge this gap by synthesizing both preclinical and clinical evidence to assess the transdiagnostic efficacy of propolis on depression, anxiety, and stress, thereby clarifying its role and informing future research in mental health care.

METHODS

Data Sources and Search Strategy

This systematic review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A systematic literature search was performed across five electronic databases: PubMed, Scopus, Web of Science, Embase, and Google Scholar, from their inception until June 2025. The literature search was optimized for sensitivity and specificity by combining predefined keywords with corresponding Medical Subject Headings (MeSH) terms: ((((((propolis [Title/Abstract]) OR ((bee bread [Title/Abstract])) OR (bee glue[Title/Abstract])) OR ("bee resin"[Title/Abstract])) OR (“Propolis”[Mesh])) AND (((((((depression[Title/Abstract]) OR (anxiety[Title/Abstract])) OR (stress[Title/Abstract])) OR ("psychological stress"[Title/Abstract])) OR ("mood disorders"[Title/Abstract])) OR ("Depression"[Mesh])) OR ("Anxiety"[Mesh]) OR ("Stress, Psychological"[Mesh])) AND (((((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (experimental[Title/Abstract])) OR (trial[Title/Abstract])) OR (clinical study[Title/Abstract]) OR (supplementation[Title/Abstract])))

No filters were applied for the study design to allow inclusion of clinical trials and experimental (preclinical) studies. Studies unrelated to the effects of whole propolis or those that did not assess outcomes related to depression, anxiety, or stress were excluded.

A total of 450 references were retrieved and screened for eligibility. Duplicate records and abstracts were excluded from the analysis. Figure 1 illustrates a flowchart that explains the study selection process for trials examining the effects of propolis on depression, anxiety, and stress, in accordance with the PRISMA 2020 framework.

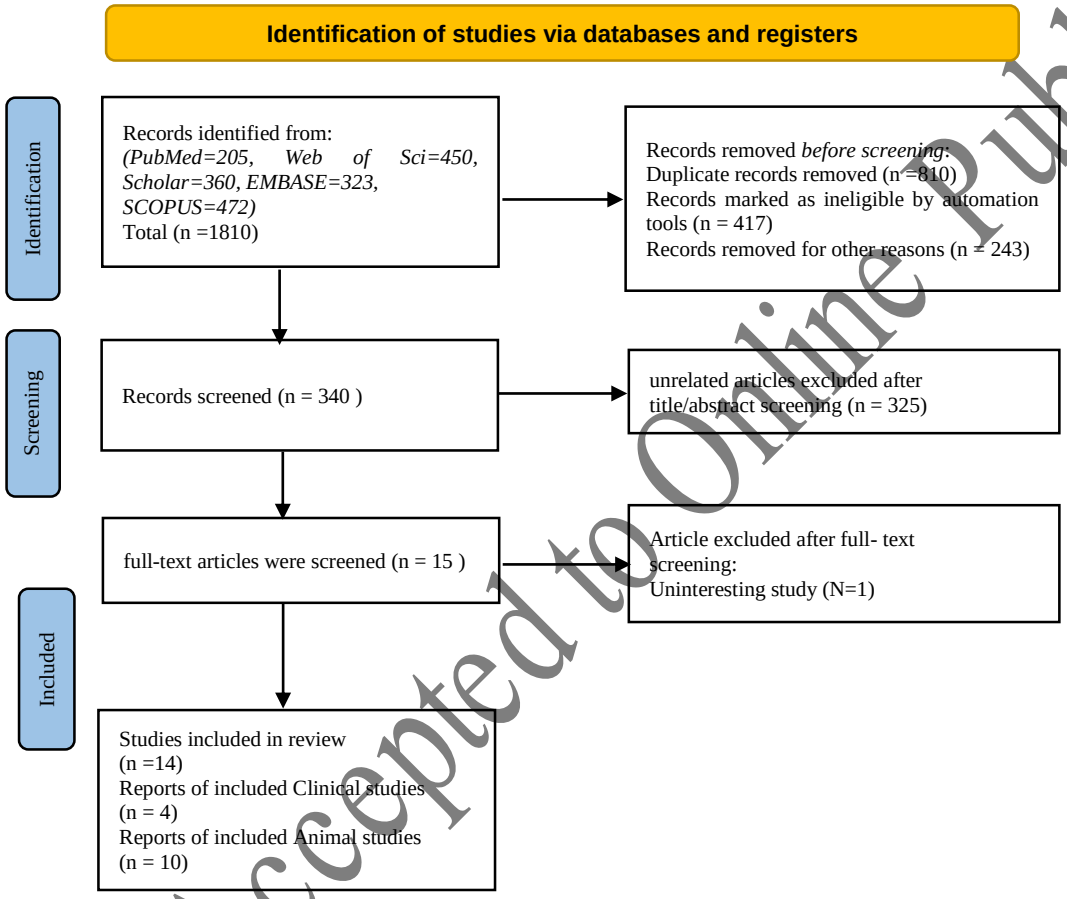

Fig. 1 Flow chart of the search and publication selection

Eligibility Criteria, Information Sources, and Search

The PICO (Population, Intervention, Comparison, Outcome) framework guided the inclusion criteria:

Population: Human participants (with or without comorbidities) or animal models exhibiting induced or naturally occurring depression, anxiety, or stress.

Intervention: Oral supplementation with any form of whole propolis (e.g., crude extract, standardized supplement).

Comparison: Placebo, no treatment, vehicle control, or standard care.

Outcome: Primary outcomes were changes in depression, anxiety, or stress levels, measured via validated psychometric scales in humans or behavioral tests (e.g., forced swim test, elevated plus maze) and biochemical markers (e.g., BDNF, cortisol) in animals.

Studies were excluded if they were reviews, commentaries, or conference abstracts; did not use propolis; or did not report relevant outcomes (Table 1).

Table 1 PICOS criteria for inclusion and exclusion of studies

Domain Criteria	Domain Criteria
Population	Human participants with or without chronic diseases, and animal models (e.g., rodents) exhibiting clinically diagnosed or experimentally induced depression, anxiety, or stress
Intervention	Intervention propolis supplementation. Both whole propolis or any product
Comparator	Placebo, no treatment, vehicle control, or standard care/intervention
outcomes	Changes in depression, anxiety, or stress levels measured using validated psychometric tools (for humans) or behavioral/biochemical markers (for animals)

Study Selection and Data Extraction

Search results were imported into reference management software, and duplicates were removed. The study selection process involved two phases: 1) screening of titles and abstracts and 2) full-text assessment of potentially eligible articles. Two reviewers (M.Z. and J.M.) independently conducted both phases; any disagreements were resolved through consensus. Data from included studies were extracted using a standardized data extraction form, capturing details on study design, population, intervention, outcomes, and key findings**.**

Quality Assessment and Ethics

For the included primary studies, ethical approval and patient/animal subject consent were assumed as per the standards of the publishing journals. The methodological quality and risk of bias of the included studies were assessed independently by two reviewers.

Clinical Trials: The Cochrane Risk of Bias tool was used, evaluating sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias.

Preclinical Studies: The CAMARADES checklist (10 items) was used to assess quality, including peer-reviewed publication, randomization, blinding, sample size justification, and compliance with animal welfare regulations.

Given the significant heterogeneity in populations, interventions, and outcome measures across the included studies, a meta-analysis was deemed inappropriate. Therefore, a narrative synthesis of the findings was performed.

Figures 2 and 3 illustrate the results of the critical appraisal of the included clinical trial studies. The findings indicate that the majority of the included trials exhibited low or unclear risk of bias.

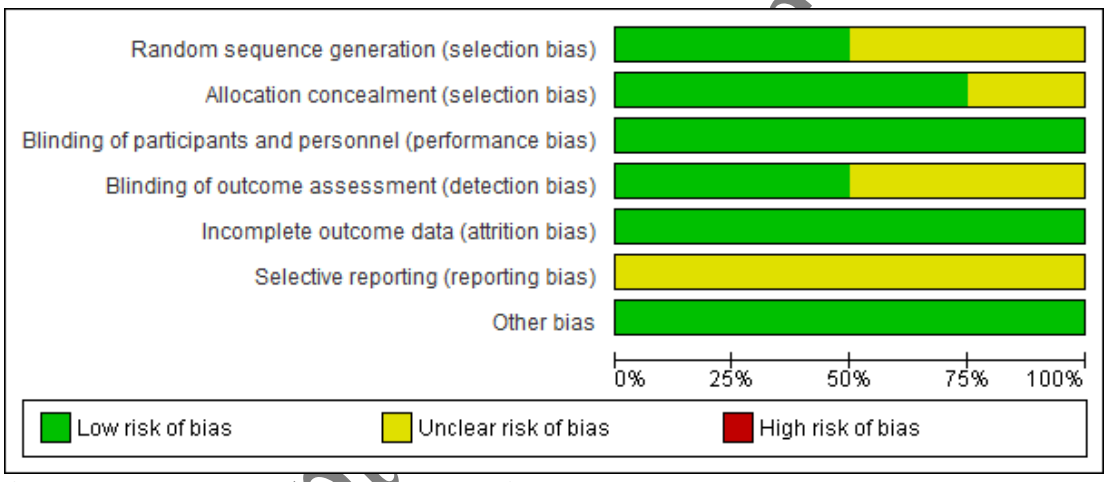

Fig. 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

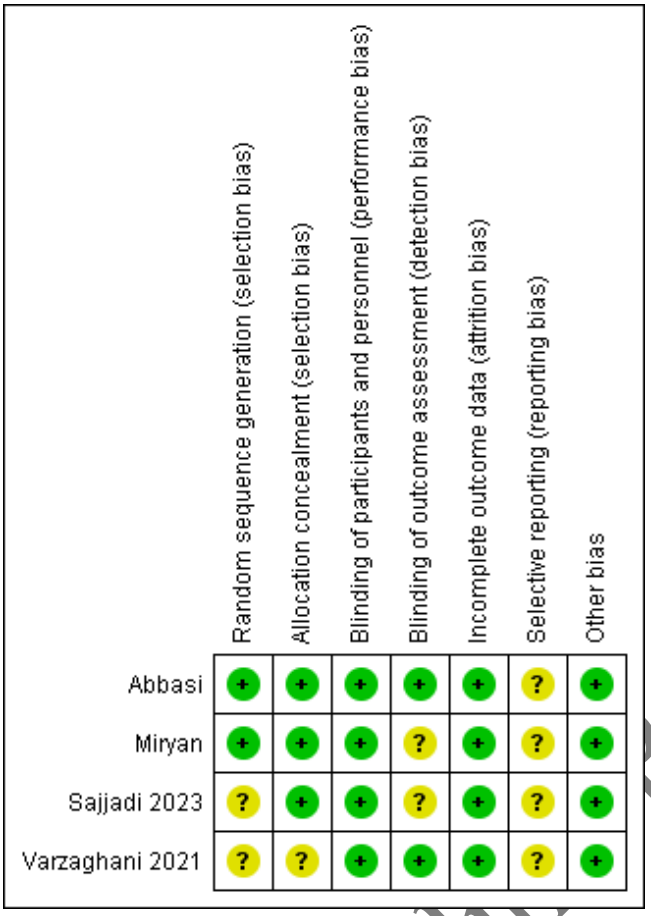

Fig. 3 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Table 2 Using the CAMARADES checklist, the quality of animal studies was assessed. According to the results.

Study ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Celebi, 2023 [11]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Kuswati, 2023[12]	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes
KELOĞLAN, 2021[13]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
TAŞKIRAN, 2024[14]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Li, 2012[15]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Reis, 2014[16]	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes
Lee, 2013[17]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Nisari, 2020[18]	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes
Wang, 2022[19]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Wang, 2020[20]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes

(1) peer-reviewed publication; (2) control of temperature; (3) random allocation to treatment or control; (4) blinded induction of ischemia; (5) blinded assessment of outcome; (6) use of anesthetic without significant intrinsic neuroprotective activity; (7) animal model (aged, diabetic, or hypertensive); (8) sample size calculation; (9) compliance with animal welfare regulations; and (10) statement of potential conflict of interests.

RESULTS

Study Selection

The systematic search identified 450 records. After removing 76 duplicates, 340 unique records were screened by title and abstract. Of these, 325 were excluded for irrelevance. Twenty-one full-text articles were assessed for eligibility, and seven were excluded (reasons: lacking outcome data, n=4; using propolis derivatives, n=2; non-English, n=1). Ultimately, 14 studies (10 preclinical, 4 RCTs) were included in the qualitative synthesis. The study selection process is detailed in the PRISMA flow diagram (Figure 1).

Preclinical evidence

The ten preclinical studies utilized various models of induced depression and stress, including chronic unpredictable mild stress (CUMS), social isolation, and restraint stress. Propolis was administered orally (9 studies; 10–200 mg/kg/day) or intraperitoneally (1 study; 10–50 mg/kg/day), over periods ranging from acute dosing to 10 weeks.

Consistent anxiolytic and antidepressant effects were observed. Behavioral tests showed propolis increased time spent in the open arms of the Elevated Plus Maze and reduced immobility in the Forced Swim Test. Mechanistically, propolis administration was associated with upregulated hippocampal and prefrontal cortex BDNF expression, reduced circulating stress hormones (ACTH, cortisol), and decreased oxidative stress markers like malondialdehyde (MDA).

Clinical evidence

The four included RCTs involved heterogeneous populations: women with polycystic ovary syndrome (PCOS), menopausal women, individuals with metabolic syndrome, and patients with moderate-to-severe depression. Propolis was administered orally at doses of 500–1000 mg/day for 6 to 12 weeks.

Propolis supplementation demonstrated significant benefits for anxiety and depression, but effects on stress were mixed. Anxiety scores were significantly reduced in three out of four trials. Depressive symptoms were significantly improved in two trials. For stress, one trial reported a significant reduction, while another found no effect compared to placebo. Detailed results for each study are summarized in Tables 2 and 3.

Table 2 Summary table of included Clinical studies

Author / Date	Study Details	Population Details	Intervention	Outcomes	Results
Abbasi *et al.* (2023)[21]	Randomized, triple-blinded, placebo-controlled trial. Country: Iran. Sample size: 72 women with PCOS. Study period: 12 weeks.	Women aged 18–40 years with PCOS.	Intervention Group: Propolis supplementation (500 mg/day). Control: Placebo capsules.	Changes in anxiety, stress, and depression (DASS-21).	Propolis group showed significant reductions in anxiety (−1.03 ± 1.57, p = 0.01) and stress (−1.86 ± 1.32, p = 0.001) compared to placebo. Depression reduced initially but was not significant after adjusting for confounders.
Sajjadi, Sana Sadat, *et al*. (2023)[22]	Randomized, double-blind, placebo-controlled trial. Country: Iran. Sample size: 66 participants. Study period: 12 weeks.	Men and Women aged 20–60 years diagnosed with metabolic syndrome (MetS), meeting NCEP ATP-III criteria.	Propolis tablets (250 mg extract, twice daily, total 500 mg/day). Control: Placebo tablets.	Mood status (DASS-21) and quality of life (SF-36).	Anxiety significantly reduced in the propolis group (p = 0.023). No significant differences in stress, depression (DASS-21). Improvements in SF-36 physical functioning (p < 0.001), general health (p < 0.001), total score (p < 0.001).
Varzaghani *et al*. (2022).	Randomized, double blind, placebo controlled Country: Iran Sample size (n): 60 enrolled, 54 completed Total study period: 6 weeks	Men and Women diagnosed with moderate-to-severe Mental Disease Disorder (HAMD-17 score >14) Age in years (average): 42	Intervention Group: propolis capsules (1,000 mg/day). Control: placebo capsules (fried bread powder). Both Groups: Continued SSRI treatment during the trial.	Reduction in depressive symptoms as measured by HAMD-17 and BDI scores.	HAMD-17: Propolis group: Significant reduction from baseline (20.92 ± 3.77) to day 42 (10.03 ± 5.55). (p < 0.0001) BDI: Propolis group: Improvement from baseline (29.25 ± 3.06) to day 42 (14.17 ± 4.86). (p < 0.0025).
Fouad *et al*. (2022)[23]	Randomized controlled study. Country: Egypt. Sample size: 63 non-diabetic menopausal women. Study period: 3 months.	Women aged 45–55 years experiencing menopausal symptoms.	Intervention Group: Enriched honey (clover honey + bee pollen, royal jelly, and propolis). Control: Clover honey only.	Improvements in Mood changes measured by anxiety and depression scales measured by Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI)	Intervention group showed significant improvement in depression and anxiety scores compared to control. Anxiety score reduced from 19.9 ± 5.7 to 8.0 ± 4.5 (p < 0.01), representing a 59.8% reduction. Depression score improved from 17.9 ± 6.2 to 8.2 ± 3.5 (p < 0.01), reflecting a 54.2% reduction.

Table 3 Summary table of included pre-clinical studies

Authors, Year, country.	Study	Population	Doses	Route	Duration	Results
Taşkıran *et al*., 2024, Turkey	Animal	Male Wistar-Albino rats	100 mg/kg	Oral	60 days	Propolis demonstrated antidepressant-like effects in behavioral tests, reducing anhedonia and anxiety-like behaviors. Improved stress-related behaviors, but no significant change in serotonin levels
Kuswati *et al*., 2023, Indonesia	Animal	Male Sprague-Dawley rats	100, 150, 200 mg/kg	Oral	14 days	Propolis increased BDNF expression in the prefrontal cortex of stressed rats, demonstrating neuroprotective effects against stress
Celebi *et al*., 2023, Turkey[11]	Animal	Male Wistar rats	100 mg/kg	Oral	5 weeks	Propolis improved depression-like behaviors in the chronic unpredictable mild stress (CUMS) model, reducing immobility time in the Forced Swimming Test (FST). It

						also ameliorated inflammatory cytokines (TNFα, IL-1β).
Keloğlan *et al*., 2021, Turkey	Animal	Male Wistar Albino rats	100 mg/kg	Oral	35 days	Propolis reduced oxidative stress and stress hormone levels (ACTH, cortisol) in a chronic stress model. Improved antioxidant enzyme levels and reduced protein oxidation
Wang *et al*., 2020, China[20]	Animal	Male C57BL/6J mice	10 mg/kg	Oral	3 weeks	Pinocembrin (PB), a component of propolis, reduced depressive-like behaviors in CUMS mice by reversing immobility time in FST and TST. PB decreased ROS and MDA levels and increased SOD activity, highlighting its antioxidant properties
Nisari *et al*., 2020, Turkey[18]	Animal	Male Wistar Albino rats	10, 30, 50 mg/kg	Oral	5 days	Dose-dependent effects observed: 30 mg/kg showed anxiolytic effects in the elevated T-maze, while 10 and 50 mg/kg had anxiogenic effects. Propolis reduced MDA levels and influenced lipid and enzymatic profiles positively in stressed rats
Wang *et al*., 2022, China[19]	Animal	Male C57BL/6J mice with alcohol-induced depression	120 mg/kg	Oral	10 weeks	Propolis alleviated alcohol-induced depressive behaviors, restored hippocampal BDNF and dopamine levels, repaired intestinal mucosal barrier function, and reduced pro-inflammatory cytokines. Improvements linked to gut-brain axis modulation
Reis *et al.*, 2014, Brazil[16]	Animal	Female Wistar rats	10, 30, 50 mg/kg	Intraperitoneal	Acute	Propolis exhibited antidepressant and anxiolytic effects, reducing anxiety and depression-like behaviors in behavioral tests. Antioxidant activity reduced nitric oxide levels
Lee *et al.*, 2013, Korea[17]	Animal	Male CD-1 mice	50, 100, or 200 mg/kg	Oral	Acute	Propolis extract demonstrated a dose-dependent antidepressant-like effect in the Forced Swim Test (FST) and Tail Suspension Test (TST) without affecting locomotor activity.
Li *et al.*, 2012, China[15]	Animal	Male ICR mice	50, 100, 200 mg/kg	Oral	14 days	Propolis essential oil (PEO) reduced anxiety-like behaviors in restraint-stressed mice. Increased time in open arms (EPM), reduced plasma ACTH and corticosterone (CORT), and mitigated oxidative stress by reducing MDA and partially restoring SOD activity

Efficacy of Propolis on anxiety, depression, and stress in Clinical Studies

Four clinical evaluated the efficacy of propolis in alleviating anxiety, depression, and stress, enrolling populations with varying clinical profiles ranging from endocrine and metabolic disorders to mental health conditions.

Anxiety

Across the four randomized controlled trials included in this review, three demonstrated significant reductions in anxiety following propolis supplementation. In a clinical trial involving 72 patients, Abbasi and colleagues (2023) carried out a study in which women with PCOS were given 500 mg of propolis per day for a period of twelve weeks. The study was controlled by a placebo and was completed in a triple-blind method. Compared with placebo, the intervention group exhibited a notable decline in anxiety scores (-1.03 ± 1.57; $p = 0.01$), indicating a clinically meaningful anxiolytic effect [21]. In a randomized trial of 66 participants, Sajjadi *et al.* (2023) reported that 12 weeks of propolis supplementation (500 mg/day, administered as two 250 mg tablets) produced a significant reduction in anxiety scores among participants with metabolic syndrome, as assessed by the DASS-21 scale, compared with placebo ($p = 0.023$) [22]. Dietary supplementation with enriched honey, containing propolis, bee pollen, and royal jelly, significantly alleviated anxiety symptoms in menopausal women. As reported by *Fouad et al.* (2022), consumption over a three-month period resulted in a 59.8% reduction in Beck Anxiety Inventory (BAI) scores among 63 non-diabetic menopausal women, decreasing from a baseline of 19.9 ± 5.7 to 8.0 ± 4.5 post-

intervention ($p < 0.01$). The improvement was significantly better than that experienced in the control group treated with clover honey [23]. Varzaghani *et al*. (2022) did not provide specific outcomes related to anxiety among 54 participants, as their investigation primarily concentrated on assessing depressive symptoms in patients diagnosed with moderate-to-severe mental health disorders [24].

DISCUSSION

Two of the four clinical studies observed significant improvements in depression scores. In a randomized study involving 63 participants, Fouad *et al*.(2022) reported a 54.2% reduction in depression scores (from 17.9 ± 6.2 to 8.2 ± 3.5, $p < 0.01$), measured by the Beck Depression Inventory, in menopausal women consuming enriched honey (containing propolis, bee pollen, and royal jelly) for 3 months compared to a control group receiving clover honey [23]. In a clinical trial involving 54 patients, Varzaghani *et al.* (2022) found significant reductions in depressive symptoms among patients with moderate-to-severe mental health disorders treated with 1,000 mg/day of propolis for 6 weeks alongside standard SSRI treatment. In this study, HAMD-17 scores decreased from 20.92 ± 3.77 to 10.03 ± 5.55 ($p < 0.0001$), and BDI scores improved from 29.25 ± 3.06 to 14.17 ± 4.86 ($p < 0.0025$) compared to placebo.[24] In an RCT study involving 72 patients, Abbasi *et al.* (2023) observed initial reductions in depression scores, assessed by the DASS-21 scale, among women with PCOS after 3 months of propolis supplementation (500 mg/day); however, these changes were nonsignificant after adjusting for confounders [21]. In a randomized trial of 66 participants, Sajjadi *et al.* (2023) reported no significant effect on depression scores (DASS-21) in participants with metabolic syndrome after 12 weeks of propolis supplementation (500 mg/day) compared to placebo [22].

Stress

Of the four clinical studies, only two reported outcomes related to stress. Abbasi *et al.* (2023) observed a significant reduction in stress scores ($n=72$, -1.86 ± 1.32, $p = 0.001$), measured by the DASS-21 scale, in women with PCOS after 3 months of propolis supplementation (500 mg/day) compared to placebo [21]. In contrast, Sajjadi *et al.* (2023) found no significant effect on stress levels, also assessed using the DASS-21 scale, in 66 participants with metabolic syndrome following 12 weeks of propolis supplementation (500 mg/day, administered as 250 mg tablets twice daily) compared to placebo [22]. Varzaghani *et al.* (2022) and Fouad *et al.* (2022) did not report specific stress outcomes, as their focus was primarily on depression and anxiety [23, 24].

Efficacy of Propolis on Anxiety, Depression, and Stress in Animal Studies

The effects of propolis on anxiety, depression, and stress-related behaviors were assessed in ten animal studies.

Anxiety

Consistent anxiolytic effects were observed across four independent animal studies investigating propolis administration. In a representative study, Reis *et al.* (2014) demonstrated that acute intraperitoneal injection of propolis extract (at doses of 10–50 mg/kg) significantly reduced anxiety-like behavior in female Wistar rats. The effect was demonstrated by a significant increase in exploration behavior in both the open field and elevated plus maze tests, which are established models for evaluating anxiety in rodents [16]. Taşkıran *et al.* (2024) demonstrated that chronic consumption of propolis significantly reduced anxiety-like behaviors provoked by continuous unpredictable moderate stress (CUMS) in a male Wistar-Albino rat model. After 60 days of therapy with propolis (100 mg per kg per day), stressed animals demonstrated a notable increase in the duration spent in the open arms of the elevated plus maze when compared to the stressed control group. This behavioral outcome is indicative of a pronounced anxiolytic effect [14]. Nisari *et al.* (2020) observed dose-dependent effects in male Wistar-Albino rats, where oral propolis at 30 mg per kg per day for 5 days exhibited anxiolytic effects in the elevated T-maze, although 10 and 50 mg/kg doses showed anxiogenic effects [18]. Oral administration of propolis essential oil (50, 100, or 200 mg per kg per day for 14 days) produced significant anxiolytic and neuroendocrine effects in a male murine model of restraint stress. Treated animals demonstrated a significant decrease in anxiety-like behaviors, as evidenced by an increase in the duration spent in the open arms of the elevated plus maze. This behavioral improvement was corroborated by a significant attenuation of the stress-induced hypothalamic-pituitary-adrenal (HPA) axis response, as evidenced by lower plasma levels of adrenocorticotropic hormone (ACTH) and corticosterone compared to stressed controls [15].

Depression

A systematic evaluation of the preclinical literature reveals consistent evidence for the antidepressant-like properties of propolis, as demonstrated in six independent animal studies. This activity is reliably quantified by behavioral despair tests. For instance, Reis *et al*. (2014) reported that acute intraperitoneal administration of propolis extract (10–50 mg/kg) significantly reduced immobility time in the forced swimming test in female Wistar rats. This reduction is a well-established behavioral correlate of antidepressant-like efficacy [16]. Chronic consumption of propolis (100 mg per kg per day) over sixty days produced significant antidepressant-like effects in a male Wistar-Albino rat model of chronic unpredictable mild stress (CUMS). Treated animals exhibited a marked reduction in behavioral despair, indicated by a notable reduction in the immobility period through the forced swim test. Moreover, propolis administration improved core depressive symptoms by significantly increasing sucrose preference, indicating a reversal of stress-induced anhedonia [14]. Kuswati *et al*. (2023) further demonstrated that the antidepressant-like mechanism of propolis may involve neurotrophic enhancement. In a study utilizing male Sprague-Dawley rats, oral administration of propolis (at doses of 100, 150, or 200 mg per kg per day for 14 days) significantly upregulated the expression of BDNF in the prefrontal cortex. This elevation in a key neurotrophic factor suggests a potential neuroprotective mechanism underpinning the efficacy of propolis against stress-induced depression [12]. Male Wistar rats that were given 100 mg per kg per day of propolis orally for 5 weeks and then put through chronic unpredictable mild stress (CUMS) had a significantly shorter immobility period in the forced swim test and lower levels of proinflammatory cytokines IL-1β and TNF-α [11]. According to Wang *et al*. (2020), male C57BL/6J mice subjected to chronic stress were observed to exhibit improvements in antioxidant biomarkers and shorter immobility periods in the forced swim and tail suspension tests after being orally administered Pinocembrin isolated from propolis (10 mg per kg per day for 21 days) [20]. Propolis taken orally at a dosage of 120 mg per kg per day for 10 weeks improved BDNF and dopamine levels in the hippocampus. Alcohol-induced maladaptive behaviors were observed in male C57BL/6J mice [19].

Stress

Four animal studies reported reductions in physiological and behavioral markers of stress with propolis treatment. Male rats given oral propolis at a dosage of 100 mg per kg per day for 35 days exhibited reduced levels of serum cortisol and ACTH, based on the experiments carried out by Keloğlan *et al.* (2021) using a chronic unpredictable mild stress (CUMS) model. Furthermore, the rats' levels of antioxidant enzymes improved, and their protein oxidation was reduced [13]. Kuswati *et al.* (2023) claimed that when male rats were given oral propolis at doses of 100, 150, or 200 milligrams per kg per day for two weeks, they experienced decreased neuronal damage and increased expression of BDNF in their prefrontal cortex [12]. Researchers found that male ICR mice that were put under stress by being restrained had lower levels of ACTH and corticosterone in their blood, as well as better indicators of oxidative stress. Malondialdehyde levels were reduced, and superoxide dismutase activity was partially recovered. The study identified these markers among others. By administering doses of 50, 100, and 200 mg per kg daily of propolis essential oil orally over a period of 2 weeks, the effects of the oil in relieving stress were demonstrated [15]. The stress-related inflammatory responses in male C57BL/6J mice with alcohol-induced depression were shown to be reduced by oral propolis (120 mg per kg per day for 10 weeks), according to Wang *et al.* (2022). This was achieved by lowering pro-inflammatory cytokines and rebuilding intestinal mucosal barrier function [19].

The findings indicate that propolis has a major impact on anxiety, depression, and stress in animal models. Improvements in behavior, protection of the nervous system, and reductions in physiological stress markers like cortisol, ACTH, and inflammatory cytokines cause these effects.

DISCUSSION

This systematic review synthesizes evidence indicating that propolis exerts significant anxiolytic and antidepressant effects across both preclinical and clinical settings. The clinical findings, while preliminary, are promising: three out of four randomized controlled trials demonstrated significant reductions in anxiety, and two showed improvements in depression. Conversely, effects on perceived stress were inconsistent. These human outcomes are strongly supported by robust preclinical data, where 10 animal studies consistently showed propolis mitigated anxiety-like and depression-like behaviors.

The included studies elucidate that a convergent set of biological mechanisms mediate the therapeutic benefits of propolis. The results collectively point to propolis acting as a multi-target agent:

1. **Neurotrophic and Neurotransmitter Modulation:** A key replicated finding in animal models was the upregulation of Brain-Derived Neurotrophic Factor (BDNF) in brain regions critical for mood regulation, such as the hippocampus and prefrontal cortex [12]. This was complemented by evidence of restored dopamine levels [19], suggesting enhanced neuroplasticity and monoaminergic signaling as core antidepressant mechanisms.
2. **HPA Axis Regulation and Antioxidant Activity:** Preclinical results consistently demonstrated that propolis normalizes the physiological stress response. This was evidenced by significant reductions in stress hormones, including corticosterone and ACTH. Concurrently, propolis reliably attenuated oxidative stress, shown by decreased levels of malondialdehyde (MDA) and increased activity of antioxidant enzymes like superoxide dismutase (SOD) [13, 15].
3. **Anti-inflammatory and Gut-Brain Axis Effects:** The anti-inflammatory properties of propolis were a prominent finding. Multiple studies reported reduced levels of pro-inflammatory cytokines, including TNF-α and IL-1β. This effect is likely driven by bioactive components like caffeic acid phenethyl ester (CAPE), which inhibits the NF-κB signaling pathway [11, 19]. Furthermore, emerging evidence from animal models suggests that propolis promotes intestinal barrier repair and modulates gut microbiota, positioning the gut-brain axis as a novel pathway for its neuroprotective actions [19].

Implications and Future Directions

Cumulative evidence from this review indicates propolis holds promise as an adjunctive treatment for anxiety and depression. Clinically, significant anxiolytic effects were reported in three out of four trials and antidepressant effects in two, particularly in populations like women with PCOS and menopausal women. Preclinical data robustly support these findings, demonstrating propolis mitigates anxiety, depression, and stress related behaviors in animal models.

These benefits are primarily attributed to propolis's antioxidant, anti-inflammatory, and neuroprotective properties. The key mechanisms involve the upregulation of brain-derived neurotrophic factor (BDNF), the reduction of stress hormones (cortisol, ACTH), and the modulation of inflammatory cytokines. Emerging evidence also implicates gut-brain axis modulation via intestinal barrier repair and microbiota changes. However, clinical application remains cautious. Challenges include the chemical variability of propolis, a lack of long-term safety data, potential for allergic reactions, and undefined optimal dosing. The heterogeneity in study designs and inconsistent stress outcomes further complicate interpretation.

Therefore, future research must prioritize:

Standardizing propolis formulations and dosages.

Conducting large-scale, multicenter randomized controlled trials to validate efficacy and safety.

Further elucidating underlying mechanisms, including neurotrophic and gut-brain pathways [12, 13, 19]

CONCLUSION

This systematic review demonstrates that propolis holds significant promise as a natural adjunctive therapy for anxiety and depression, supported by consistent preclinical data and encouraging, though preliminary, clinical findings. Its multi-target action on inflammation, oxidative stress, and neurotrophic support aligns with the complex pathophysiology of mood disorders. For clinical practice, this dissertation suggests propolis could be considered a complementary option, particularly for individuals seeking natural interventions.

However, the current evidence base is not yet sufficient to dictate standardized clinical protocols. Therefore, the translation of these findings into mainstream mental health care is contingent upon future rigorous, well-designed research that addresses the existing gaps in standardization, dosing, and safety.

Acknowledgments

The authors gratefully acknowledge the Medical Philosophy and History Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, for their generous support and commitment, which significantly facilitated the completion of this study.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

Data Availblity

The authors affirm that the data underpinning the findings of this study are accessible within the publication and its supplementary materials.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

During the preparation of this work, the authors utilized QuillBot to fix grammar mistakes and make the language more clear and coherent. The authors carefully examined and revised the content after utilizing this tool or service. They wholeheartedly accept responsibility for the publication's content.

REFERENCES

1. Babich O., Larina V., Ivanova S., Tarasov A., Povydysh M., Orlova A., Strugar J., Sukhikh S. Phytotherapeutic approaches to the prevention of age-related changes and the extension of active longevity. Molecules. 2022;27(7):2276.
2. Abdoli N., Salari N., Darvishi N., Jafarpour S., Solaymani M., Mohammadi M., Shohaimi S. The global prevalence of major depressive disorder (MDD) among the elderly: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews. 2022;132:1067–73.
3. Pitman A., Suleman S., Hyde N., Hodgkiss A. Depression and anxiety in patients with cancer. BMJ. 2018;361.
4. Menezes da Silveira C.C., Luz D.A., da Silva C.C., Prediger R.D., Martins M.D., Martins M.A., Fontes-Júnior E.A., Maia C.S. Propolis: A useful agent on psychiatric and neurological disorders? A focus on CAPE and pinocembrin components. Medicinal Research Reviews. 2021;41(2):1195–215.
5. Zullkiflee N., Taha H., Usman A. Propolis: Its role and efficacy in human health and diseases. Molecules. 2022;27(18):6120.
6. Bankova V., Trusheva B., Popova M. Propolis extraction methods: A review. Journal of Apicultural Research. 2021;60(5):734–43.
7. Kasote D., Bankova V., Viljoen A.M. Propolis: Chemical diversity and challenges in quality control. Phytochemistry Reviews. 2022;21(6):1887–911.
8. Bragança Castagnino G.L., Meana A., Cutuli de Simón M.T., Batista Pinto L.F. Propolis and its effects on bee diseases and pests: a systematic review. Journal of Apicultural Research. 2023;62(1):171–84.
9. Braakhuis A. Evidence on the health benefits of supplemental propolis. Nutrients. 2019;11(11):2705.
10. Bahari H., Jazinaki M.S., Goudarzi K., Namkhah Z., Taheri S., Golafrouz H., Pahlavani N. Effects of propolis consumption on blood pressure, lipid profile and glycemic parameters in adults: a GRADE-assessed systematic review and dose–response meta-analysis. British Journal of Nutrition. 2024:1–24.
11. Celebi G., Gocmez S.S., Ozer C., Duruksu G., Yazır Y., Utkan T. Propolis prevents vascular endothelial dysfunction by attenuating inflammation and oxidative damage in the chronic unpredictable stress model of depression in rats. Journal of Pharmacy and Pharmacology. 2023;75(11):1418–29.
12. Kuswati K., Handayani E.S., Nugraha Z.S. Propolis Increases Brain Derived Neurotrophic Factor Expression in the Prefrontal Cortex of Rat Stress Model. Paper presented at the 3rd International Conference on Cardiovascular Diseases (ICCvD 2021). 2022.
13. KELOĞLAN R., DEMİRTÜRK Z., UÇKAN F. Regulative Influence of Propolis on Oxidative Stress and Hormonal Changes in Chronic Unpredictable Mild Stress-induced Depression Model of Rats. The Pharmaceutical and Chemical Journal. 2021;8(2).
14. TAŞKIRAN A., CANBOLAT F., YÜCELLİ S.N., ÇEVRELİ B. Evaluation of the Antidepressant Effect of Propolis in Chronic Unpredictable Mild Stress-Induced Depression Model in Rats. Namık Kemal Medical Journal. 2024;12(3):145–54.
15. Li Y., Xuan H., Shou Q., Zhan Z., Lu X., Hu F.-L. Therapeutic effects of propolis essential oil on anxiety of restraint-stressed mice. Human & Experimental Toxicology. 2012;31(2):157–65.
16. Reis J.S., Oliveira G.B., Monteiro M.C., Machado C.S., Torres Y.R., Prediger R.D., Maia C.S. Antidepressant-and anxiolytic-like activities of an oil extract of propolis in rats. Phytomedicine. 2014;21(11):1466–72.
17. Lee M.-S., Kim Y.H., Park W.-S., Ahn W.G., Park O.K., Kwon S.-H., Morita K., Shim I., Her S. 10.1155/2013/217853. Evidence-Based Complementary and Alternative Medicine. 2013;2013(1):217853.
18. Nisari M., Emre M., Dolu N., Acer H., Pektaş F. Investigation of dose related effects of propolis on anxiety and some biochemical parameters with sympathetic skin response and increased T-maze. Journal of Surgery and Medicine. 2020;4(5):346–50.
19. Wang P., Guo P., Wang Y., Teng X., Zhang H., Sun L., Xue M., Liang H. Propolis ameliorates alcohol-induced depressive symptoms in C57BL/6J mice by regulating intestinal mucosal barrier function and inflammatory reaction. Nutrients. 2022;14(6):1213.
20. Wang W., Zheng L., Xu L., Tu J., Gu X. Pinocembrin mitigates depressive-like behaviors induced by chronic unpredictable mild stress through ameliorating neuroinflammation and apoptosis. Molecular Medicine. 2020;26:1–11.
21. Abbasi E., Bagherniya M., Soleimani D., Ghasemi-Tehrani H., Abbaspour M., Clark C.C., Askari G. The effects of propolis supplementation on high-sensitivity C-reactive protein, testosterone hormone, and metabolic profile in women with polycystic ovary syndrome: A randomized, triple-blinded, placebo-controlled clinical trial. Phytotherapy Research. 2023;37(11):5366–77.
22. Sajjadi S.S., Bagherniya M., Soleimani D., Siavash M., Askari G. Effect of propolis on mood, quality of life, and metabolic profiles in subjects with metabolic syndrome: a randomized clinical trial. Scientific Reports. 2023;13(1):4452.
23. Fouad S., El Gendy A., Monir R., Abdel-Wahhab K.G., Shafei H.F., Hegazi A.G. Bee Products for Relieving Menopausal Symptoms. Open Access Macedonian Journal of Medical Sciences. 2022;10(B):632–38.
24. Varzaghani V., Sharifi M., Hajiaghaee R., Bagheri S., Momtaz S., Tarassoli Z., Razmi A. Propolis add-on therapy alleviates depressive symptoms; A randomized placebo-controlled clinical trial. Phytotherapy Research. 2022;36(3):1258–67.