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REVIEW

Salivary Biomarkers and Temporomandibular Disorders: A Systematic Review conducted according to PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions

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Abstract

Background: The present review aimed to investigate the association between salivary biomarkers and temporomandibular disorders (TMD). TMD is a multifactorial condition characterised by pain and dysfunction in the temporomandibular joint (TMJ) and surrounding structures. Salivary biomarkers have emerged as potential diagnostic tools due to their non-invasiveness and easy accessibility. However, the literature on salivary biomarkers in relation to TMD is limited and inconsistent.

Methods: Electronic databases of Pubmed, Embase, Web of Science, Scopus, Cochrane Library, PsychINFO, CINAHL and Medline were searched using specific search terms and Boolean operators. The search was limited to articles published in English that assessed salivary biomarkers in individuals diagnosed with TMD. Two reviewers independently screened the articles and extracted data. ROB-2 was used to assess the risk of bias.

Results: Eleven clinical papers met the inclusion criteria and were included in the review. The findings provided consistent evidence of a clear association between salivary biomarkers and TMD. Various biomarkers, including cortisol, IL-1, glutamate and several others, were assessed. Some studies reported higher levels of cortisol and IL-1 in TMD patients, indicating potential involvement in stress and inflammation. Glutamate levels were found to be elevated, suggesting a role in pain modulation. Other biomarkers also showed alterations in TMD patients compared to controls:

Conclusion: The findings from the included studies suggest that salivary biomarkers may play a role in TMD pathophysiology. Though a definitive conclusion can be drawn regarding the specific salivary biomarkers and their association with TMD, the results must be interpreted with caution considering the heterogeneity of the biomarkers assessed. Further research with larger sample sizes, standardised

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methodology and rigorous study designs is needed to elucidate the role of salivary biomarkers in TMD.

KEYWORDS
Bruxism, pain evaluation, risk of bias, salivary biomarkers, systematic review, temporomandibular disorders, TMD

1 | INTRODUCTION

TMDs encompass a group of musculoskeletal and neuromuscular conditions affecting the temporomandibular joint and associated structures, leading to pain, functional limitations and psychological distress.[1] The aetiology and pathophysiology of TMDs are multifactorial and complex, involving various biological, psychological and sociocultural factors. In recent years, there has been growing interest in exploring the potential role of salivary biomarkers in TMDs.[2-4] Saliva, as a readily accessible biofluid, offers numerous advantages as a diagnostic medium, such as non-invasiveness, cost-effectiveness and ease of collection. Salivary biomarkers, such as proteins, enzymes, inflammatory mediators and genetic markers, hold promise as objective indicators of disease presence, progression and treatment outcomes in TMDs.[5-7] Saliva also plays an important role in the sealing of removable dentures.[8-12] By examining the molecular signatures present in saliva, researchers aim to unravel the complex pathophysiological processes associated with TMDs and identify novel diagnostic and therapeutic targets. Recent advancements have propelled the utilisation of biological markers as diagnostic indicators for different types of joint disorders.[13,14] In this context, saliva has emerged as a promising medium for obtaining real-time biomarker levels due to its non-invasive nature, continuous availability and cost-effectiveness.[15-18] Notably, alterations in protein levels have demonstrated detectability in the serum several years before the radiographic manifestation of TMDs.[19] One study unveiled a correlation between specific TMD biomarkers and morphological variations in distinct anatomical regions of the TMJ condylar surface. In particular, areas of bone resorption were seen, especially at the lateral pole of the condyle, while the front surface of the condyle showed bone apposition and repair proliferation.[20] These findings shed light on the intricate molecular dynamics and structural changes occurring in the TMJ during the development and progression of TMDs.

Salivary and temporomandibular disorders (TMD) are linked by a number of different processes. Saliva is essential for lubricating the temporomandibular joint (TMJ) during movement. A decrease in salivary flow or a change in the content of the saliva could cause insufficient lubrication, which would increase friction and damage the TMJ structures.[21] Salivary inflammatory mediators can affect the temporomandibular joint's inflammatory response. Increased amounts of inflammatory chemicals may be a factor in the development of TMD symptoms and joint inflammation. Immunoglobulins in the saliva and antimicrobials help to keep the mouth healthy and ward off infections. The development of TMD may be influenced by dysregulation of the immune response in the oral cavity.[22] The oral environment may change as a result of pH and buffering capacity changes in saliva. Acidic environments can trigger enamel demineralization, which might result in dental issues and worsen TMD symptoms.[23] Cortisol and other stress-related indicators can be found in saliva. For those who are sensitive, chronic stress and its effects on saliva composition may affect muscle tension and exacerbate the symptoms of TMD.

However, despite the burgeoning interest in salivary biomarkers, the existing literature on their association with TMDs remains limited and fragmented. Previous studies have reported conflicting findings, with variations in study design, biomarker selection and analytical methods contributing to the discrepancies.[24-28] Therefore, there is a compelling need for a systematic review to consolidate the available evidence, critically evaluate the methodologies employed and provide a comprehensive overview of the current state of knowledge regarding salivary biomarkers in TMDs.

Henceforth, the present investigation aimed to synthesise the existing literature on the expression of salivary biomarkers in individuals affected by TMDs. By systematically evaluating the available evidence, this review aims to provide a comprehensive understanding of the current state of knowledge regarding salivary biomarkers in TMDs, identify potential biomarkers of interest and also highlight areas for future research.

2 | MATERIALS AND METHODS

2.1 | Eligibility criteria

This review adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[29] to ensure transparency, rigour and reproducibility in the review process (as shown in Figure 1). The PRISMA guidelines were systematically applied in the different stages of the study, including study identification, screening, eligibility assessment, data extraction and synthesis of the findings. The review is applied for PROSPERO registration.

This review employed the PECOS (population, exposure, comparison, outcome and study design) strategy to formulate a clear research question and guide the study selection process.

Population (P): Human population, of any age and gender.

Exposure (E): It included individuals or groups affected by temporomandibular disorders.

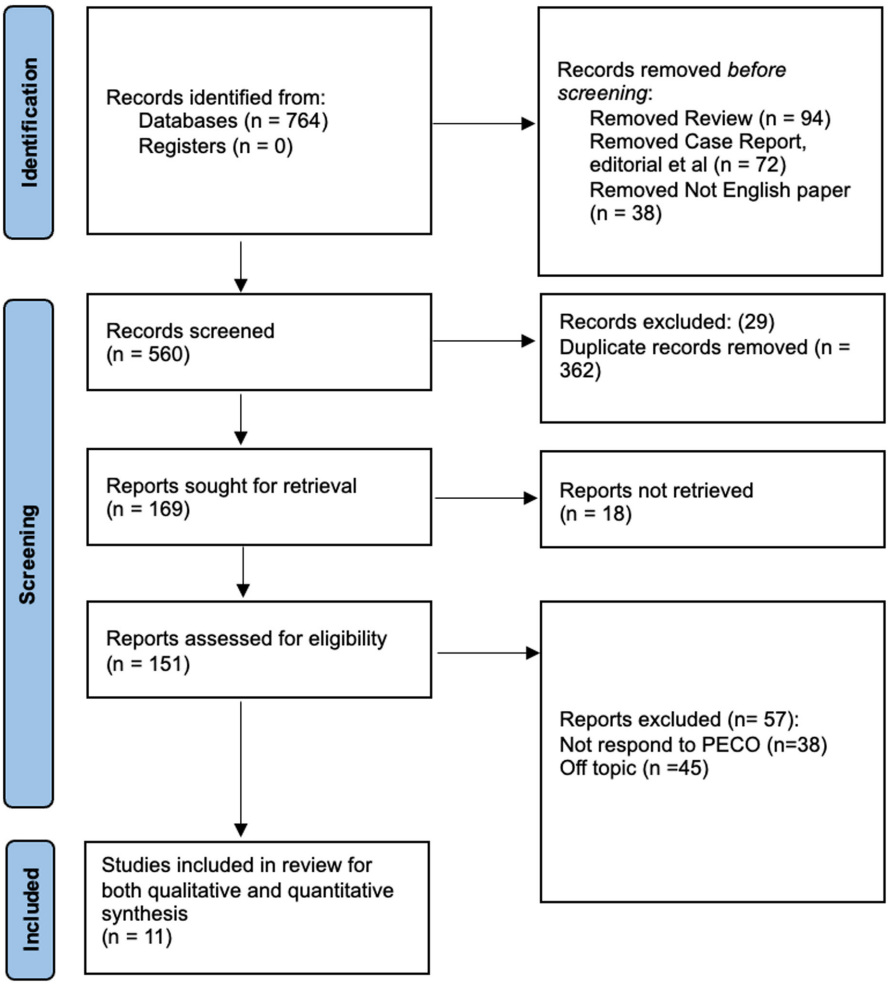

FIGURE 1 Graphical representation of the PRISMA guideline utilisation in the review.

Comparison (C): The comparison component involved groups or cohorts without TMDs.

Outcome (O): The primary outcome of interest was the expression of salivary biomarkers. This included biomarkers such as cortisol, IL-1, glutamate, SAA, PA, DMA and other relevant biomarkers identified in the studies.

Study Design (S): The review included observational, case–control studies and other cohort-based clinical papers. This study design was selected to explore the relationship between salivary biomarkers and TMDs.

Observational studies conducted on human subjects, irrespective of age or gender, who were diagnosed with TMDs, with no restrictions on geographical location, were included. Articles published in the English language were considered for inclusion. Case reports, reviews and editorials were excluded. Studies conducted on animal models or in vitro experiments were also excluded Table 1.

2.2 | Search strategy

A comprehensive search was done across eight different databases using Boolean operators and MeSH (Medical Subject Headings) keywords (presented in Table 2). The search strategy was designed to identify relevant studies related to salivary biomarkers and their association with TMDs. The primary search terms used in the search strategy included variations of 'salivary biomarkers', 'temporomandibular disorders' and related concepts. These terms were combined using the Boolean operator 'OR' to capture a broad range of relevant articles. Additionally, MeSH keywords specific to each database were incorporated to enhance search precision and retrieve more focused results. To further refine the search, the Boolean operator 'AND' was used to combine the sets of search terms related to salivary biomarkers and TMDs.

2.3 | Data extraction

Standardised data extraction forms were developed, encompassing various domains and variables of interest. These forms were meticulously designed to capture essential information from each selected study, including study characteristics, participant demographics, intervention details (if applicable), biomarker assessment methods, TMD assessment tools, pain assessment methods and reported results. The data extraction was carried out independently by two reviewers. Each reviewer carefully examined the full text of the articles and extracted the relevant data based on the standardised

TABLE 1 Terms and their abbreviations utilised in the review.

Term	Abbreviation used
Brain derived neurotropic factor	BDNF
Control group	CG
Dimethylamine	DMA
Electrochemiluminescence immunoassay	ELICA
Enzyme-linked immunosorbent assay	ELISA
Epithelial-derived neutrophil-activating peptide	ENAP
Granulocyte-macrophage colony-stimulating factor	GM-CSF
H-nuclear magnetic resonance	H-NMR
Human quantibody protein microassay	HQPM
Interferon-gamma	IFN
Malondialdehyde	MDA
Malondialdehyde	MDH
Matrix metalloproteinase	MMP
Nerve growth factor	NGF
Numeric rating scale	NRS
Pain intensity	PI
Perceived Stress Scale	PSS
Phenylacetate	PA
Plasminogen activator inhibitor	PAI
Research diagnostic criteria for temporomandibular disorders	RDC/TMD
Salivary alpha-amylase	SAA
Substance P	SP
Symptom Severity Index	SSI
Temporomandibular disorders	TMDs
Temporomandibular joint	TMJ
Total antioxidant capacity	TAC
Vascular Endothelial Cadherin	VED
Vascular Endothelial Growth Factor	VEGA
Visual analog scale	VAS

data extraction forms. Following the initial extraction, the reviewers convened to compare and cross-validate their extracted data. Any discrepancies or differences were resolved through thorough discussion and consensus among the reviewers. The extracted data was then qualitatively synthesised and systematically analysed.

2.4 | Quality assessment

The risk of bias assessment was conducted using the ROBINS-I tool[30] (Risk of Bias in Non-Randomised Studies of Interventions). The bias assessment involved a systematic evaluation of various domains by two reviewers, during which potential biases were identified and evaluated within each domain. Any deviations from the intended interventions, such as nonadherence or incomplete implementation of the interventions, were evaluated for their potential impact on the study outcomes. The assessment also considered the potential biases arising from missing data and the measurement of outcomes (Figures 2, 3).

3 | RESULTS

3.1 | Study characteristics

The selection process for this systematic review involved a comprehensive search across multiple databases using predefined search terms and inclusion criteria. Initially, a total of 764 articles were identified through the literature search. These articles were then subjected to a rigorous screening process to identify relevant clinical papers for inclusion in the review. The screening process consisted of two stages: title/abstract screening and full-text assessment. During the title/abstract screening, articles that clearly did not meet the inclusion criteria were excluded. This initial screening resulted in the exclusion of a significant number of articles, narrowing down the pool of potential studies. Subsequently, the remaining articles underwent full-text assessment to determine their eligibility for inclusion. During the full-text assessment, each article was carefully reviewed to assess its relevance to the research question and its adherence to the predefined inclusion criteria. This involved a thorough examination of the study design, population characteristics, biomarkers assessed and TMD and pain assessment methods employed. Studies that did not meet the specific criteria or did not report on salivary biomarkers in relation to TMDs were excluded from the final selection. After applying these rigorous selection criteria, a total of 11 clinical papers[31-41] were found to be eligible for inclusion in the systematic review.

Table 3 represents the demographic variables of the 11 selected studies[31-41] that explored the relationship between salivary biomarkers and TMDs. The studies were conducted in various regions, including India,[31] Brazil,[32,35,36] Sweden,[33] Iran,[34,37,38] Turkey,[39] Canada[40] and the USA,[41] with different sample sizes ranging from 30 to 84 participants. The mean age of the participants varied across the studies, ranging from 10.63 to 49 years, with some studies not specifying the mean age. The majority of the studies reported a higher proportion of female participants, with female participants accounting for 38% to 100% of the total sample size. Sanches M. L.[36] and Patricia S. Ce et al.[32] included only female samples in their study.

3.2 | Main findings

Table 4 shows the different protocols assessed in the selected papers. The biomarker assessment techniques included ELISA, ELICA, spectrophotometric assays, H-NMR spectroscopy, Aebi's technique and the MDA assay. Salivary biomarkers assessed in relation to TMDs were cortisol, IL-1, glutamate, 5-HT, NGF, BDNF, SP, SAA, PA, DMA, maltose, acetoin, isovalerate, TAC, catalase, MDA, TNF-,

TABLE 2 Search strings utilised across different databases for this review.

Database	Search thread	Boolean operators	MeSH keywords
PubMed	('salivary biomarkers' OR 'saliva biomarkers' OR 'salivary markers')	AND	Temporomandibular Disorders [MeSH] OR TMDs [MeSH]
Embase	(salivary biomarkers OR saliva biomarkers OR salivary markers)	AND	Temporomandibular Disorders [MeSH] OR TMDs [MeSH]
Web of Science	TOPIC: (salivary biomarkers OR saliva biomarkers OR salivary markers)	AND	Temporomandibular Disorders OR TMDs
Scopus	TITLE-ABS-KEY (salivary biomarkers OR saliva biomarkers OR salivary markers)	AND	Temporomandibular Disorders OR TMDs
Cochrane Library	Salivary biomarkers OR saliva biomarkers OR salivary markers	AND	Temporomandibular Disorders OR TMDs
PsycINFO	Salivary biomarkers OR saliva biomarkers OR salivary markers	AND	Temporomandibular Disorders OR TMDs
CINAHL	Salivary biomarkers OR saliva biomarkers OR salivary markers	AND	Temporomandibular Disorders OR TMDs
Medline	(Salivary biomarkers OR saliva biomarkers OR salivary markers) AND (Temporomandibular Disorders OR TMDs)	AND	–

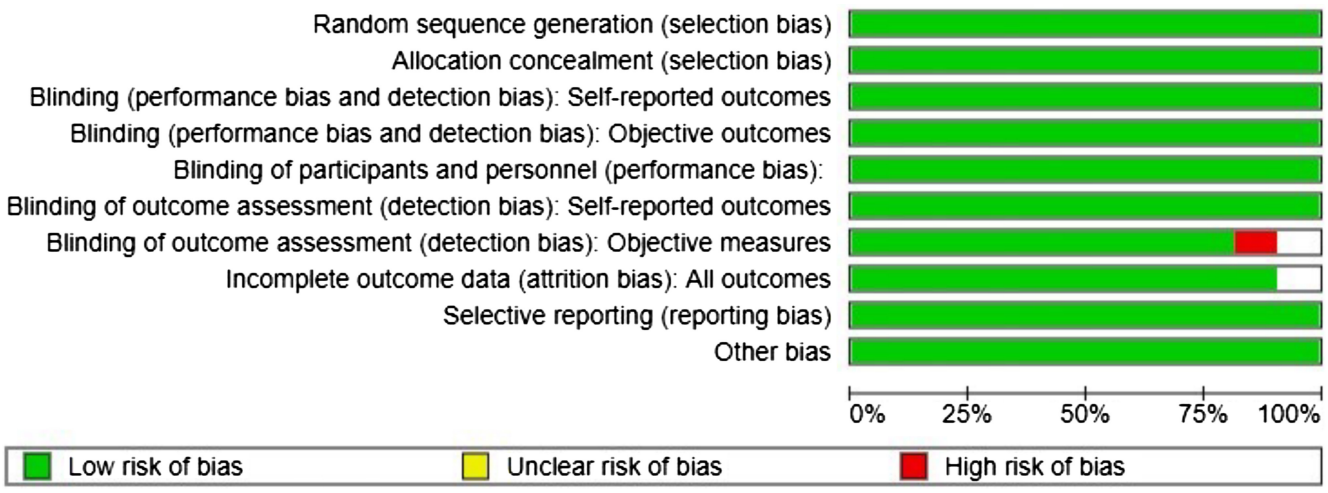

FIGURE 2 Assessment of bias in the selected papers using ROBINS-I tool.

MMP-3, 8-OHdG, 6Ckine, ANG, CXCL16, ENA-78, GM-CSF, IFN-, IL-1, IL-6, PAI-1, TGF-1, TIMP-1, VE-Cadherin and VEGF The TMD assessment methods were RDC/TMD in nine studies.[31-33,35,36,38-41]

TMD disorders were confirmed both clinically and radiographically in the study of B. Shukri et al.[41] Hajer Jasim et al.[33]; Kobyashi FY et al.[35] also tested for the diurnal variation of saliva on TMD. The study of B. Shukri et al.[41] correlated the detected biomarkers of inflammation with the morphological presentation of condyles using artificial intelligence (AI) among patients affected by TMJ osteoarthritis. A clear female predilection was noted in the study of Hajer Jasim et al.[33] Sanches M. L.[36] and Patricia S. Ce et al.[32] conducted their study with only female recruits. A significant correlation of biomarkers with TMD was noted in seven studies but not in the study of Kobyashi FY et al.[35]

The findings from the included articles revealed interesting associations between salivary biomarkers and TMDs. For instance,

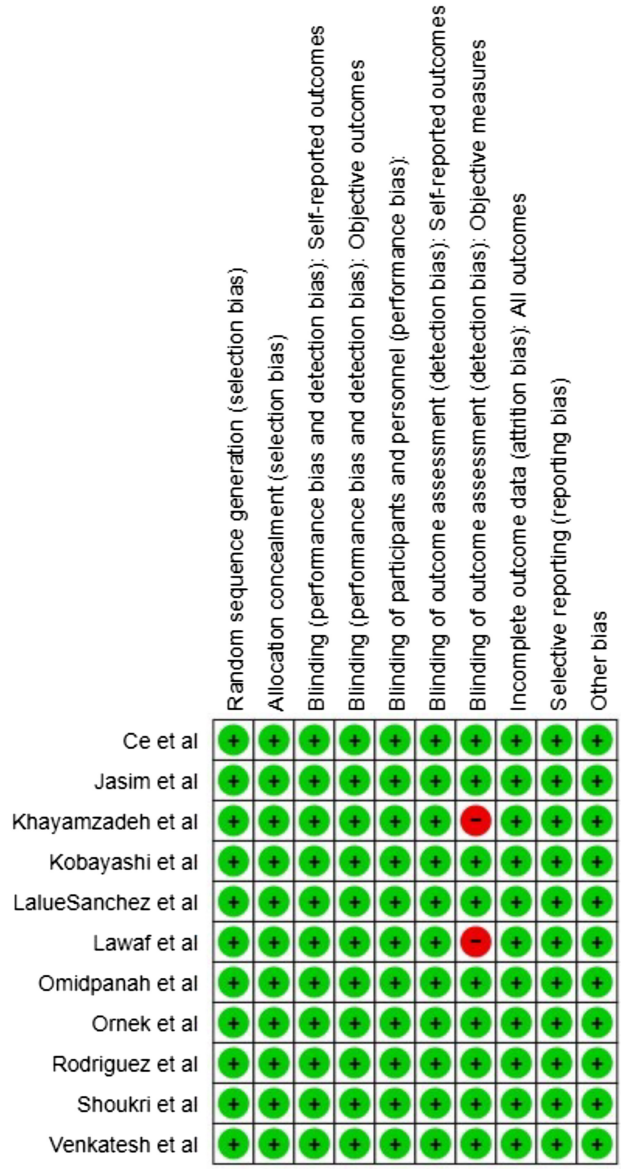

FIGURE 3 Assessment of bias in the selected papers using ROBINS-I tool.

in one study,[31] TMD patients reported feeling more stressed along with significantly elevated salivary cortisol levels as compared to the CG. In another study,[32] patients with TMD alone had significantly higher IL-1 levels, while those with fibromyalgia alone did not differ significantly from the CG. In one study,[33] glutamate levels were found to be significantly higher in the TMD group compared to the CG group. Cortisol and SAA levels were significantly higher in the TMD group compared to the CG in certain studies.[34,35] Alterations in various biomarkers, such as PA, DMA, maltose, acetoin, isovalerate, MDA and 8-OHdG, were consistently more pronounced in the TMD group compared to the CG. However, there were also instances where no significant differences in biomarker levels were observed.[35,37] Considering the complex nature of salivary biomarkers, their potential association with TMDs must be carefully considered.

Overall, nine studies[31-34,36,38-41] showed some association of TMD with salivary biomarkers, while studies[35,37] reported no significant difference. Although salivary biomarkers and TMD are undoubtedly connected, researchers have not yet discovered the gold standard salivary biomarker for TMD diagnosis.

3.3 | Risk of bias assessment

Methodological quality assessed showed low risk of bias. The only risk was noted was that of objective measure in the studies of Khayamzadeh et al[34] and Lawaf et al[37] as they did not specify the TMD assessment method.

4 | DISCUSSION

The findings of this review contribute to the existing body of knowledge by shedding light on specific salivary biomarkers that may be associated with TMDs. For instance, the observation that TMD patients had elevated levels of IL-1, glutamate, cortisol and SAA in certain studies indicates potential underlying biological mechanisms involved in TMD pathophysiology. These findings open up avenues for further investigations into the role of these biomarkers in TMD development, progression and pain mechanisms. Moreover, the identification of alterations in biomarkers such as PA, DMA, maltose, acetoin, isovalerate and oxidative stress markers (e.g. 8-OHdG) provides insights into potential metabolic and microbial dysregulation as well as oxidative damage in individuals with TMDs. Understanding these molecular changes can contribute to a more comprehensive understanding of the complex aetiology and pathogenesis of TMDs.[42] The significance of this review extends beyond the mere identification of biomarker correlations. The findings serve as a foundation for future research endeavours aimed at developing diagnostic tools with improved accuracy and specificity for TMDs. By identifying salivary biomarkers associated with TMDs, healthcare professionals may have access to non-invasive and easily accessible diagnostic indicators, facilitating early detection and intervention. Additionally, the insights gained from this systematic review can pave the way for personalised treatment approaches tailored to the specific biomarker profiles of individuals with TMDs. By understanding the biomolecular alterations associated with TMDs, targeted therapeutic strategies can be developed to alleviate symptoms and improve patient outcomes. Upon analysing the included articles, certain patterns and findings emerge. The studies conducted by Venkatesh SB et al.[31] in India, Ce et al.[32] in Brazil and Jasim et al.[33] in Sweden reported a significantly higher representation of female participants. Meanwhile, the study by Kobayashi et al.[35] in Brazil specifically focused on a relatively younger age group with a mean age of 10.63 years. Additionally, Lalue et al.[36] in Brazil and Rodriguez et al.[40] in Canada consisted entirely of female participants, indicating a potential gender-related aspect in the context of TMDs. The study of Ornek

TABLE 3 Demographic factors as assessed in the included articles.

Author	Year	Region	Sample size (*n*)	Mean age (in years)	Sex ratio
Venkatesh SB et al[31]	2021	India	40	20.5	57% females
Ce et al[32]	2018	Brazil	69	49 ± 3.25	All females
Jasim et al[33]	2020	Sweden	78	28.8 ± 7.15	64 females
Khayam et al[34]	2019	Iran	64	Unspecified	Unspecified
Kobayashi et al[35]	2017	Brazil	64	10.63 ± 1.68	48 females
Lalue et al[36]	2020	Brazil	53	41 ± 12.14	All females
Lawaf et al[37]	2015	Iran	84	29.50 ± 3.8	42 females
Omidpanah et al[38]	2020	Iran	60	30.7 ± 13.2	25 females
Ornek et al[39]	2023	Turkey	68	Unspecified	All females
Rodríguez et al[40]	2011	Canada	30	40.50 ± 15.53	All females
Shoukri et al[41]	2019	USA	34	39.65 ± 13.45	Unspecified

et al.[39] in Turkey also consisted entirely of female participants, although the mean age was not specified. Khayam et al.[34] in Iran and Shoukri et al.[41] in the USA did not provide explicit information regarding the mean age or the sex ratio of their participants. Among the studies that assessed cortisol levels, Venkatesh et al.[31] reported a statistically significant difference in salivary cortisol between the TMD group and the CG. They also observed TMD patients feeling more stressed. Khayam et al.[34] also observed considerably higher cortisol levels in the TMD group compared to the CG, suggesting a potential association between elevated cortisol and TMD. Though Ornek et al.[39] found that cortisol levels were not significantly different between the TMD and CGs, cortisol and depression/anxiety scores were higher in the TMD group. Salivary cortisol refers to the measurement of cortisol, a steroid hormone, in saliva. Cortisol is a hormone produced by the adrenal glands in response to stress and is involved in regulating various physiological processes in the body, including metabolism, immune function, and stress response. The current review revealed a complex relationship between salivary cortisol levels, chronic stress and TMD. These findings align with previous investigations conducted by Jones et al., which reported higher perceived stress levels in TMD patients compared to controls but did not observe significant differences in salivary cortisol levels.[43] Similar results were also supported by multiple articles.[44-46] By contrast, other studies have demonstrated a significant positive correlation between salivary cortisol levels in both the case and the CG.[47-51] These discrepancies in the literature suggest that individual variations in stress thresholds may contribute to the diverse findings across studies.[52-54]

Regarding IL-1, Ce et al.[32] reported significantly higher levels in patients with TMD alone compared to the CG, irrespective of fibromyalgia assessment. However, IL-1 levels did not differ significantly between the CG and the fibromyalgia groups. This suggests that IL-1 may be specifically associated with TMD rather than fibromyalgia alone. Glutamate levels were found to be significantly higher in the TMD group compared to the CG in the study by Jasim et al.[33] This finding suggests that glutamate dysregulation may play a role in the pathophysiology of TMD. Glutamate is an excitatory neurotransmitter involved in pain signalling, and its elevated levels may contribute to the increased pain perception observed in TMD patients. SAA (serum amyloid A) levels were assessed in several studies. Kobayashi et al.[35] found no significant correlation between SAA levels and TMD, while Khayam et al.[34] reported significantly higher SAA levels in the TMD group compared to the CG. These divergent findings may indicate the need for further investigation into the role of SAA in TMD. PA, DMA, maltose, acetoin and isovalerate were among the biomarkers assessed using H-NMR spectroscopy in the study by Lalue et al.[36] These biomarkers demonstrated consistently more pronounced alterations in the TMD group compared to the CG. The specific implications of these alterations require further exploration, but they suggest potential metabolic and microbial involvement in TMD. Regarding oxidative stress markers, Rodriguez et al.[40] reported significantly higher levels of 8-OHdG, a marker of DNA damage, in the TMD group compared to the CG. By contrast, Lawaf et al.[37] found no significant differences in mean TAC levels between the observed groups. These findings indicate that oxidative stress and DNA damage may be associated with TMD, but the overall antioxidant capacity may not be significantly altered. In terms of pain-related biomarkers, Shoukri et al.[41] assessed multiple biomarkers associated with pain, inflammation and tissue repair. Among these, MMP-3, VE-Cadherin, 6Ckine and PAI-1 were positively expressed and significantly correlated with condylar variance in TMD patients. This suggests their potential involvement in the pathology and tissue remodelling processes associated with TMD.

Previous investigations have conducted comprehensive assessments of distinct biomarkers present in the synovial fluid of individuals affected by internal joint derangement in the TMJ.[55-63] Saliva involves a less invasive approach to evaluating these biomarkers. The study of Mehra et al. involved venipuncture, a minimally invasive procedure involving the insertion of a needle into a vein to collect blood samples, which was employed for biomarker analysis.[64] It is noteworthy that arthrocentesis, another method commonly used for biomarker collection in TMJ studies,

TABLE 4 Biomarkers observed and their correlation observed in the selected articles.

Author	Protocol	Groups assessed	Biomarker assessment method	Biomarkers assessed	TMD and pain assessment method	Results assessed
Venkatesh SB et al[31]	Case–control	TMJ group and control group	ELISA	Cortisol	RDC/TMD Axis I	Salivary cortisol was significantly higher in the TMD group as compare to control group (1.107 ± 0.17 vs. 0.696 ± 0.16)
Ce et al[32]	Case-cohort	TMJ group, non-TMJ CG, fibromyalgia group and fibromyalgia + TMD group	ELISA	IL-1β	RDC/TMD	Regardless of a fibromyalgia assessment, the patients with TMD alone had significantly higher IL-1 levels, whereas the group with fibromyalgia alone did not differ significantly from the CG.
Jasim et al[33]	Case-cohort	TMJ group and non-TMJ CG	ISCUSS, ELISA and ELICA	Glutamate, 5-HT, NGF, BDNF and SP	RDC/TMD and NRS	The TMD group's glutamate levels were found to be considerably greater than those of the CG group.
Khayam et al[34]	Case-cohort	TMJ group and non-TMJ CG	ELISA and Photometric assay	SAA and cortisol	Unspecified	In comparison to the CG, the TMD group had considerably higher levels of cortisol and SAA.
Kobayashi et al[35]	Case-cohort	TMJ group and non-TMJ CG	ELISA and automated assay	SAA and cortisol	RDC/TMD	SAA and cortisol levels were assessed to not be significantly linked to TMD, although anxiety-related symptoms were more severe in the TMD group
Lalue et al[36]	Case-cohort	TMJ group and non-TMJ CG	H-NMR spectroscopy	PA, DMA, maltose, acetoin and isovalerate	RDC/TMD and VAS	PA, DMA, maltose, acetoin and isovalerate concentrations all demonstrated alterations that were consistently more pronounced in the TMD group than the CG.
Lawaf et al[37]	Case-cohort	TMJ group with pain, TMJ group without pain and non-TMJ CG	Spectrophotometric assay	TAC	Unspecified	No significant differences could be reported in terms of differences in mean TAC levels between the observed groups.
Omidpanah et al[38]	Case-cohort	TMJ group and non-TMJ CG	Aebi's technique and MDA assay	Catalase, MDA and TAC	RDC/TMD	MDA levels in saliva were noticeably greater in TMD patients than in the CG. However, there were no appreciable variations between the total antioxidant capacity and catalase levels of TMD patients and healthy controls.
Ornek et al[39]	Case-cohort	TMJ group and non-TMJ CG	ELISA	Cortisol, IL-1β, TNF-α and MMP-3	RDC/TMD	Although not significantly greater, cortisol and depression/anxiety were higher in the study group. Additionally, there was no discernible difference in the levels of TNF-, IL-1 and MMP-3 between the two groups.
Rodríguez et al[40]	Case-cohort	TMJ group and non-TMJ CG	ELISA	TAC, 8-OHdG and MDH	RDC/TMD, PI and SSI scores	Only 8-OHdG was observed to be statistically higher in the TMD group than the CG, with the other two biomarkers exhibiting nonsignificant differences between the assessed cohorts.
Shoukri et al[41]	Case-cohort	TMJ group and non-TMJ CG	HQPM	6Ckine, ANG, BDNF, CXCL16, ENA-78, GM-CSF, IFN-γ, IL-1α, IL-6, MMP-3, MMP-7, PAI-1, TGF-β1, TIMP-1, TNF-α, VEC and VEGF	RDC/TMD and VAS	MMP-3, VE-Cadherin, 6C-Kine and PAI-1 were positively expressed and significantly correlated to condylar variance in TMD patients among all the biomarkers evaluated.

necessitates intravenous or general anaesthesia, along with continuous monitoring of respiratory function throughout the procedure.[65,66] Both venipuncture and arthrocentesis carry a potential risk of complications such as swelling, hematoma formation and potential nerve or mucosa damage.[42,65,66] Hence, biomarker assessment in saliva gives it a great edge when compared to other body fluids. Despite the valuable insights gained from this investigation, it is essential to acknowledge and address the limitations inherent in the study. These limitations can impact the generalizability and robustness of the findings and should be taken into consideration when interpreting the results. One limitation of this study lies in the heterogeneity of the included studies. The selected studies employed different protocols, biomarker assessment methods and TMD and pain assessment techniques. This heterogeneity introduces variations in the study designs, sample sizes, demographics and methodologies used, making it challenging to directly compare the findings and draw definitive conclusions. Another limitation pertains to the sample sizes of the included studies. Some studies had relatively small sample sizes, which may limit the statistical power and precision of the findings. Small sample sizes can also increase the risk of selection bias and limit the generalizability of the results to larger populations. Additionally, the studies varied in their demographic characteristics, such as age, sex ratio and geographic region, which may further affect the generalizability of the findings to other populations with different demographic profiles. Lastly, the reliance on salivary biomarkers as indicators of TMDs has its own limitations. Saliva samples may not fully capture the complex multifactorial nature of TMDs, as these disorders involve a combination of genetic, environmental, psychological and behavioural factors. Additionally, saliva samples may be influenced by various factors, such as time of collection, stress levels, oral health and medication use, which can introduce variability and confound the interpretation of biomarker levels.

5 | CONCLUSION

This review reveals intriguing correlations and variations in the expression of salivary biomarkers among individuals with TMDs compared to CG, shedding light on potential underlying mechanisms and offering insights into TMD pathophysiology. However, the review also identifies limitations, including heterogeneity among studies, small sample sizes, potential publication bias, retrospective design and the inherent limitations of relying solely on salivary biomarkers. These limitations call for further research with standardised methodologies, larger sample sizes, longitudinal designs and consideration of multiple factors influencing TMDs. Moreover, continued research in this field will advance our knowledge and facilitate the development of more precise diagnostic tools and targeted treatments for individuals with TMDs.

Salivary biomarkers have emerged as invaluable tools for revolutionising oral health assessment and care. These intricate molecules, secreted within the oral cavity, wield the power to reveal hidden tales of disease, risk and treatment response. Their ability to detect early signs of oral cancer and precancerous lesions heralds a new era of timely interventions, potentially saving countless lives. They also offer a window into the microbial world of periodontal diseases, aiding in diagnosis and gauging treatment effectiveness. Furthermore, they serve as sentinels, monitoring the progression of oral infections and illuminating the efficacy of therapeutic regimens. Salivary biomarkers contribute to personalised care by shaping orthodontic treatments and dental implant success by assessing individual responses to interventions. Their significance extends to the realm of medication monitoring and lifestyle assessment, enabling tailored plans for medication dosages and nutritional recommendations. As these molecular messengers traverse the bridge between basic research and clinical practise, they pave the way for a more holistic, precise and patient-centred approach to oral health management.

AUTHOR CONTRIBUTIONS

Giuseppe Minervini was involved in conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing—original draft preparation, writing—review and editing and supervision. Mohammad Khursheed Alam was involved in conceptualization, software, validation and formal analysis. Mahmud Uz Zaman was involved in writing—original draft preparation and visualisation. Nasser Raqe Alqhtani was involved in investigation and data curation. Abdullah Saad Alqahtani was involved in writing—review and editing and supervision. Fawaz Alqahtani and Marco Cicciù were involved in writing—review and editing and supervision. All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

All data described in the study are presented in the manuscript. The datasets analysed are available from the corresponding author on reasonable request

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