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Salivary hormones in depression: the future in diagnosis and treatment

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Abstract

Depression is associated with a significant burden on individuals, families, and communities. It leads to impaired social and occupational functioning, increased disability, decreased quality of life, and higher mortality rates, often due to suicide. A recent estimate from the World Health Organization (WHO) states that over 280 million people of all ages suffer from depression, which equals approximately 3.8% of the world population. Despite effective treatments for mental disorders, a dire treatment gap persists. This treatment gap could be reduced by effective and available diagnostic methods that have the potential to aid in depression diagnosis, stratification of patient subgroups, and treatment monitoring. In this regard, salivary hormones have been studied as potential markers for different types and etiologies of depression due to the convenience of non-invasive sample collection and their correlation with certain aspects of mood and mental health. The literature suggests they can help clinicians assess an individual's stress response, hormonal imbalances, and treatment response, leading to more personalized and effective interventions. In this review, we offer an up-to-date look at all studied salivary hormones associated with depression, including Cortisol, Melatonin, Oxytocin, Serotonin, Dehydroepiandrosterone, Testosterone, Progesterone, and Estradiol.

Keywords Depression, Salivary, Biomarkers, Cortisol, Melatonin, Oxytocin

Introduction

Depression is a common mental health disorder affecting people of all ages and backgrounds worldwide [1]. It ranges from mild, short episodes of sadness to severe or persistent depression, where Major Depressive Disorder (MDD) represents the clinical, more severe form. Depression is a significant burden on individuals, families, and communities. It leads to impaired social and occupational functioning, increased disability, decreased quality of life, and higher mortality. Comorbidities such as anxiety disorders and substance use disorders are common. These comorbidities can complicate diagnosis and treatment.

The epidemiology indicates that depression was a widespread and significant global health concern even before the COVID-19 pandemic [2, 3]. A recent estimate from the World Health Organization (WHO) says that over 280 million people of all ages suffer from depression. This equals approximately 3.8% of the world's population grappling with depression, with prevalence rates differing among age groups and genders. The prevalence of depression also varies across different regions and countries. Socioeconomic factors, cultural norms, and access to mental health care contribute to these variations.

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Depression can occur at any age, but its onset often peaks during adolescence and young adulthood. However, it can affect individuals across the lifespan, including children, adults, and older adults. Among adults, 5% experience depression, comprising 4% of men and 6% of women. In individuals aged 60 and older, the prevalence rises to 5.7% [3]. Notably, depression is about 50% more prevalent among women than men globally. This gender difference is thought to be influenced by biological, hormonal, and psychosocial factors. Furthermore, over 10% of pregnant women and new mothers worldwide contend with depression [4]. Tragically, the global toll of suicide stands at over 700,000 lives lost annually, making it the fourth leading cause of death among 15–29-year-olds. Due to not only these facts, depression is considered a leading cause of disability worldwide, with considerable economic implications due to healthcare costs, lost productivity, and increased healthcare utilization [5].

Despite effective treatments for mental disorders, a dire treatment gap persists, with more than 75% of individuals in low- and middle-income countries lacking access to necessary care [6]. This treatment gap is fueled by numerous barriers, including inadequate investment in healthcare systems, especially mental health services, a shortage of trained healthcare providers, non-existing quantifiable diagnostic methods, and the enduring social stigma associated with mental disorders. This gap could be partially filled by effective and available diagnostic strategies to support depression management. Possible biomarkers for depression include neuroimaging, the microbiome, neuropeptides, hormones, or markers of oxidative stress [7].

This review article addresses the lack of quantifiable diagnostic methods for various types of depression, focusing on salivary hormones as biomarkers obtainable by non-invasive liquid biopsy methods (Fig. 1). To effectively convey the vast, up-to-date knowledge about salivary hormone biomarkers that could have the potential to aid in depression diagnosis, stratification of patient subgroups, and treatment monitoring, we searched PubMed, SCOPUS, and Web of Science. Mostly articles published within the last 15 years were considered.

Functions and variations of salivary hormones in depression

Salivary hormones have been studied as potential markers for depression due to the convenience of non-invasive sample collection and their correlation with certain

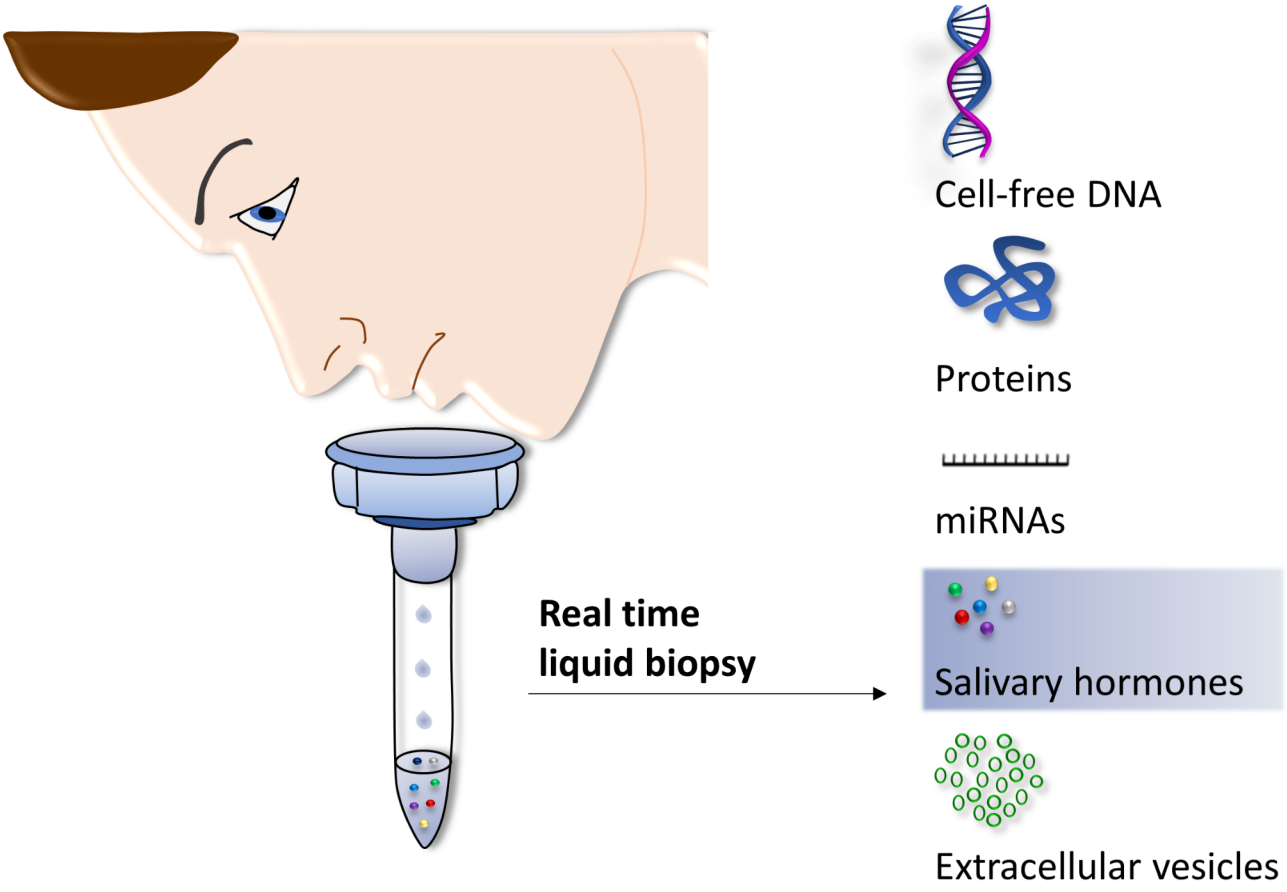

Fig. 1 Liquid biopsy sample collection and possibilities of examination

aspects of mental disorders. By exploring their functions and associations with depression, we gain valuable insights into the physiological factors contributing to this challenging condition. Table 1 addresses the possible functions of salivary hormones in depression.

Cortisol

Cortisol is a steroid hormone produced in the zona fasciculata of the adrenal cortex and is classified as a glucocorticoid due to its regulatory effects on glucose metabolism. Reported often higher in males, it profoundly affects intermediary metabolism, immune functions, and inflammation [16]. Cortisol is widely recognized as the primary stress hormone, acting through the hypothalamic-pituitary-adrenal (HPA) axis to help the body respond to stress by mobilizing energy reserves, modulating blood pressure, and dampening immune responses [17]. Its release follows a diurnal rhythm, with peak levels in the early morning, supporting alertness and energy balance throughout the day [8].

The research on the level of salivary cortisol and its relation to depression dates back to the 1980s when several research teams tried to establish the clinical utility of the dexamethasone suppression test regarding its potential to lower salivary cortisol and thus alleviate depressive symptoms. The results were ambiguous [18, 19]. Focusing on juvenile depression, Foreman and Goodyer compared salivary hypercortisolism in 30 depressed inpatients between 7 and 16 years of age. There was a positive correlation between salivary cortisol and depression [20].

Hypothesis Chronic stress activates the HPA axis, leading to hypercortisolemia or a blunted cortisol diurnal rhythm. Prolonged cortisol elevation results in neurotoxic effects, particularly in the hippocampus, and impairs feedback regulation of the HPA axis. This contributes to emotional dysregulation, cognitive deficits, and an increased vulnerability to depressive symptoms.
Several pathophysiological hypotheses explain how this dysregulation can contribute to the onset and progression of depressive and stress-related symptoms [21]. Hyperactivity of the HPA axis is commonly observed in MDD, with reduced hippocampal volume linked to high cortisol levels [22].

Melatonin

Melatonin is a hormone secreted in humans, mainly in the pineal gland and various extrapineal sites like the skin and gut. Apart from vertebrates, it is also found in invertebrates, plants, bacteria, and fungi. Although the pivotal function of melatonin is the regulation of circadian rhythms, especially the sleep/wake cycle, it has pleiotropic action, including immunostimulation and cytoprotection [23].

Hypothesis Depression is associated with disruptions in the circadian system, including impaired melatonin synthesis and secretion. Reduced melatonin levels desynchronize circadian rhythms, exacerbating sleep disturbances and impairing mood regulation.
Disrupted melatonin synthesis (often due to low exposure to natural light or irregular sleep patterns) contributes to a misalignment of circadian rhythms, resulting in mood instability, cognitive impairment, and increased stress sensitivity [9]. Studies highlight reduced nocturnal melatonin levels in depressed patients, suggesting that circadian misalignment contributes to mood instability [24].

Oxytocin

Oxytocin is a peptide hormone with nine amino acid residues linked with disulfide bonds. It is secreted in pulses from the hypothalamic supraoptic and paraventricular nuclei, stored and released from the posterior pituitary, and degraded by oxytocinase [25]. It is mainly released into the bloodstream, with some secreted to other brain regions such as the hippocampus, amygdala, striatum, prefrontal cortex, anterior cingulate cortex, or nucleus accumbens [10, 26].

Table 1 Salivary hormones with their possible functions in depression

Hormone	Possible Functions in Depression	Ref.
Cortisol	Contributes to depressive symptoms when chronically elevated due to chronic stress.	[8]
Melatonin	Regulation of sleep-wake cycles - disturbances may lead to sleep problems, which are commonly linked to depression.	[9]
Oxytocin	May influence social bonding and emotional well-being, potentially affecting depressive symptoms.	[10]
Serotonin	Plays a key role in mood regulation - low serotonin levels are associated with depressive disorders.	[11]
DHEA	A precursor hormone - imbalance can contribute to mood disturbances and depressive symptoms.	[12]
Testosterone	Imbalance can influence mood regulation and potentially contribute to symptoms of depression.	[13]
Progesterone	Plays a role in the menstrual cycle and pregnancy– fluctuations can affect mood and may be linked to premenstrual and postpartum depression.	[14]
Estradiol	Primarily associated with the female reproductive system - hormonal changes can influence mood and may be relevant in depression among women.	[15]

Hypothesis Deficient oxytocin secretion or receptor insensitivity affects emotional processing, social bonding, and stress reactivity. Oxytocin's influence on the amygdala and hippocampus may alter emotional memory and increase vulnerability to depressive symptoms.

Reduced oxytocin levels have been linked to social withdrawal and heightened stress sensitivity in individuals with depression [27, 28].

Serotonin

Serotonin (5-HT) is a monoamine neurotransmitter synthesized from the amino acid tryptophan. It is primarily produced in the raphe nuclei of the brainstem and released in a tonic or pulsatile manner depending on physiological and environmental stimuli. Once synthesized, serotonin is distributed through neuronal pathways, especially to regions including the hippocampus, amygdala, basal ganglia, prefrontal cortex, and hypothalamus, where it plays a key role in regulating mood, cognition, and various physiological functions [11]. Serotonin is also present in the gastrointestinal tract, contributing to gut motility, and is degraded by the enzyme monoamine oxidase (MAO) after cellular uptake [29].

Hypothesis Impaired serotonin synthesis, release, or receptor signaling contributes to mood dysregulation, particularly in brain regions like the prefrontal cortex, hippocampus, and amygdala. This leads to reduced serotonergic activity, manifesting as low mood, anxiety, and anhedonia.
Reduced serotonin availability and receptor sensitivity are central to the monoamine hypothesis of depression; however, the latest research questions these theories [30]. The monoamine theory thereof needs to be revisited; until then, antidepressants still remain an effective way of treatment [31, 32].

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a steroid hormone synthesized in the zona reticularis of the adrenal cortex and, to a lesser extent, in the gonads. Over the last decade, it has been heavily marketed as a dietary supplement due to its alleged influence on physical and psychological well-being, including enhanced muscle strength, improved bone density, fat loss, and potential anti-aging effects. DHEA is a precursor to androgens and estrogens, allowing it to influence various physiological processes. However, the scientific evidence supporting these health claims remains inconclusive [33]. DHEA has anti-glucocorticoid properties, counteracting some effects of cortisol.

Hypothesis Low DHEA levels fail to counterbalance the neurotoxic effects of cortisol, promoting neuroinflammation, impaired neuroplasticity, and hippocampal damage. DHEA deficiency may also reduce resilience to stress and emotional regulation.

In a 2022 article, Nenezic et al. reviewed that DHEA is considered a neurosteroid with a profound effect on the CNS regarding its neuroprotective, cognition-supporting, anxiolytic, and antidepressant action [12].

Testosterone

Testosterone is an essential circulating androgen whose secretion is controlled by gonadotropin-releasing hormone (GnRH). The gonads and adrenal cortex are the primary sites of testosterone synthesis. Testosterone is produced in males and females; however, its concentration is ten times higher in males. On the other hand, females are much more sensitive to its concentration changes [13]. Additionally, a small amount of testosterone is synthesized de novo from cholesterol or neurosteroids, such as DHEA.

Hypothesis Low testosterone levels impair serotonin and dopamine pathways, which are critical for motivation, reward, and mood regulation. Testosterone deficiency may also exacerbate stress responses and reduce emotional resilience.
Testosterone influences the serotonin and dopamine systems, which are crucial for mood regulation and motivation. Fluctuations in testosterone levels may impair these neurotransmitter pathways. Among men, both high and low levels have been associated with depression [34].

Progesterone

Progesterone is a steroid sex hormone produced in the female gonads, primarily in the yellow body or corpus luteum, following ovulation. Its principal role is maintaining pregnancy before the placenta takes over; hence the name originates from the Latin pro gestationem, meaning "in favor of pregnancy" [35]. In addition to preparing the endometrium for potential implantation, progesterone also modulates immune tolerance, reducing the likelihood of maternal immune rejection of the developing embryo.

Hypothesis Reduced progesterone levels impair GABAergic signaling, leading to heightened anxiety and mood instability. Additionally, progesterone influences gut microbiota composition, which may mediate its effects on mood and emotional resilience.
In 1997, Bixo et al. studied the brain samples of 17 deceased women and discovered that progesterone most significantly accumulates in the amygdala, so its effect on mood is unsurprising [36].

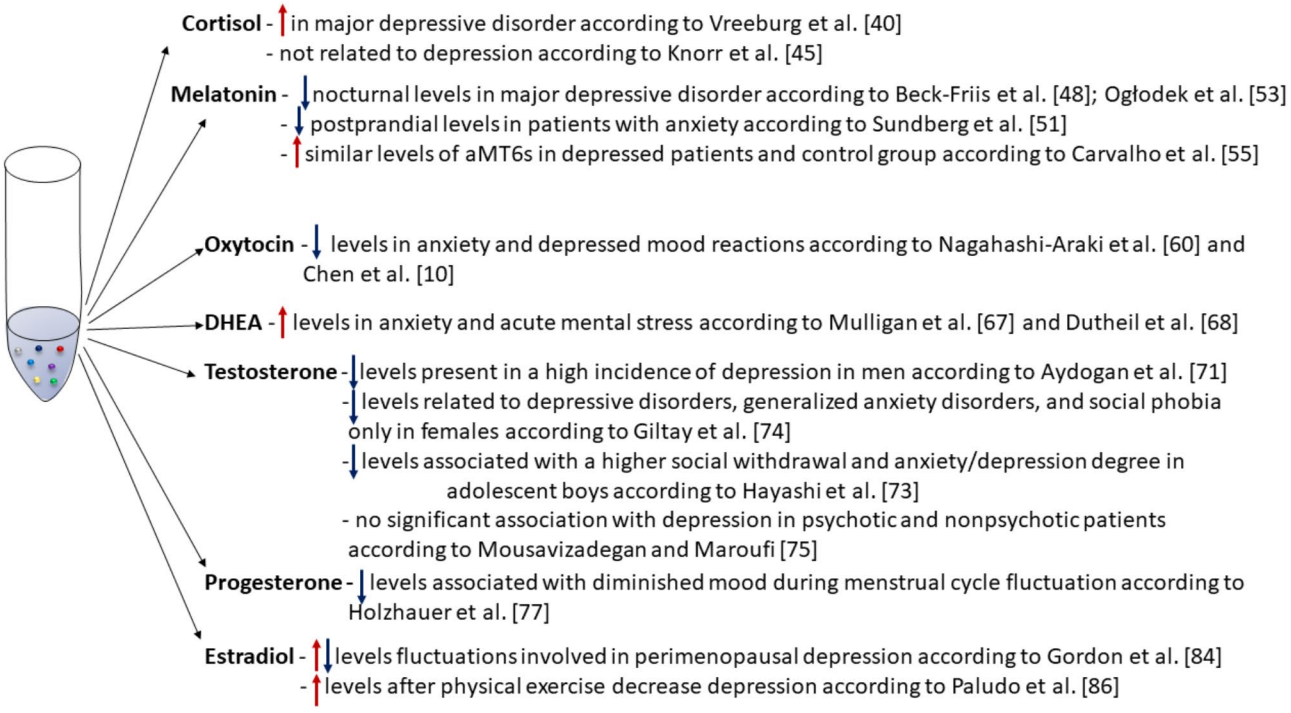

Fig. 2 Associations of salivary hormones with major studies and their results

Estradiol

Estradiol (E2) is one of four steroid hormones in the estrogen category. While it is physiologically produced mainly in the female ovaries, male tissues also produce estradiol, albeit in significantly smaller amounts. E2 is one of the most potent and abundant estrogens involved in menstrual cycle regulation, promoting the development and maintenance of reproductive tissues. Beyond reproductive health, estradiol plays critical roles in the cardiovascular system by influencing vascular function, in the skeletal system by preserving bone density, and in the central nervous system by modulating mood, cognition, and neuroprotection [37].

Hypothesis Estradiol fluctuations impair serotonin synthesis and receptor function, reducing serotonergic signaling. Estradiol also affects neuroplasticity, with low levels diminishing brain-derived neurotrophic factor (BDNF) and promoting neuronal vulnerability to stress.
Estradiol modulates serotonin synthesis and receptor sensitivity, influencing mood and anxiety. Low estradiol levels reduce serotonin availability and neuroplasticity, potentially leading to depressive symptoms. It has long been known that women in perimenopause have fluctuating E2 levels responsible for many signs and symptoms, including mood changes and increased sensitivity to psychosocial stress [15].

Possible uses in diagnosis, prognosis and treatment

Hormonal shifts impact mood regulation, stress response, and overall mental health, providing insight into the biochemical links between endocrine function and depressive disorders. In Fig. 2, associations of salivary hormones with significant studies and their results are presented.

The first, **cortisol**, is widely studied for its role in depression, given its involvement in stress responses and HPA axis dysregulation. Elevated evening salivary cortisol levels correlate with treatment-resistant depression, while flattened diurnal rhythms are common in chronic cases [22]. Measuring salivary cortisol provides a non-invasive means to identify at-risk individuals and track responses to interventions like cognitive-behavioral therapy [38]. Emerging pharmacological approaches, such as glucocorticoid receptor antagonists, also target cortisol pathways to alleviate symptoms.

In a recent study, Vreeburg et al. investigated whether salivary cortisol levels can predict a 2-year course of anxiety and depression. It was the first longitudinal study examining salivary cortisol in detail. They analyzed seven timepoints covering 1-hour awakening and evening levels and included a dexamethasone suppression test. The authors found that low cortisol awakening response (CAR) was an independent predictor of an unfavorable course of anxiety and depression over the two years [39]. The research team discussed their previous results, which

were contradictory at first glance. They found that CAR levels are elevated in MDD patients and patients with panic disorder with agoraphobia [40, 41]. Recently, Sujik et al. studied salivary cortisol levels in elderly depressed patients referred for electroconvulsive therapy. The authors found no relation between salivary cortisol, depression, or the therapy outcome [42].

On the other hand, Dziurkowska et al. investigated salivary cortisol levels in MDD patients treated with SSRIs and found that the treatment strongly suppressed salivary cortisol levels. Moreover, combination treatment had a more profound effect than monotherapy [43]. It has long been known that physical exercise can alleviate depressive symptoms. Rahman et al. investigated this notion, focusing on salivary cortisol levels. The principal finding was that physical exercise reduced salivary cortisol, correlating with the attenuation of depressive symptomatology [44]. However, Knorr et al. performed a systematic review and meta-analysis and found no conclusive evidence of the utility of salivary cortisol as a reliable marker of depression [45]. This might be rooted in the fact that most studies on salivary cortisol are quite heterogeneous and lack a standardized methodology of salivary cortisol measurement [46]. Future research must address these drawbacks before the salivary cortisol measurement in clinical practice can be implemented routinely.

Melatonin, critical for regulating circadian rhythms, is often deficient or misaligned in depressive patients, particularly those with sleep disturbances. Based on the long-established circadian rhythm disturbances found in depressed patients, melatonin signaling pathways and the pathophysiology of depressive disorder have been extensively studied [9]. Salivary melatonin assays help identify circadian rhythm disruptions, guiding interventions like light therapy or melatonin receptor agonists such as agomelatine, which improve mood by restoring sleep-wake cycles [47].

The relationship between melatonin and affective disorders was first studied in the 1980s. For instance, Beck-Friis et al. studied 30 patients with an acute major depressive episode and 24 patients diagnosed with unipolar or bipolar disorder (in remission at the time of the experiment). The principal finding was that maximum nocturnal serum melatonin was lower in both study groups than healthy control subjects. The authors indicated that the level of nocturnal melatonin could serve as a marker of MDD [48]. Salivary melatonin levels were reported to correlate strongly with plasma levels [49]. Considering the advantages of salivary sampling over phlebotomy in terms of accessibility and the learning curve of the procedure, measuring melatonin levels in the saliva has become a more prominent approach in many fields, including psychiatric research. In 2016, Sundberg et al. reported that low bedtime salivary melatonin levels negatively correlate with depressive symptomatology in young adults [50, 51]. Later, in 2020, the same research team investigated salivary melatonin and its association with various inflammatory markers in young adults with anxiety. Contrary to the initial hypothesis, only daytime salivary melatonin, but not bedtime melatonin, was related to the studied inflammatory markers. More specifically, patients with anxiety had elevated postprandial levels of melatonin and cytokines VEGF-A and CCL3/MIP-1α. The authors also discussed the possibility that postprandial melatonin is released from the gut [52]. A recent 2021 experiment by Kudo et al. evaluated salivary melatonin in postpartum mothers to investigate its possible association with depression. The results revealed that salivary melatonin concentration can predict the Edinburgh Postnatal Depression Scale (EPDS) score. Most importantly, the authors showed that high melatonin levels could be as detrimental to normal mood regulation as low levels. The patients with salivary melatonin levels out of the reference range of 4–16 pg/l tended to have elevated EPDS scores [53]. On the other hand, Ogłodek et al. revealed that severely depressed patients had the highest salivary melatonin secretion at 3:00 a.m. compared to subjects with mild and moderate depression. The authors also found that the concentrations of neurotrophins (neurotrophin-3, brain-derived neurotrophic factor, and nerve growth factor) were decreased in all depressed subjects [54]. Interestingly, melatonin can be considered a neurotrophic factor modulating neuronal survival, apoptosis, or even structural polarization of neurons [55]. Controversially, Carvalho et al. evaluated 6-sulphatoxymelatonin (aMT6s)– a major urinary metabolite of melatonin and found similar levels between the study group of depressed individuals and controls [56]. Apart from methodological differences, these inconsistencies most likely result from the fact that the action of melatonin is not purely mechanistic. However, it is a sort of integrative molecule affecting the brain in many complex ways, affecting neuroplasticity (i.e., the brain's ability to reorganize and rewire its neural networks) [57]. The latest research indicates that depression impacts neuroplasticity in a deleterious manner [58].

While **oxytocin** levels seem to increase in reaction to stress, low salivary oxytocin levels correlate with increased social withdrawal and emotional dysregulation [59]. Intranasal oxytocin has shown promise in improving emotional recognition and reducing symptoms of social isolation, making it a potential adjunctive treatment.

Holt-Lunstad found salivary oxytocin levels to positively correlate with perceived stress, especially in women [60]. In the postpartum period, women with higher salivary oxytocin during breastfeeding showed significantly lower state anxiety [61]. Bellosta-Batalla described reduced state anxiety and improved mood correlating

with an increase in salivary oxytocin after a brief mindfulness session in 42 psychology students [49]. Much discussion has been regarding the reliability of measuring oxytocin levels in various body fluids. Some authors have suggested that peripheral oxytocin levels do not reflect CNS levels and activity [62]. However, there has also been research pointing to the opposite. Chen et al. measured oxytocin levels in CSF, plasma, and saliva in women suffering from postpartum depression. They found oxytocin levels in all three compartments to correlate negatively with depressive symptoms. Moreover, the salivary plasma levels of oxytocin correlated with the OXT levels in CSF more closely than its plasma levels [10]. These findings point to salivary oxytocin as a reliable correlate of central oxytocinergic activity and the alterations in oxytocin levels in depressive disorder.

Salivary **serotonin** reflects peripheral serotonergic activity and has been linked to mood dysregulation in depression [63]. While peripheral serotonin differs from its central counterpart, changes in salivary serotonin concentrations may correlate with central serotonin dysfunction, offering a minimally invasive method for monitoring treatment responses. Selective serotonin reuptake inhibitors (SSRIs) remain the primary pharmacological treatment targeting serotonergic pathways. Additionally, interventions such as dietary tryptophan supplementation may influence serotonin production and improve depressive symptoms (Richard et al., 2009).

There is a difference in the circadian rhythm of salivary serotonin in depressed and healthy subjects—moreover, the circadian rhythm in patients with depression changes after treatment with antidepressants. Nevertheless, the serotonin levels in saliva do not seem to reflect central serotoninergic activity [64, 65]. A possible solution to this might be using a substitute substance that would better correlate with central serotoninergic activity - Lindell et al. describe a positive correlation between salivary prolactin and 5-hydroxyindoleacetic acid (a serotonin metabolite) in cerebrospinal fluid of rhesus monkeys [66]. Yet this topic needs to be further researched in the future.

In a recent 2022 article, Nenezic et al. reviewed that **DHEA** is considered a neurosteroid with a profound effect on the CNS regarding its neuroprotective, cognition-supporting, anxiolytic, and antidepressant action [12].

Interestingly, Mulligan et al. authored a study focusing on the salivary levels of DHEA in adolescent girls with anxiety and found that salivary concentration of DHEA positively correlated with generalized anxiety disorder symptoms [67]. A 2021 systematic review and meta-analysis showed that increased salivary DHEA is a biomarker of acute mental stress, having a protective role by counteracting the effect of cortisol. The most significant correlation was found in women, youngsters, and obese. One of the bottom lines of the study was that DHEA seems to have a positive effect on well-being [68].

Circulating **testosterone** levels strongly correlate with salivary testosterone, predominantly in males [69, 70]. Testosterone replacement therapy has shown mixed results, with notable benefits in hypogonadal men but inconsistent findings in women [71]. Research shows that samples must be collected very carefully to avoid interference effects caused by the leakage of blood into saliva, which can increase the final testosterone concentration [72]. Recently, Hayashi et al. found that lower testosterone level is associated with higher social withdrawal and anxiety/depression degree in early adolescent boys (mean age 11,5) [73].

The salivary level of testosterone in psychiatric disorders has so far been examined only by a few research groups. For instance, Giltay et al. conducted a large "Netherlands Study of Depression and Anxiety (NESDA)" with 722 male and 1380 female patients with lifetime diagnoses of depressive or anxiety disorders. The study aimed to analyze whether salivary testosterone levels are related to the mentioned psychiatric disorders. Samples were taken regularly in the morning and evening by the participants themselves, and patients also underwent medical exams, face-to-face interviews, and several questionnaires. According to the results, depressive disorders, generalized anxiety disorders, social phobia, and agoraphobia were associated with lower testosterone levels, surprisingly only in females. The authors also concluded that saliva samples are a valuable tools for non-invasive screening [74]. In another study, Mousavizadegan and Maroufi compared salivary testosterone levels in bipolar patients during different phases of the disorder (mania, depression, euthymic); however, there were no differences in terms of testosterone levels between psychotic and nonpsychotic patients, or subjects who attempted suicide [75].

Progesterone interacts with GABAergic pathways to regulate mood. Low progesterone or fluctuations in its levels can lead to reduced GABAergic signaling in the brain, heightening anxiety and mood instability. In conditions like premenstrual dysphoric disorder (PMDD) and postpartum depression, these hormonal shifts are strongly linked to mood disturbances [76]. In 2021, Sovijit et al. investigated the relationship between decreased serum progesterone levels and menopause-associated affective disorders, namely anxiety and depression. The authors reported that the gut microbiome is the mediator through which progesterone regulates mood. Depression and anxiety mitigation were correlated with the increase in Lactobacillus spp. growth by the action of progesterone [14].

Holzhauer et al. studied the relationship between alcohol use, mood and hormonal fluctuations during the menstrual cycle. Interestingly, the authors observed that women with a more pronounced decrease in salivary progesterone levels were more likely to drink alcohol due to progesterone-mediated diminished mood [77]. On the other hand, Hsiao et al. published a clinical trial where they reported no correlation between plasma progesterone levels and depressive and anxious symptomatology in women diagnosed with premenstrual dysphoric disorder [78]. However, according to Konishi et al., plasma and salivary progesterone are not always in sync and may depend on interindividual variations and intraindividual diurnal pattern differences [79].

Estradiol modulates serotonin and neuroplasticity. The neuroprotective effects of E2 were previously reported in several neurological and psychiatric conditions, e.g. cerebral ischemia or schizophrenia [80, 81]. These effects of estradiol are most probably mediated by cell death prevention, axonal sprouting, enhanced regeneration, and synaptic transmission [82]. The results of Gordon et al. on the link between salivary E2 fluctuations and perimenopausal depression corroborated the notion that E2 fluctuation is involved in the etiopathogenesis of this condition [83].

In 2020, Gordon et al. evaluated the sensitivity of 101 perimenopausal women to E2 changes and its predictive value in determining the risk of depression. The authors reported that E2 sensitivity could predict the development of depressive symptoms, mainly in women with a low baseline risk of affective disorders [84]. The paper published by Bartley et al. focused on women with premenstrual dysphoric disorder who experienced an increased response to nociceptive stimuli. The assessment of salivary E2 revealed that this hormone has a hypoalgesic effect [85]. Salivary E2 was also studied by Paludo et al., who conducted an experiment investigating its role on mood, anxiety, and performance in physically active women. The authors observed that basal salivary E2 increased due to physical activity. Moreover, aerobic exercise decreased depression, which could have been explained by the effect of physical activity on the levels of E2 as measured in the saliva [86]. Finally, Lončar-Brzak et al. focused on evaluating salivary E2 in postmenopausal women with burning mouth syndrome. Significantly lower salivary E2 correlates were reported in the study group [87]. At first glance, the relationship between this syndrome and affective disorders might be elusive. Nonetheless, Bogetto et al. found that patients with the burning mouth syndrome have higher rates of psychiatric comorbidities [88]. Taken together, salivary E2 is a good predictor of serum E2, as also concluded by Tivis et al. [89].

Conclusions

The current body of research highlights the complex interplay between salivary hormone levels and depression, offering a promising avenue for non-invasive diagnostic and treatment strategies. While evidence supports the association of certain hormones with depressive symptoms, significant variability exists in findings due to methodological differences, individual factors, and the multifaceted nature of depression.

Key findings from the literature suggest that nocturnal melatonin levels are frequently reduced in individuals with depression, contributing to circadian rhythm disruptions and sleep disturbances. Oxytocin levels are generally lower in anxiety and depression, correlating with increased social withdrawal and emotional dysregulation. Conversely, DHEA appears elevated in chronic stress and anxiety, potentially counteracting cortisol's effects and promoting resilience. Testosterone levels vary across demographic groups; lower levels are associated with higher social withdrawal and depressive symptoms in young boys and postmenopausal women. Estradiol fluctuations, particularly increases following physical exercise, show mood-lifting effects, supporting its role in managing depressive symptoms.

Despite these findings, salivary hormones are influenced by numerous factors, including age, sex, medications, and lifestyle, which may confound their utility as standalone biomarkers. Furthermore, inconsistent methodologies and the lack of standardization in salivary hormone measurement limit the comparability of studies and the translation of findings into clinical practice.

Future research should focus on standardizing methodologies and investigating the longitudinal relationships between salivary hormone dynamics and depression. Integrating salivary hormone analysis into personalized treatment strategies could enhance diagnostic precision and therapeutic outcomes, particularly in stratifying patient subgroups and monitoring treatment responses. These advancements hold the potential to bridge gaps in depression management, especially in settings with limited access to traditional diagnostic tools.

Author contributions

Conceptualization, S.H. and I.K.; methodology, S.H.; validation, S.H, M.K.; investigation, M.K and M.C.; resources, S.H.; writing—original draft preparation, I.K., M.C. and S.H.; writing—review and editing, all authors; supervision, S.H.; All authors have read and agreed to the published version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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