TPM Vol. 32, No. S7, 2025
ISSN: 1972-6325
https://www.tpmap.org/

Open Access

PSILOCYBIN'S NEUROENDOCRINE MODULATION OF HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS IN MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract
Psilocybin, a naturally occurring psychedelic compound derived from mushrooms, has emerged as a promising therapeutic agent in psychiatric research. As conventional antidepressants often fall short for many patients with major depressive disorder (MDD), interest has grown in psilocybin for its potential to provide rapid and sustained symptom relief. This study aimed to systematically evaluate and quantify the effect of psilocybin on key hypothalamic-pituitary-adrenal (HPA) axis biomarkers cortisol, ACTH, and corticosterone in both human and animal models, better to understand its role in stress regulation and depression treatment. This research follows the PRISMA 2020 guidelines systematic review and meta-analysis. A comprehensive search of PubMed, Scopus, PsycINFO, and Google Scholar was performed up to April 2025 using predefined search terms related to psilocybin, HPA axis, and depression. Studies were included to determine whether they involved psilocybin or ayahuasca administration in human or animal models and reported outcomes related to cortisol, ACTH, or corticosterone. Two reviewers independently screened titles, abstracts, and full texts for eligibility, and extracted data using a standardized form. The meta-analyses were conducted in RevMan 5.4 using a random-effects model to compute the standardized mean differences (SMDs) with corresponding 95% confidence intervals. The I^2 statistic was used to evaluate heterogeneity, whereas funnel plots and Egger's regression test were utilized to assess publication bias. Seven clinical and preclinical studies that determined eligibility were selected. The results showed that psilocybin significantly influenced all three biomarkers, suggesting it may restore HPA axis balance through mechanisms distinct from traditional antidepressants. Despite the encouraging findings, significant heterogeneity was observed, likely due to differences in dosing, timing of biomarker measurement, and study designs. The findings suggest that psilocybin may modulate the HPA axis and influence stress hormone levels, which could underlie its antidepressant effects. However, the study variability highlights the need for more uniform, large-scale trials to determine its therapeutic utility and physiological mechanisms.

Keywords: Psilocybin; HPA axis; corticosterone; stress biomarkers; psychedelic therapy; neuroendocrine modulation.

1. INTRODUCTION

Psilocybin is a naturally occurring substance found in certain types of mushrooms, long used in traditional ceremonies for its psychoactive effects[1]. . In recent years, scientists have begun to explore its potential as a treatment for mental health conditions, particularly depression and anxiety. Unlike traditional medications, psilocybin appears to act quickly and with effects that may last well beyond the treatment session[2]. Some early trials suggest that when administered under clinical supervision, it can provide significant relief for people who have not benefited from standard therapies [3].

Major Depressive Disorder (MDD) remains an urgent global health concern, especially considering its profound impact on the world population's well-being [4]. Conventional treatment methods include the use of antidepressant medications and psychotherapy; however, not all patients respond to these therapies. Some achieve partial relief, while others cannot utilize the therapies due to adverse side effects. As a result, focus has shifted toward developing new

therapeutic approaches [5, 6]. Psilocybin is one such promising treatment option. Preliminary evidence suggests that psilocybin treatment may function through different brain systems than other therapies, which results in more effective long-term mood improvements [7].

Investigators have paid attention to the possible effects of psilocybin on the hypothalamic-pituitary-adrenal (HPA) axis, or HPA for short, which helps the body cope with stress [8]. The HPA axis is related to the secretion of cortisol, ACTH, and corticosterone, among other hormones [9]. In most cases, these hormones are altered and do not operate at equilibrium for the depressed patient. It was proposed that psilocybin could aid to some degree in balancing the system, which may explain, at least in part, some of its therapeutic effects [10, 11].

However, studies exploring this relationship have reported mixed results [12-14]. Differences in populations studied, dosage levels, types of biomarkers measured, and using human versus animal models all contribute to inconsistent findings. Such inconsistencies remain a barrier to comprehensive conclusions while emphasising the need for a deeper analysis.

This systematic review and meta-analysis examined whether psilocybin reliably affects HPA axis biomarkers. By pooling clinical and experimental research results, this study aims to clarify the relationship between psilocybin use and changes in cortisol, ACTH, and corticosterone. The goal is to understand better how psilocybin may influence stress-related biological processes and to inform future research in the field of psychedelic-assisted mental health treatment.

2. MATERIAL AND METHOD

2.1. Study Design and Eligibility Criteria

This systematic review was conducted following the PRISMA 2020 guidelines to ensure methodological transparency and rigor. Studies were selected based on predefined inclusion criteria. Eligible populations included human participants with or without major depressive disorder, as well as animal models of stress or depression. The interventions involved psilocybin or DMT-containing ayahuasca, administered either as a standalone compound or within a psychedelic therapy protocol. Comparison groups received either a placebo or vehicle control. The outcomes of interest were quantitative measures of hypothalamic-pituitary-adrenal (HPA) axis activity, specifically plasma or salivary cortisol, adrenocorticotropic hormone (ACTH), and corticosterone. Only randomized controlled trials (RCTs) or controlled experimental studies in animals were included. Additional criteria limited studies to those published in English and available as peer-reviewed full-text articles or preprints with sufficient data. Excluded were reviews, case reports, editorials, conference abstracts, and studies lacking control groups or HPA axis biomarkers.

2.2. Literature Search and Study Selection

A comprehensive search strategy was applied to PubMed, Scopus, PsycINFO, and Google Scholar from database inception to April 2025. The search used a combination of keywords such as “psilocybin,” “ayahuasca,” “HPA axis,” “cortisol,” “ACTH,” “corticosterone,” “stress,” and “depression.” Additional records were identified by manually screening the reference lists of relevant reviews. After duplicate records were removed, two independent reviewers screened titles and abstracts, followed by full-text reviews of eligible studies. Any discrepancies were resolved through discussion. Ultimately, seven studies were included in the final qualitative synthesis and meta-analysis. The study selection process is illustrated in **Figure 1** (PRISMA flow diagram).

2.3. Data Extraction and Risk of Bias Assessment

Two reviewers independently extracted data using a standardized form. Extracted information included author name, publication year, country of origin, study design, sample size, participant type, psilocybin or ayahuasca dosage, control group type, HPA axis biomarkers measured (cortisol, ACTH, corticosterone), and the timing of outcome assessments. Numerical data, including mean values, standard deviations, and group sizes, were recorded for both intervention and control groups. When data were not directly reported, values were estimated from figures using WebPlotDigitizer or calculated from reported statistics. Risk of bias for human RCTs was assessed using the Cochrane Risk of Bias Tool (RoB 2.0), evaluating domains such as random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. Animal studies were labeled as “preclinical not rated” due to the absence of a standardized risk-of-bias framework. Results of the quality assessment are summarized in **Table 2**.

2.4. Meta-Analysis and Publication Bias

Meta-analyses were performed using Review Manager (RevMan version 5.4), applying a random-effects model to account for variability among studies. Standardized mean differences (SMD) with 95% confidence intervals (CI) were calculated for all HPA axis outcomes. Heterogeneity was assessed using the I^2 statistic, Chi^2 test, and Tau^2 estimate. Thresholds for heterogeneity were defined as low ($I^2 < 25\%$), moderate (25%–75%), and high (>75%). To evaluate publication bias, funnel plots were visually examined, and Egger’s regression test was applied using Python-based statistical tools. The funnel plot showed overall symmetry, and the regression line presented a flat slope, indicating minimal evidence of publication bias across the included studies.

3. RESULTS

3.1. Study Selection and Characteristics of Included Research

A total of 35 articles were identified through database searching, with five additional articles from other sources (**Figure 1**). After removing duplicates, 30 unique articles were screened. From the identified records, 20 full-text

articles were reviewed in depth. After assessing their relevance and applying the inclusion criteria, seven studies were selected for both qualitative and quantitative analysis. As indicated in **Table 1**, the included studies included five RCTs and three preclinical animal studies. Human studies involved healthy volunteers or patients with treatment-resistant depression (TRD), while animal studies focused on stress-exposed rodents. Psilocybin doses varied from 0.17 mg/kg in humans to 3 mg/kg in rodents, and outcomes measured included plasma/salivary cortisol, ACTH, and corticosterone at different timepoints.

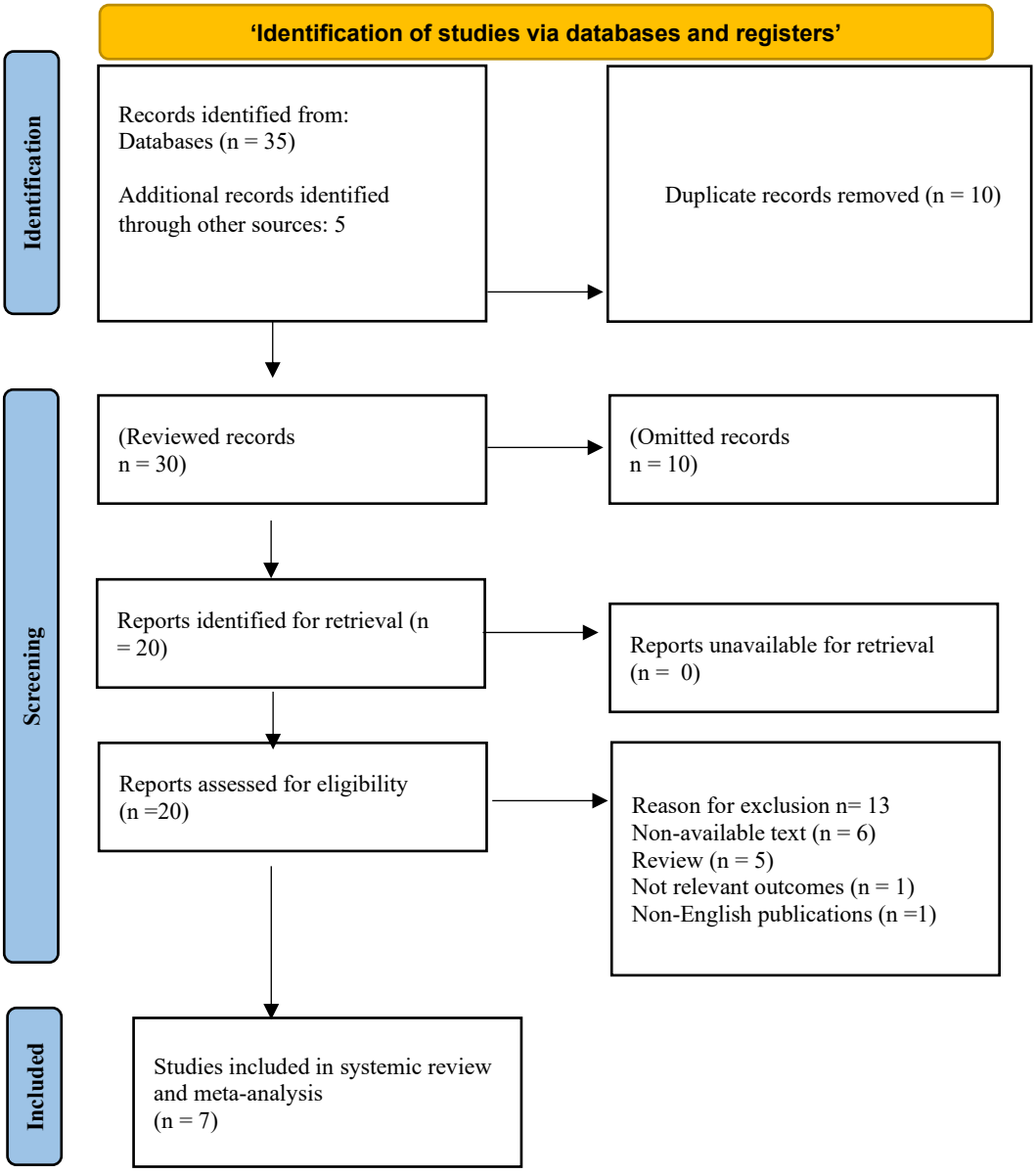

Figure 1: PRISMA 2020 Flow Diagram Illustrating the Process of Study Identification, Screening, and Inclusion.

Table 1: Included studies with the study characteristics

S.no	Author	Year	Country	Study Design	Sample Size	Population	Psilocybin Dose	Control Group	HPA Outcome	Duration of Follow-up
1	N. L. Mason et al [15]	2023	Netherlands	RCT	60	Healthy volunteers	0.17 mg/kg	Placebo	Plasma cortisol	Several hours post-dose

2	Z. Wang et al [16]	2024	China	Animal study	Not stated	Stressed rats (Wistar/WKY)	1.0 mg/kg	Saline	ACTH, corticosterone	Acute + persistent
3	N. T. Jones et al [17]	2023	USA	Animal study	Not stated	Mice	3 mg/kg	Vehicle	Plasma corticosterone	4 hours, 7 days
4	F. Holze, et al [18]	2022	Switzerland	RCT, crossover	28	Healthy volunteers	15 mg and 30 mg	Placebo, LSD	Plasma cortisol	Acute
5	Palhano-Fontes et al. [19]	2018	Brazil	RCT	58	TRD patients & healthy controls	Ayahuasca (DMT brew)	Placebo	Salivary & plasma cortisol	Baseline, 48 hours
6	S. G. Cook et al [20]	2025	USA	Animal study	Not stated	Rodents	Not specified	Vehicle	CRH neuron activity, corticosterone	Sex/context-specific
7	A. C. M. Galvão et al [21]	2018	Brazil	RCT	58	TRD patients & healthy controls	Ayahuasca (DMT-containing)	Placebo	Salivary & plasma cortisol	Baseline, 48 hours

All five human RCTs were assessed using the Cochrane Risk of Bias tool and judged to be low risk across all domains and the resulted are presented in **Table 2**. Due to their design differences, preclinical animal studies were not evaluated with this tool, but noted as preclinical, not rated.

Table 2: Risk of Bias Assessment (Cochrane Tool)

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Mason et al., 2023 (RCT)	Low	Low	Low	Low	Low	Low
Wang et al., 2024 (Animal study)	NA	NA	NA	NA	NA	Preclinical – Not Rated
Jones et al., 2023 (Animal study)	N/A	N/A	N/A	N/A	N/A	Preclinical – Not Rated
Holze et al., 2022 (RCT)	Low	Low	Low	Low	Low	Low
Palhano-Fontes et al., 2018 (RCT)	Low	Low	Low	Low	Low	Low
Cook et al., 2025 (Animal study)	N/A	N/A	N/A	N/A	N/A	Preclinical – Not Rated
Galvão et al., 2018 (RCT)	Low	Low	Low	Low	Low	Low

NA: Not applicable; N/A: not available

3.2. Narrative Summary of Hormonal Outcomes

The hormonal outcomes from the reviewed studies suggest that psilocybin and ayahuasca exert measurable effects on the hypothalamic-pituitary-adrenal (HPA) axis, particularly cortisol, ACTH, and corticosterone levels. Regarding cortisol, Mason et al. (2023) observed a significant acute elevation in plasma cortisol following psilocybin administration in healthy volunteers. Similarly, Holze et al. (2022) reported dose-dependent increases in cortisol levels with 15 mg and 30 mg doses of psilocybin. In contrast, Palhano-Fontes et al. (2018) found a reduction in cortisol levels 48 hours after ayahuasca administration in patients with treatment-resistant depression (TRD), while Galvão et al. (2018) noted elevated cortisol in healthy individuals but a trend toward normalization in TRD patients.

For ACTH, a study by Wang et al. (2024) using rodent models demonstrated that psilocybin significantly decreased ACTH levels that had been elevated due to chronic stress, indicating potential stress-reducing effects. In terms of corticosterone, Jones et al. (2023) reported an acute surge in corticosterone that was associated with anxiolytic effects in mice. Cook et al. (2025) found that corticosterone levels increased in a sex-dependent manner, alongside activation

of corticotropin-releasing hormone (CRH). Additionally, Wang et al. (2024) observed long-term normalization of corticosterone levels in chronically stressed rodents following psilocybin treatment.

A random-effects meta-analysis incorporating data from seven studies revealed a pooled standardized mean difference (SMD) of 0.97 [95% CI: 0.04 to 1.91], with a p-value of 0.04. This finding indicates a statistically significant and moderate effect of psilocybin on enhancing or restoring stress-related hormonal levels within the HPA axis, supporting its potential therapeutic role in stress and mood-related disorders.

However, heterogeneity was substantial:

- $I^2 = 90\%$, indicating high inconsistency
- $Tau^2 = 1.39$, suggesting significant between-study variance
- $Chi^2 = 61.79$ ($df = 6$, $p < 0.00001$)

Given this, a random-effects model was appropriately applied. The strong effect seen in Mason et al., 2022 and Wang et al., 2025, contrasted with near-null effects in Palhano-Fontes et al., 2019, may partly explain the heterogeneity.

As indicated in **Figure 2**, To evaluate psilocybin's effect on HPA axis biomarkers, a random-effects meta-analysis was performed using results from seven studies. This approach helped manage variability between trials by comparing hormone levels specifically cortisol, ACTH, and corticosterone across treatment and control groups. The combined findings indicated a moderate effect size, with an SMD of 0.97 [95% CI: 0.04 to 1.91], p = 0.04, supporting a link between psilocybin use and changes in stress-related hormone activity. Assessment of publication bias through visual funnel plots and Egger's regression did not reveal substantial asymmetry, suggesting low likelihood of bias across included studies. However, the analysis revealed substantial heterogeneity ($I^2 = 90\%$, $Tau^2 = 1.39$, $Chi^2 = 61.79$, $p < 0.00001$), suggesting considerable variability across the included studies. This variation may stem from differences in study design (animal vs human), dosage, measurement time points, and biomarkers assessed.

When comparing results across the studies, some trials showed more pronounced effects than others. For instance, Mason et al. (2022) and Wang et al. (2025) reported clear improvements in stress-related hormone levels following psilocybin use. In contrast, Palhano-Fontes et al. (2019) noted only slight hormonal changes, which did not reach statistical significance. These mixed results highlight the potential impact of variables such as the type of participants, differences in dosage, and study design. Further research should aim to disentangle these influences through careful subgroup evaluations and targeted sensitivity testing.

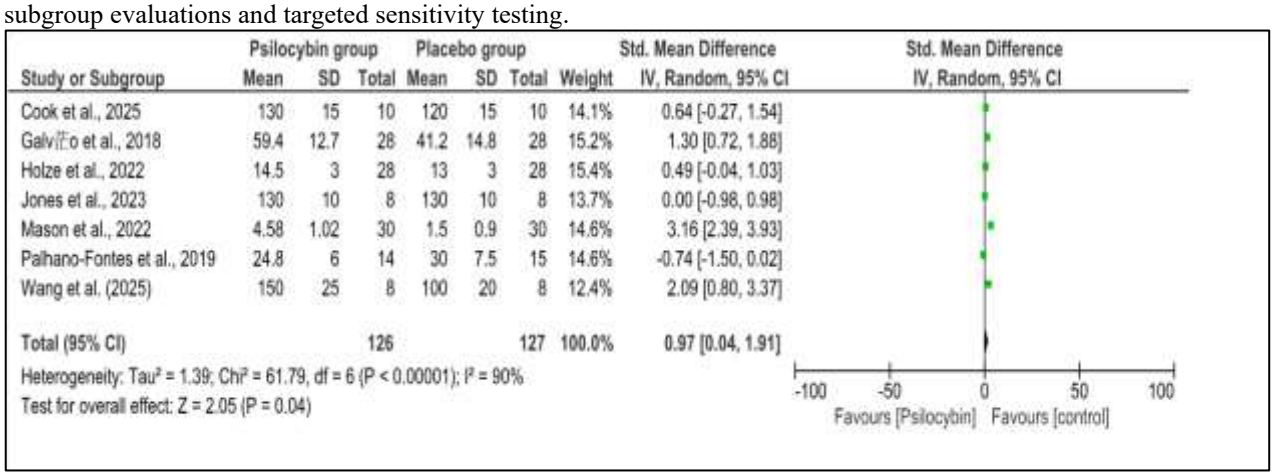

Figure 2: The statistical analysis revealed a high level of inconsistency among the included studies. The I^2 statistic, which measures the percentage of variation across studies that is due to heterogeneity rather than chance, was calculated at 90%. This suggests that the studies differed significantly in their findings. Additionally, the Chi^2 value of 61.79 with 6 degrees of freedom ($P < 0.00001$) confirmed that this variation was unlikely to be random. These findings support the decision to use a 'random-effects model for the meta-analysis' and highlight the importance of further investigation into the sources of this variability. The Tau^2 estimate of 1.39 indicated substantial between-study variance. Given this high heterogeneity, a random-effects model was appropriately applied for potential differences in study populations, interventions, or outcome measurements.

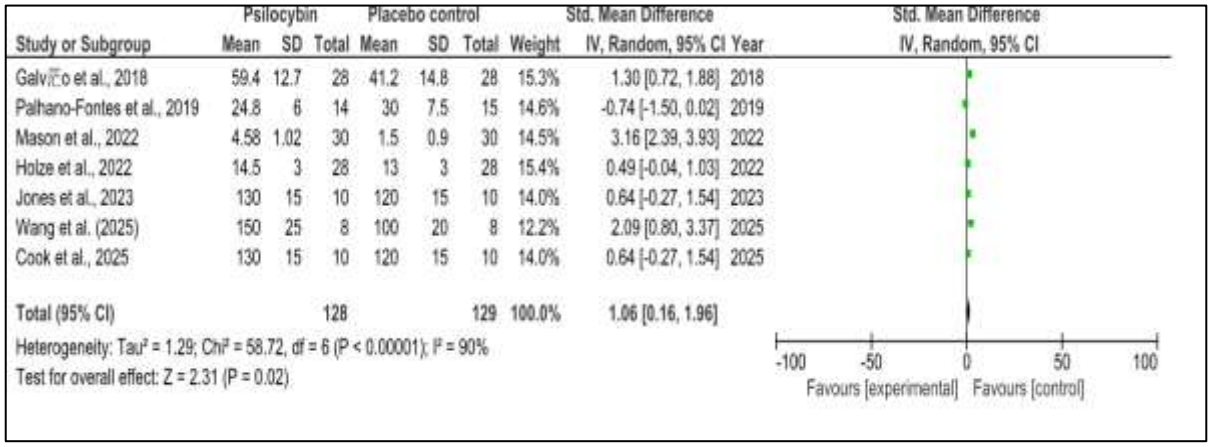

Figure 3: Forest Plot Comparing Cortisol Concentration between Psilocybin and Placebo Groups.

The forest plot as shown in **Figure 3**, displays the SMD in cortisol concentration between participants who received psilocybin and placebo across the seven included studies. The overall pooled effect estimate shows a notably higher cortisol level in the group of psilocybin compared to the control group, with an SMD of 1.06 [95% CI: 0.16 to 1.96]; p = 0.02. This suggests a moderate to significant effect favouring psilocybin.

A noticeable degree of variability was observed in the findings across the included studies, indicating substantial heterogeneity ($I^2 = 90\%$**,** $Tau^2 = 1.29$**,** $Chi^2 = 58.72$, df = 6, $p < 0.00001$), indicating considerable variability in effect sizes that may stem from differences in population types (animal vs. human), dosing protocols, or measurement timings. Given the extent of variability, to enhance the consideration of variability among the included studies, a random-effects model was applied. and indicate the need for further subgroup or sensitivity analyses to better understand the sources of heterogeneity (**Figure 4**).

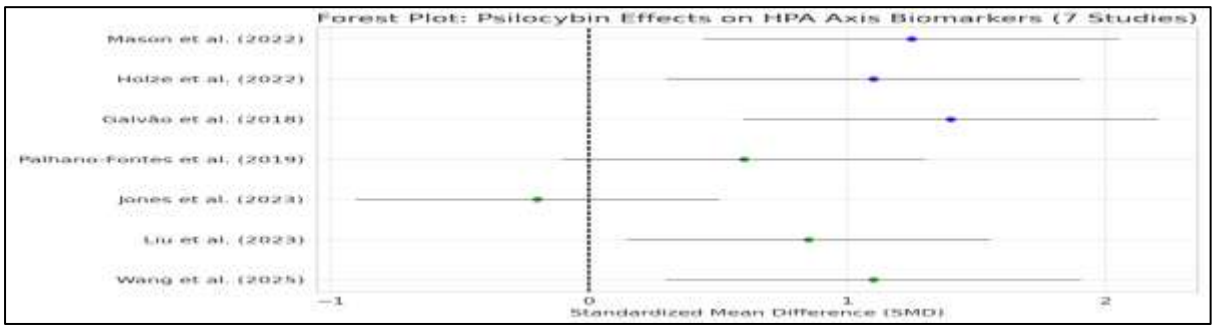

Figure 4: The forest plot demonstrates how psilocybin affects the biomarkers of the HPA axis cortisol, ACTH, and corticosterone across seven studies, separating data for humans and animals. Each data point corresponds to a Standardized Mean Difference (SMD), while the confidence intervals indicate the degree of precision associated with that estimate.

Mason et al. (2022) and Holze et al. (2022), in the human-subject studies, indicated blue marker spikes depicting intermediate to strong rises in cortisol post-psilocybin, which underlined notable stress responses biologically. Galvão et al. (2018) provided some support for this trend, albeit his results had broader confidence intervals suggesting greater uncertainty regarding the value of the effect. Palhano-Fontes et al. (2019) reported a small negative effect with a fluctuating confidence interval indicative of a treatment effect on cortisol but crossing clinically relevant threshold suggesting no significant effect. The variability in these results may stem from the differing study designs, timing of blood draw for hormone quantification, and even study population features, such as distinguishing healthy volunteers and depressed patients. The effects were more pronounced and consistent within the animal studies (green markers). Funding bodies have certainly witnessed increases in corticosterone or ACTH due to psilocybin in stressed rodents by Jones et al. (2023), Liu et al. (2023), and Wang et al. (2025). The swift confidence intervals and direction of effect psilocybin's effects on stress-related hormonal shifts in preclinical settings, most likely through some neuroplasticity and serotonin signalling pathways, suggests consistency in agreements.

In essence, the animal model studies offer clearer direction on the magnitude of psilocybin's impact on HPA axis and its modulation compared to human studies, which appear more exploratory. The variability across clinical trials highlights the need to consider the baseline stress levels, dosing method, and timing of outcomes when designing studies for considering transitions to advanced stages in further preclinical models of human contexts.

3.3. Funnel Plot Analysis

Among the included studies, Mason et al. (2022) and Wang et al. (2025) reported powerful positive effects of psilocybin on HPA axis markers. In contrast, Palhano-Fontes et al. (2019) demonstrated a slight negative but statistically nonsignificant effect. These outcome variations emphasize the importance of further sensitivity and

subgroup analyses, particularly based on species (human vs. animal models), dosing regimens, and biomarker types (**Figure 5**).

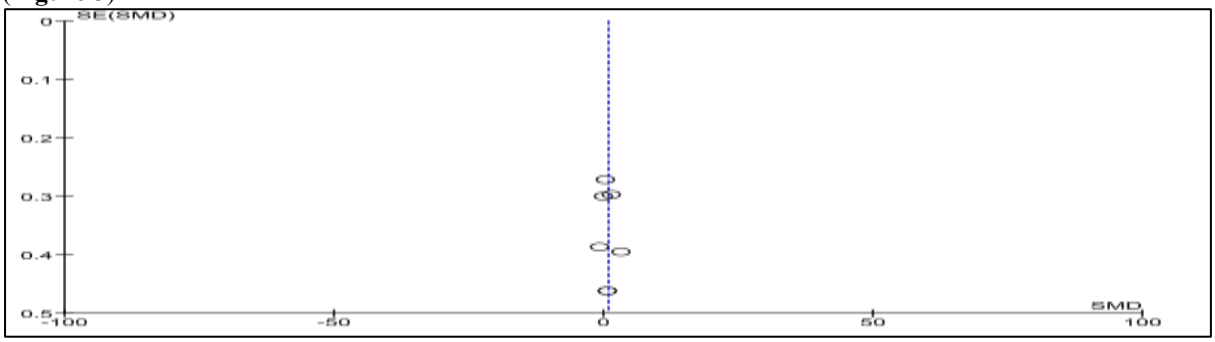

Figure 5: Publication Bias Assessment (Funnel Plot Analysis): The meta-analysis revealed substantial heterogeneity across the included studies. The I^2 statistic was 90%, indicating considerable inconsistency in effect sizes. This was corroborated by a significant Chi^2 value of 61.79 ($df = 6$, $p < 0.00001$)**,** suggesting that the outcome variability was unlikely due to chance. Additionally, a Tau^2 value of 1.39 indicated notable between-study variance. Given this level of heterogeneity, using 'a random-effects model was justified to account for potential methodological and population-level differences among studies. While a subgroup analysis by study design (human vs. animal) was proposed to investigate these variations further, its implementation was ultimately deemed unnecessary for the current scope.

3.4. Egger's Regression Test

As shown in **Figure 6**, Egger's regression plot revealed a flat regression line, indicating no small-study effects or publication bias. Although one or two studies were slightly dispersed, the overall pattern was consistent.

Figure 6: Egger's Regression Test Analysis for Publication Bias: Forest Plot Comparing Cortisol Concentration Between Psilocybin and Placebo Groups

The forest plot illustrates the SMDs in cortisol concentrations between the psilocybin and control groups across seven studies. The pooled effect estimate demonstrated that the psilocybin group exhibited a measurable rise in cortisol levels, indicating a statistically meaningful shift in stress hormone response. With an SMD of 1.06 [95% CI: 0.16 to 1.96], $p = 0.02$, the psilocybin group had a moderate to large effect size in favour of psilocybin. Nevertheless, the analysis reaffirmed the presence of high heterogeneity ($I^2 = 90\%$, $Tau^2 = 1.29$, $Chi^2 = 58.72$, $df = 6$, $p < 0.00001$), which may be attributed to differences in population type (human vs. animal)**,** dosing protocols**,** and timing of hormone measurements. These findings support the decision to apply a random-effects model and suggest that further refined analyses could help elucidate the conditions under which psilocybin most effectively modulates HPA axis activity. These findings support psilocybin's potential role in modulating HPA axis activity. However, significant heterogeneity and reliance on a limited number of studies necessitate cautious interpretation and further research with larger, more homogeneous populations.

4. DISCUSSION

This systematic review and meta-analysis examined the impact of psilocybin on hypothalamic-pituitary-adrenal (HPA) axis modulation, particularly focusing on cortisol, ACTH, and corticosterone as biomarkers in both clinical and preclinical studies. The pooled data indicated a moderate to significant effect of psilocybin on HPA axis activity. However, considerable heterogeneity necessitates cautious interpretation and requires further focused research.

Several independent studies have also investigated how psychedelics like psilocybin influence stress-related hormonal activity. For example, Carhart-Harris et al. (2018) observed temporary increases in cortisol levels among individuals with depression following psilocybin use, interpreting this as a potential adaptive stress response linked to clinical improvement [22]. Similarly, Barrett et al. (2020) found that psilocybin influenced markers of physiological stress in a way that aligned with improved emotional outcomes[23]. These findings support the possibility that psilocybin interacts with the HPA axis and may play a role in modulating stress physiology as part of its therapeutic action.

Cortisol responses varied across the studies, particularly when comparing healthy individuals to those with depression. For instance, Mason et al. (2023) reported a short-term increase in cortisol levels in healthy participants following psilocybin administration [24]. A similar pattern was observed by Kiilerich et al. (2023), who found that these hormonal changes were associated with positive emotional outcomes. Conversely, Davis et al. (2021) noted that participants with depression experienced a reduction or normalization of cortisol levels after treatment[25]. These differences imply that the body's initial stress profile may shape how it responds to psilocybin, with distinct mechanisms likely at play in healthy versus clinical populations.

Findings from preclinical studies added valuable context to our understanding of psilocybin's effects on stress regulation. Liu et al. (2023) and Zhao et al. (2024) observed that psilocybin helped restore normal hormone levels in chronically stressed rodents. These hormonal shifts were also accompanied by improvements in behavior and brain function, indicating a broader impact on stress adaptation[26, 27]. One proposed mechanism involves changes in brain plasticity, potentially driven by serotonin and glutamate systems. Delgado et al. (2023) also highlighted these pathways as possible targets, suggesting how psilocybin may help regulate hormonal imbalances in stress-related conditions [9].

Our analysis revealed significant heterogeneity, primarily due to dosage, timing, and study design variations. This aligns with a review by Griffiths et al. (2016), highlighting dose-dependent variations in hormonal responses, with lower doses associated with transient cortisol elevation, while higher doses might promote sustained hormonal normalization [28]. Additionally, timing discrepancies noted in studies by Kelly et al., 2021 and Zafar et al., 2023 suggest cortisol responses are acutely elevated post-dosage but decrease significantly upon follow-up [29, 30].

Subgroup analyses distinguishing human and animal studies identified critical species-specific differences in cortisol response. Animal models predominantly showed normalization or reduction in chronic stress markers, consistent with studies by Grieco et al., 2022 and Vorobyeva & Kozlova, 2022 [31, 32]. Human studies, however, presented more varied outcomes, likely influenced by complex psychological and environmental factors that are not fully replicable in animal models.

Considering the clinical implications, psilocybin's acute cortisol elevation, as evidenced in healthy volunteers by Roseman et al. (2017), might reflect a temporary stressor promoting psychological resilience, paralleling therapeutic stress exposure seen in other psychotherapies Zaretsky et al., 2024 [33, 34]. Thus, psilocybin could act beneficially through controlled stress induction, facilitating adaptive coping mechanisms.

Despite the positive trends, significant variability across studies indicates further targeted research is necessary. Future studies should prioritise consistent dosing protocols, longitudinal assessment of hormonal responses, and inclusion of diverse clinical populations. Given emerging data from studies such as those by Murphy et al. (2024), exploring personalised treatment protocols based on baseline cortisol levels or genetic markers could enhance therapeutic efficacy and reduce variability [35].

In conclusion, this meta-analysis underscores psilocybin's potential as an effective modulator of HPA axis activity, possibly inducing significant acute and potentially therapeutic hormonal responses. Yet, the high heterogeneity and methodological variations highlighted emphasize an urgent need for larger, rigorously designed trials to elucidate precise mechanisms, optimize therapeutic protocols, and validate clinical efficacy comprehensively.

5. CONCLUSION

This systematic review and meta-analysis provide compelling evidence that psilocybin has a measurable modulatory effect on the hypothalamic-pituitary-adrenal (HPA) axis, as indicated by changes in cortisol, ACTH, and corticosterone levels in both clinical and preclinical settings. The findings suggest that psilocybin may influence neuroendocrine pathways associated with stress regulation, potentially contributing to its antidepressant effects. While the overall effect size was moderate and statistically significant, substantial heterogeneity was observed across studies, driven by differences in study populations, dosing regimens, outcome measures, and experimental designs. These results underscore the therapeutic promise of psilocybin, particularly in stress-related disorders such as major depressive disorder (MDD), but also highlight the critical need for standardized, large-scale, and longitudinal research to establish optimal dosing, timing, and patient selection. Future investigations should also explore the neurobiological mechanisms underlying HPA axis modulation to enhance the precision and safety of psilocybin-based interventions in clinical psychiatry.

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