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REVIEW ARTICLE

Salivary Proteins Biomarkers in Neuro-psychiatric Disorders: A Systematic Review

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ABSTRACT
This systematic review was designed to answer the question "protein biomarkers also serve as direct indicator of diagnosis and prognosis of neuro-psychiatric disorder?" Following the inclusion and exclusion criteria, we have identified 659 studies through search on PubMed with "key words" systematic literature review according to PRISMA guidelines and finally total 58 studies (for all disorders) were included. In this systematic review article, we have been analysed protein biomarkers in schizophrenia (SCZ), bipolar disorder (BD), Attention deficit Hyperactivity Disorder (ADHD), stress, obsessive Compulsive Disordered (OCD), and Post Traumatic Stress Disorder (PTSD). Recent analyses of the human saliva using advance proteomics technique have characterised between 2000-3000 differentially expressed proteins or derived hormones and about 3000 mRNA found in saliva with a varied concentration range. Early diagnosis is crucial for halting the progression of neuro-psychiatric disorders involved in the abnormal development or up-down regulation of proteins in neuro-psychiatric illnesses found in human saliva. The painful and risky tests might be replaced with salivary proteins as a biomarker and these protein biomarkers also serve as direct indicator of brain health. Typically, nerve impulses trigger the release of substances that adhere to glandular cells and stimulate them to release the proteins, water, and other components of human saliva. Cortisol is a stress hormone, and it can impact our sleep, mood, and energy levels. In addition to several other biomarkers found in blood, urine, and CSF, saliva may be more useful biomarker being non-invasive for the diagnosis or progression of neuro-psychiatric diseases.
Keywords: *Saliva, Proteins, proteomics, Biomarker, and Neuro-psychiatric disorders.*

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INTRODUCTION

Salivary Proteome

Three pairs of main salivary glands release whole saliva (1) and these are submandibular gland, sublingual gland, and parotid gland. (2). The proteins, enzymes, and other elements of human spit are released by the gland cells in response to nerve signals that cause substances that adhere to them to release (3). The ultrafiltrate of plasma is directly passed into saliva from the blood by passing through the space between cells (1). Most of the salivary proteins reflect brain health and serve as variety of vital functions. The 20 most common proteins make up 40% of the total protein in the composition of human saliva with different concentrations. The alpha-amylase is found in abundant amounts, whereas IL-6 and IL-8 cytokines are found in trace amount (2). In addition to salivary proteins, about 3000 mRNA molecules are also found in human saliva (3). According to the molecular weight of proteins, the low molecular weight proteins (20 kDa) constitute a major amount (14.5%) of the saliva proteome than those are present in plasma (26%), which has the largest percentage of proteins between 20-40 kDa. A total of 65% of the proteins in saliva have molecular weights under 60 kDa which pertains to the proteins present in saliva. The most prevalent protein in saliva, alpha-amylase, has a molecular weight range of 46-60 kDa and is highly variable in mental disorders (4). Whereas cortisol may be useful as a biological marker that

can help determine the possibility of psychiatric illness, its impending onset, and the severity of disorder, which is especially important in the increasing prevalence of psychiatric disorders (5).

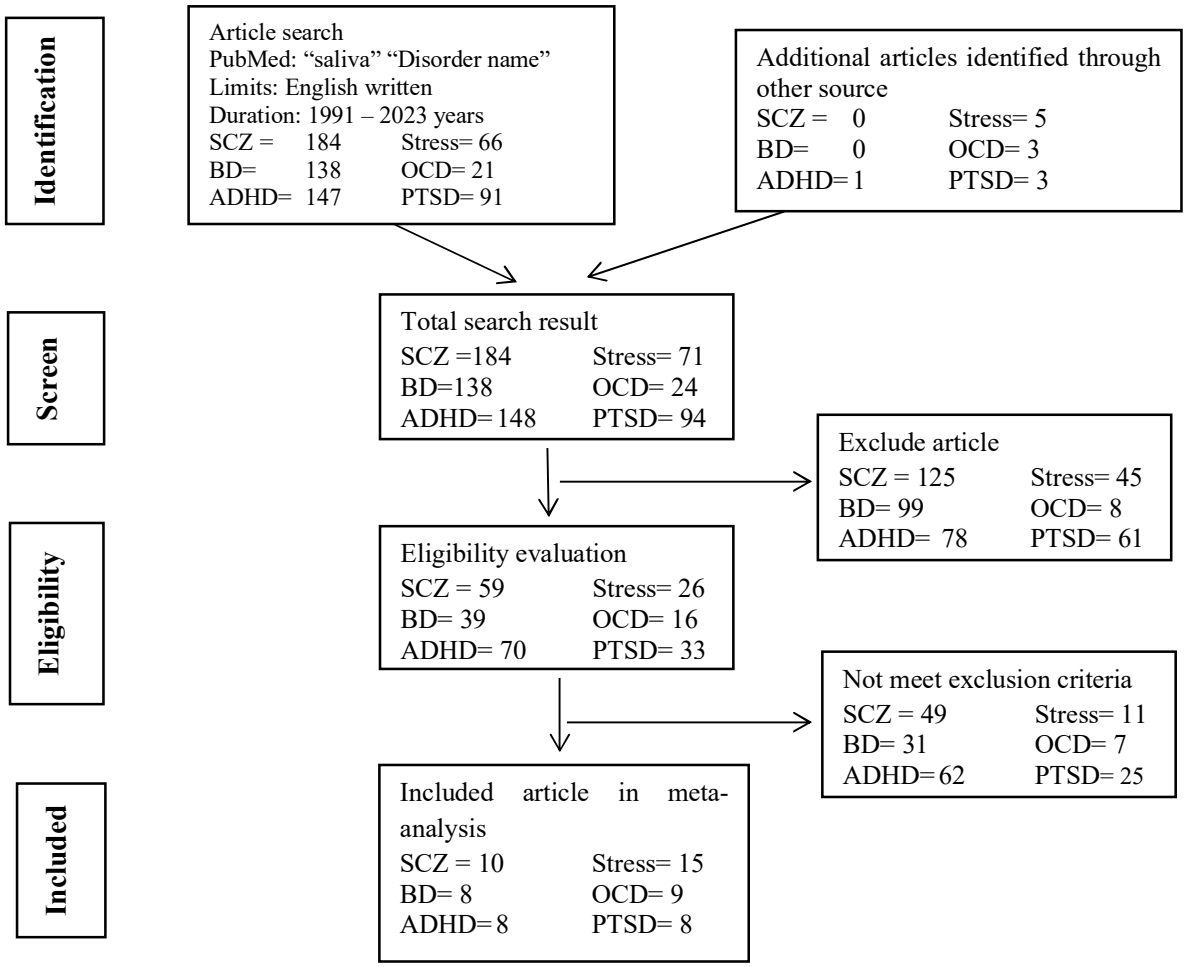
MATERIAL AND METHODS

Literature Search Strategies

Two independent psychiatrists conducted the systematic literature search for review articles using the electronic database of PubMed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. If there was an unreliable selection and lack or poor of agreement, a last decision was made through consensus. Search terms was "Saliva Schizophrenia" for schizophrenia, "Saliva Bipolar" for bipolar disorder, "Saliva ADHD" for ADHD disorder, "Saliva Protein Biomarker Stress" for Stress, "Saliva OCD" for OCD disorder, and "Saliva Protein Post-Trauma Stress" for PTSD. All selected articles available between years of 1991 to 2023 were selected with the limitation of those only written in English language.

Flowchart Diagram

In this review article the flow diagram depicts the flow of information through the several phases of a systematic review. It maps out the number of records identified, included, and excluded, and the reasons for exclusions (Figure: 1).



Inclusion and Exclusion Criteria

Only quantitative articles were eligible for inclusion criteria. Inclusion criteria were informed using Population, Intervention, Comparison, Outcome, Setting (PICOS) guidelines and some other factors, summarized in table: 1.

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Table: 1 Inclusion and exclusion criteria included in this review article

Parameters	Inclusion criteria	Exclusion criteria
Population	Selected neuropsychiatric disorder	Other than selected
Intervention	NA	NA
Comparison	Healthy control or other groups	NA
Outcomes	Salivary protein and their derivate hormones	All biomarkers except include criteria
Study design	Case-control, cohort, cross-sectional and longitudinal studies	Literature reviews, case reports, expert opinion, letters to editor, conference reports
Duration	From 1991-2023 years	Not comes under limits
Gender	Both Male female	NA
Age	All age considered	NA

Data Extraction

The variables were extracted from each original manuscript by applying a structured template: first author's surname, year of publication, patient demographics (age and gender), type of assay and the mean and standard deviation of disease duration, diagnostic criteria of disorder through Diagnostic and Statistical Manual of Mental Disorder (DSM-III to DSM-V). Psychological test and disease severity was measured through various psychological tests in all disorders.

Proteomic Platforms and Its Validation

In 21st century, "bottom-up" and "top-down" proteomic strategies are being used to discover and describe proteins. Top-down proteomics may describe intact proteins from complicated biological systems, while bottom-up proteomics involves the proteolytic breakdown of proteins before examination by mass spectrometer (6) (figure: 2).

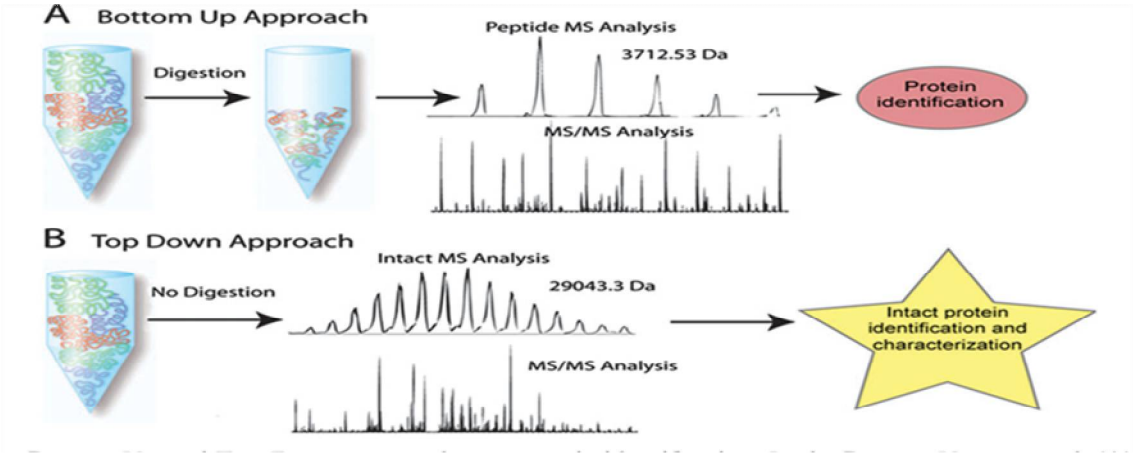

Figure 2: Diagrammatic differentiates between bottom-up and top-down approach of salivary proteomics (6).

Research using proteomic methods have already provided plentiful information on quantitative and qualitative protein arrays in saliva sample. The salivary proteomes of patients with psychological disorders and healthy control showed up-down and bottom-up differences in protein levels (7). Through the experimental mass values, and theoretical values from the Swiss-Prot data repository were used to compared (8). In contrast to LC-MS/MS examination, where the peptide solution can be examined with or without C18 ziptip treatment, MALDI-MS examination requires additional treatment of the tryptic solution with C18 ziptip (9).The first measurement of quantify protein assessments is ion intensity changes, such as peptide peak areas or different peak heights in chromatography. And second is spectral counting of proteins that have been identified using MS/MS analysis (10). If research work includes

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multiple categories or subgroups, one may combine an equivalent quantity of saliva samples loaded with SDS-PAGE or MALDI-TOF for further analysis using the pooled approach. The m/z value analyses through various mass analysers, such as quadrupole mass analysers, ion trap analysers, Time Of Flight (TOF) analysers etc., the charged ions are detected and then quantified (11). There are lots of methods to validate the proteins in samples such as western blotting, ELISA, enzymes immunoassay, and Radioimmunoassay (RIA). The Western blot technique identifies and validates specific proteins from a complex mixture of proteins from bands of saliva sample. Polyvinylidene fluoride (PDVF) or nitrocellulose (NC) membrane are read finally by ECL (Enhanced-Chemiluminescence) and viewed in the dark using a ChemiDoc mix (12). Other validation methods are such as Enzyme Immunoassay (EIA) and the Enzyme-Linked Immunosorbent Assay (ELISA) and have been used in medical laboratories for diagnostic purposes. Both processes use the same immunoassay concept and use enzymes rather than radioactivity as the reporter label (13). In radioimmunoassay, it is a competitive binding, where a radioactive antigen ("tracer") competes with a non-radioactive antigen for a fixed number of antibody or receptor binding sites. It also finds extensive application in the analysing of many substances which are present in minute amount in saliva (14).

Discussion on Neuropsychiatric Biomarkers

Schizophrenia (SCZ)

Total ten studies on Schizophrenia were included in this systematic review. The heme oxygenase-1 (HO-1) was found with higher levels (p= 0.026) in saliva of SCZ with acute psychotic episode, when compared to controls (15). Resulted psychiatric symptom severity and disability were positively correlated with overexpression of HO-1. Salivary cortisol levels in SCZ patients were correlated with the PANSS and significantly positively associated with negative and positive (PANSS) scales existed baseline cortisol levels (16). And that found lower levels of salivary cortisol in SCZ with no clinical sign of symptoms (17). Whereas cortisol is associated with IL-6 during stress in SCZ patients, that cause of irregularities in inflammatory and stress pathways found in the illness, and implicating disregulated stress response in the chronic inflammatory state in schizophrenia (18). The findings of Monteleone *et al.,* (19) indicated that level of cortisol increased in SCZ & HC, while α-amylase concentrations showed decrease in HC but not in SCZ. Supported by Inagaki *et al.,* (20) study, amylase and psychiatric symptoms were positively correlated (r=0.37), these findings indicate that higher sAA may indicate severe psychiatric symptoms. According to results of Steen *et al.,* (21) study, the cortisol concentration also, varies on time factor; it decreased significantly more during the day in SCZ as comparison to HC, and indicated that decrease HPA axis sensitivity is related to increase in negative symptom severity (22). Using HPLC-ESI-MS top-down methods, Iavarone *et al.*, (9) conclude that Defensins 1-4, S100A12, 25 cystatin-A, and S-derivatives of cystatin-B protein levels have increased by 10-fold change as compared to healthy non-smokers and healthy smoker control. Some studies have suggested that an imbalance in immune system may play a key role in schizophrenia disease. Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine, and it functions in various biological processes, including inflammation and neurogenesis. The elevated levels of MIF in human saliva, might indicate the severity of schizophrenia. Whereas Van Rijn *et al.,* (23) found that levels of testosterone were significantly lower in adolescents with prodromal symptoms as compared with non-clinical controls (Table: 2).

Table: 2 List of 10 studies description and salivary protein biomarkers in Schizophrenia.

Authors	Study descriptions	Methods	Biomarkers Name (MW)	Main Results
Bertrand *et al.,* (15)	16 SCZ, 17 HC	ELISA	Heme oxygenase-1 (HO-1)	Higher
Rossini Gajšak *et al.,* (16)	53 SZ, 63 HC	Electro chemiluminescence	Cortisol	Positively correlated with PANSS
Tobolska *et al.,* (17)	10 SZ, 38 HC	CORT-CT2 radioimmunoassay kit	Cortisol	Lower
Chiappelli *et al.,* (18)	34 SCZ, 40 HC	ELISA	Cortisol, IL-6	Positive correlate in SCZ, negatively in HC

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Monteleone *et al.,* (19)	30 SZ, 22 HC	ELISA	Cortisol	Unchanged
			sAA	Decreased
Iavarone *et al.,* (9)	32 SCZ, 31 HC	HPLC-ESI-MS	α-defensin1-4, Cystatin A (13.3 kDa), Cystatin B glutathionyl (14 kDa), Cystatin B cysteinyl (14 kDa) & S100A12 (11.63 kDa)	Increased
Steen *et al.,* (21)	SCZ 49, HC 98	Radioimmunoassay	Cortisol	Blunted cortisol in male
Van Rijn *et al.,* (23)	21 SCZ, 21 HC	ELISA	Testosterone	Lower
Hempel *et al.,* (22)	27 SCZ, 38 HC (only male)	ELISA	Cortisol	Decreased
Inagaki *et al.,* (20)	54 SCZ, 55HC	Test-strip paper	sAA (58.4 kDa)	Increased

Bipolar Disorder (BD)

Total eight studies on bipolar disorder were included in this systematic review. Hypothalamic-pituitary-adrenal (HPA) axis dysregulation may contribute to the symptom burden in bipolar disorder. Mukherjee *et al.,* (24) studied that cortisol levels were found elevated (P=0.01) in BD as compared to HC at the 10:00 p.m. Whereas daily salivary cortisol significantly decreased in depressed BD as compared to HC (25). According to Havermans *et al.,* (26), the number of frequency episode in patients reflect to fluctuate cortisol level and reduced cortisol reactivity to negatively daily life events, and flatter diurnal slopes than patients with fewer episodes. Whereas according to Steen *et al.,* (21), cortisol level between male and female participants was differing (p=0.006) and found flattened slope in men as compared to women. A study conducted through Ellenbogen *et al.,* (14) stated that higher level of cortisol in offspring (FH+) than offspring of no BD affected (FH-). It looks like that this change in HPA functioning is linked with an increased vulnerability for the development of an affecting disorder. But Ellenbogen *et al.,* (27) stated that elevated risk offspring had elevated cortisol levels after awakening (p=0.05) and at 1500 h (p=0.005) than the low-risk offspring. A pilot study results suggested that salivary levels of GHS and oxidised form GSSG found to elevated in BD as compared to HC however the ratio of GSH:GSSG was unchanged (28). Using HPLC-ESI-MS top-down techniques, defensins 1-4, S100A12, 25 cystatin-A, and S-derivatives of cystatin-B level were found increased in healthy smokers and non-smokers groups. It indicates that schizophrenia and bipolar patients showed a strong innate immune system activation (Table: 3).

Table 3: List of 8 studies description and salivary protein biomarkers in bipolar disorder.

Authors	Study descriptions	Methods	Biomarkers Name (MW)	Main Results
Mukherjee *et al.,* (24)	27 BD, 31 HC	ELISA	Cortisol	Elevated at 10 pm
Herane-Vives*et al.,* (25)	59 Unipolar, 12 BD, 40 HC	ELISA	Cortisol	Reduced
Ngamchuea *et al.,* (28)	22 BD, 20 HC	Tietze enzymatic assay	GSH, GSSG	Higher in BD
Iavarone *et al.,* (9)	17 SCZ, 31 HC	HPLC-ESI-MS	α-defensin 1-4, Cystatin A (13.3 kDa), Cystatin B (14 kDa), S100A12 (14 kDa)	Increased
Havermans *et al.,* (26)	36 BD, 38 HC	Radioimmunoassay	Cortisol	Higher in negative events
Steen *et al.,* (21)	81 BD, 98 HC	Radioimmunoassay	Cortisol	Male having a blunted cortisol release
Ellenbogen *et al.,* (27)	24 FH+, 22 FH-Offspring	Radioimmunoassay	Cortisol	Higher in FH+
Ellenbogen *et al.,* (14)	10 BD, 10 HC	Radioimmunoassay	Cortisol	Higher in BD offspring

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Attention Deficit Hyperactivity Disorder (ADHD):

Total eight studies on ADHD were included in this systematic review. Attention deficit hyperactivity disorder (ADHD) is a quite common disorder in both children and adults. According to Dück *et al.,* (5) the level in macrophage of the melatonin and cortisol rhythm was significantly lower (p=0.002) for the ADHD group. Lowest awakening salivary cortisol levels may indicate the role of abnormal HPA axis and inflammation in ADHD (29). The lower brain-derived neurotrophic factor (BDNF) in ADHD may act as a potential biomarker for ADHD. Whereas results of cross-sectional study by Krahel *et al.,* (30) stated that elevation sAA, sIgA and IgM biomarkers were used to analysis ADHD prognosis, and which represent the hypothalamus–pituitary–adrenal axis, as HPA axis, and sympathetic activity. Corominas-Roso*et al.,* (31) found negative correlation with cortisol awakening response in inattentive subtype, and IL-6 and cortisol were also present in the control group. According to Vogel *et al.,* (32) none of the indicators of ADHD symptomatology were related with IL-6 or with TNF-α, but inattentive symptoms were associated with lower, rather than higher CRP. Whereas Wilmot *et al.,* (33) VIPR2 probes indicated that hypo methylation in ADHD samples and lower CpG methylation in ADHD children, which show as desired property of a marker to be investigated. After analysis of five SNPs in FKBP5, Isaksson *et al.,* (34) concluded that associations between three polymorphisms with ADHD were found and rs9470080 was associated with lower diurnal cortisol levels. Increase thiols levels in ADHD affected children as compared to HC. It reflects that, thiols and pseudocholinesterase might play a role in the pathogenesis of ADHD and saliva may be efficiently used as a non-invasive tool for biomarker (35) (Table: 4).

Table 4: List of 8 studies description and salivary protein biomarkers in ADHD.

Authors	Study description	Methods	Biomarkers Name (MW)	Main Results
Dück *et al.,* (5)	ADHD, HC	ELISA	Melatonin and Cortisol	lower
Krahel *et al.,* (30)	60 ADHD, 72 HC	ELISA	sAA (58.4 kDa)	Increased
			sIgA (160 kDa)	
			IgM (900-1050 kDa)	
Chang *et al.,* (29)	98 ADHD, 21 TD	Enzymatic Immunoassay kit	Cortisol	Decreased at bed and morning time
Corominas-Roso*et al.,* (31)	108 ADHD 27 HC	ELISA	IL-6, TNF-α Cortisol	Negative Correlation with HC
Vogel *et al.,* (32)	2307 ADHD	ELISA	BDNF	No indicator
			IL-6	
			TNF-α	
Wilmot *et al.,* (33)	44 ADHD, 41 HC	DNA GenotekPrepIt kit	VIPR2 (49 kDa)	Hypo methylated
Isakssone*t al.,* (34)	81 ADHD, 88 HC	Radioimmunoassay	rs9470080	rs9470080, associated with ADHD and lower cortisol.
Archana *et al.,* (35)	20 ADHD, 20 HC	Spectrophotometrically	Thiol	Increased

Stress

A total of 15 studies on stress were included in this systematic review. Several researchers postulate that salivary cortisol and α-amylase levels function as stress biomarkers. The levels of cortisol, sAA, and chromogranin were significantly higher in the presenter group than the audience group that showed presenters were having more stress than the audience (36). But salivary IgA secretion rate was lower at examination (p=0.07), but cortisol concentration increased during exams (p <0.05) (37). Whereas cortisol levels were higher in chronic periodontitis with positive depression level with a history of smoking patients when compared with antagonistic group (38). IVF mothers had higher cortisol levels at first trimester of pregnancy (P=0.043) due to more anxiety and stress but decrease at after 3 months of

delivery (p=0.059). Whereas α-amylase, which showed a decrease from third trimester to birth (P = 0.049) and increase from birth to after 3 months of birth (P=0.53) (39). Cortisol and alpha-amylase interaction between maternal prenatal cortisol and infant sex to predict distress to limits approached significance (p =0.067) at 30-min post-waking and 12 h post-waking (40). In systemic Lupus Erythematous (SLE), a higher salivary amylase was found but no difference in cortisol levels in SLE compared with NCs (41) and it also increased in response to stressful conditions (42). 3-methoxy-4-hydroxy phenyl glycol (MHPG) was found in higher level in saliva during their initial hospital visits rather than healthy human being (43). Fibroblast Growth Factor-2 (FGF2) is a neurotrophic protein that was found lower with Trier Social Stress Test (TSS). Resulted higher level of FGF2 reactivity may be associated with protective cognitive processes (44). Other stress biomarkers, CgA that were higher at 4-6 days postpartum, then decreased later and constant from 2-4 months of postpartum (45). But it was found higher in women with late-luteal phase compared to follicular phase (46). Stress may influence secretions of CgA that link to attenuation of the sympathetic–adrenomedullary activity (47) and was found increased in stressful situations (48). Whereas Goodyer *et al*., (49) observed that depressed patients had higher level of cortisol/DHEA ratio in morning as compared to teenagers who have either cured or never faced depressed condition. Perera *et al.,* (50) studied that the lower concentrations of lysozyme found in saliva of students before exam, than after the exam (Table: 5).

Table 5: List of 15 studies description and salivary protein biomarkers in stress.

Authors	Study description	Methods	Biomarkers Name (MW)	Main Results
Bryant *et al.,* (44)	87 Stress, 25 No stress	ELISA	FGF2	Lower
Tammayan *et al.,* (36)	26 students	ELISA	sAA (58.4 kDa)	Increased in presenter
			Cortisol	
			Chromogranin	
Zhang *et al.,* (38)	600 participants	ELISA	Cortisol	Higher in chronic periodontitis
Irshad *et al.,* (37)	58 HC	ELISA	IgA	Lower
			Cortisol	Increased
			DHEA	Unchanged
García-Blanco *et al.,* (39)	243 pregnant women	Kinetic enzyme assay.	sAA (58.4 kDa)	Unchanged T1-T2, Increased T2-T3
			Cortisol	Higher at T1
Braithwaite *et al.,* (40)	88 pregnant women	Enzyme immunoassay kit	sAA (58.4 kDa)	Increased in females and decreased in males.
			Cortisol	Negative associated in females and males
Jung *et al.,* (41)	100 SLE, 49 HC	ELISA	sAA (58.4 kDa)	Higher
Yamada, (43)	N=270	ELISA	MHPG (0.18 kDa)	Decreased after treatment
Mori *et al.,* (45)	21 (20-29 Yrs), 21 (≥35 Yrs)	ELISA	CgA (48kDa)	Highest at T1 & T2 in Younger
Matsumoto *et al.,* (46)	45 Women	Radio immunoassay kit	CgA (48 kDa)	Higher
Den *et al.,* (47)	40 HC	ELISA	CgA (48 kDa)	CgA high at low GHQ-28
Strahler *et al.,* (42)	62 children, 78 young, 74 older	Test-strip paper	sAA (58.4 kDa)	Increased
Goodyer *et al,* (49)	30 Never depressed, 19 adolescents, 11 depressed	ELISA	Cortisol/dehydroepiandrosterone	Increased
Nakane *et al.,* (48)	Male volunteers	Radioimmuno-assay	CgA (48 kDa)	Increased
Perera *et al.,* (50)	39 participants	Lysoplate method	Lysozyme (14-15 kDa)	Decreased

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Obsessive Compulsive Disorder (OCD)

A total of 9 studies of OCD were included in this systematic review. In saliva of OCD patients, a higher level of DNA methylation of oxytocin receptor gene was inversely associated with gene expression (51). It showed that a significant reduction of 5mC levels at BDNF gene in OCD ($p < 0.0001$), that might influence protein variation in patients (52). According to Westwell-Roper *et al.,* (13) the inflammatory biomarkers such as IL-6 was significantly higher, while TNF-α, and IL-1β increased in severity of OCD. Three HPA axis were measured by Labad *et al.,* (53) and concluded that the more flattened FTP diurnal cortisol slope was observed in OCD with comorbid MDD. Whereas females with postpartum OCD have also showed significantly increased cortisol levels in comparison to HC (54). HPA axis dysregulation is showed in OCD patients with increased cortisol levels (55). Buts AA levels in OCD patients were found significantly higher in both, before and after electrical stimulation (56). Whether level of cortisol, TNF- α, and IL-6 changed when OCD patients were exposed to aversive conditions (57). Whereas patients showed significantly decrease level of TNF-α and IL-6 as compared to HC (58) (Table: 6).

Table 6: List of 9 studies description and salivary protein biomarkers in OCD.

Authors	Study Descriptions	Methods	Biomarkers Name (MW)	Main Results
D'Addario *et al.,* (51)	64 OCD	LC-MS	Oxytocin receptor	Inversely correlated
D'Addario *et al.,* (52)	50 OCD, 50 HC	LC-MS	BDNF DNA methylation	Reduced
Westwell-Roper *et al.,* (13)	41 OCD, 46 HC	ELISA	IL-6 (23.7 kDa)	Increased
			IL-1β (17.3 kDa)	
			TNF-α (25.89 kDa)	
Labad *et al.,* (53)	52 OCD, 138 HC	ELISA	Cortisol	Diurnal slope
Kawano *et al.,* (56)	45 OCD, 75 HC	ELISA	Salivary alpha amylase (62 kDa)	Increased
Lord *et al*., (54)	8 OCD, 10 HC	ELISA	Cortisol	Increased
Fluitman *et al*., (57)	10 OCD, 10 HC	ELISA	IL-6 (23.7 kDa)	Decreased
Gustafsson et al. (55)	23 OCD	Immunoassay	Cortisol	Increased
Denys *et al*., (58)	50 OCD, 55 HC	ELISA	TNF-α (17.3 kDa)	Decreased
			IL-6 (23.7 kDa)	Negative correlated

Post Trauma Stress Disorder (PTSD)

A total of 8 studies on PTSD were included in this systematic review. Szabo *et al.,* (59) stated that both IL-1β and IL-10 were increased in response to the stressor and suggest that both cumulative trauma exposure and positive emotions have implications for cytokine responses to acute stress. Whereas according to Kuras *et al.,* (60) childhood trauma had a higher level of sAA response with Trier Social Stress Test and a positive correlation was found between sAA reactivity and the CTQ subscales of childhood physical abuse ($r=0.46$) and emotional abuse ($r=0.37$). Male with PTSD had lower basal oxytocin levels and did not differ in AVP levels compared to male trauma-exposed HC (61). It depicts that potential dys-functioning of the OT system in male with PTSD, whereas sAA levels were higher ($p< 0.001$) after dressing removal as compared to baseline levels and cortisol showed blunted effect after dressing removal with decreased ($p< 0.001$) as compared to baseline levels (62). According to Gill *et al., (*63), females with PTSD (exposed to the 9/11 attacks) show decreased salivary cortisol level and increased DHEA, TNF-α, and IL-6 as compared to females without PTSD. Interestingly again, Dekel *et al.,* (64), studied that cortisol levels were increased only in male patients associated with lower severity of PTSD avoidance symptoms. Whereas Mean levels of CRP was also found to be significantly higher in PTSD as compared to without PTSD (65). It was also found increased in PTSD affected twins as compared to

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without PTSD, as well as significantly decreased IL-6 levels in PTSD twins as compared to without PTSD (66) (Table: 7).

Table 7: List of 8 studies description and salivary protein biomarkers in PTSD

Authors	Study Descriptions	Methods	Biomarkers Name (MW)	Main Results
Szabo *et al.,* (59)	73 PTSD	Multiplex Assay	IL-1β	Increased
			IL-10	
Kuras *et al.,* (60)	41 HC	Enzyme kinetic	sAA (58.4 kDa)	Higher
Frijling *et al.,* (61)	40 PTSD, 40 HC	Radioimmunoassay	Oxytocin	Lower in male
			Arginine vasopressin	Not differ in male
Brown *et al.,* (62)	77 burn children	LC-MS	sAA (58.4 kDa)	Higher to baseline
			Cortisol	Lower to baseline
Dekel *et al.,* (64)	32 Men 29 Women	Enzyme-immune assay	Cortisol	Increased in male
Plantinga *et al*., (66)	Twins study	ELISA	CPR (120 kDa)	Increased
			IL-6 (23.7 kDa)	Decreased
Spitzer *et al*., (65)	12 PTSD, 38 No PTSD	ELISA	CPR (120 kDa)	Increased
Gill *et al*., (63)	21 HC, 26 PTSD24 Trauma	ELISA	TNF-α (17.3 kDa)	Increased
			Cortisol	Decreased female
			IL-6 (23.7 kDa)	Increased in female

CONCLUSION

According to this review article having studied the salivary proteomics biomarkers, it may help to identify early psychiatric illness signs. Salivary levels of several biomarkers are known to change in the presence of psychiatric disorders and may be valuable for their diagnosis and prognosis purpose. In clinical trials, prognostic biomarkers are used to recognize patients more likely to develop a clinical event or disease progression at various stages. Indeed, biomarkers are integral to drug development; these are critical because it requisite to measure the effects of investigational drugs on subjects during the clinical trials. So that, conclusively any protein biomarker test could show that that the disorder has a certain biomarker that are targeted by a known medication. It means that such medication may work to treat human psychiatric disorder(s). The matching treatment may be available as approved treatment, an off-label treatment, or through participation in a clinical trial and body responds well to a treatment for a disease or condition. The most effective possible salivary indicators of psychiatric illnesses included cortisol, lysozyme, sAA, and CgA. The cortisol level is important for regulation for HPA axis and managed sleep, appetite, energy, cognition, and immune functioning. It is directly related with depressive symptoms, and self-reported measure severity.

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