ORIGINAL RESEARCH

Synergistic Application of *Psidium Guajava* in the Periodontal Management of Diabetic Patients: Influence on Orosomucoid Expression in Gingival Crevicular Fluid

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Abstract

Introduction: Diabetes mellitus has been unequivocally confirmed as a major risk factor for Periodontitis. Periodontal disease and diabetes exhibit a bidirectional interplay with elevated inflammatory biomarkers exacerbating the severity of both conditions. Phytotherapy has emerged as a promising adjunct in periodontal disease management, particularly in diabetic patients, where inflammation-driven tissue destruction is exacerbated.

Aim: To formulate and evaluate guava leaf extract and assess its therapeutic effects on orosomucoid levels in periodontitis patients with diabetes mellitus.

Materials And Methods: A total of 40 patients were enrolled in the study. A Psidium guajava leaf extract-based periodontal film was developed and used as an adjunct to therapy. Among the study groups, Group 1 received Scaling and Root Planing (SRP) alone, while Group 2 received SRP with the guava leaf extract chip. Clinical parameters and Glycosylated Hemoglobin (HbA1c) levels were recorded for both groups. Clinical parameters and orosomucoid levels were reassessed one-month post-treatment and compared with baseline values.

Results: Comparative analysis revealed that the group that received periodontal therapy with the Psidium guajava film had exhibited statistically significant improvements only in the gingival index, glycosylated hemoglobin, and orosomucoid levels ($P \leq .000$, .000, and .001, respectively).

Conclusion: The adjunctive use of Psidium guajava leaf extract along with scaling and root planing demonstrated favourable improvement in periodontal clinical parameters and reduction in orosomucoid levels among diabetic patients with periodontitis. These findings suggest a possible adjunctive anti-inflammatory role of Psidium guajava leaf extract in periodontal therapy.

Keywords: Psidium guajava, Periodontitis, Diabetes Mellitus, orosomucoid, Gingival crevicular fluid

Introduction

Periodontal disease is a chronic inflammatory condition affecting the supporting structures of teeth, leading to irreversible damage such as attachment loss, periodontal ligament breakdown, and alveolar bone resorption. While subgingival biofilm accumulation initiates periodontitis, disease susceptibility is influenced by various factors beyond plaque levels. Among these, diabetes is a key environmental risk factor.[1] Diabetes, a metabolic disorder marked by hyperglycaemia, significantly amplifies periodontitis risk, with severity correlating to glycaemia control. Studies estimate that individuals with diabetes face a 2–3 times higher likelihood of developing periodontitis, similar to the increased risk observed in other diabetes-related complications.[2]

Periodontal disease and diabetes mellitus (DM) are chronic, multifactorial, and inflammation-driven conditions that frequently coexist, sharing a complex interplay of risk factors. These include advancing age, male gender, genetic predisposition, socioeconomic disparities, racial and ethnic

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background, smoking, excessive alcohol consumption, poor diet, obesity, physical inactivity, and stress.[3] Diabetes not only heightens the prevalence, severity, and extent of periodontitis but also worsens its progression. Mounting evidence supports a bidirectional relationship between the two, with diabetes compromising periodontal health and severe periodontitis contributing to poor glycaemic control, underscoring the need for an integrated, multidisciplinary approach to managing both conditions effectively.[4]

The intricate mechanisms intertwining diabetes and periodontitis remain incompletely elucidated, encompassing dysregulated inflammation, altered immune modulation, aberrant neutrophil dynamics, and cytokine perturbations.[5] Moreover, limited empirical evidence exists regarding differential therapeutic outcomes in diabetic versus non-diabetic periodontitis patients.

Psidium guajava emerging as a widely utilized oral insulin substitute. Periodontal therapy aims to resolve inflammation, reduce pathogens, and regulate host responses. While mechanical debridement and chemotherapeutic agents are standard treatments, the latter poses risks of toxicity and bacterial resistance.[6] Emerging research in phytosciences highlights medicinal plants with antimicrobial properties, offering safer therapeutic alternatives. These bioactive secondary metabolites present promising potential for periodontal and diabetic management with minimal side effects and reduced toxicity.

Guava leaves harbour two pivotal flavonoids - quercetin, renowned for its spasmolytic, antioxidant, antimicrobial, and anti-inflammatory properties, and guaijaverinrecognized for its potent antibacterial efficacy.[7,8] Quercetin exhibits remarkable antibacterial activity against periodontal pathogens, while flavonoid derivatives impede bacterial proliferation by disrupting membranes and forming irreversible complexes with extracellular proteins.[9] Guava's anti-inflammatory properties stem from its inhibition of prostaglandins, kinins, and histamines, making it a potential therapeutic candidate.[10]

Orosomucoid (ORM), also referred to as alpha-1-acid glycoprotein (AAG), is an acute-phase protein comprising 1–3% of total plasma proteins, with normal concentrations ranging from 0.6 to 1.2 mg/mL.[11] While predominantly synthesized in hepatocytes, it is also found in extrahepatic tissues, particularly white adipose tissue. As a critical inflammatory mediator, ORM is upregulated by IL-1, TNF-α, and IL-6. It modulates immune responses by inhibiting lymphocyte proliferation, platelet aggregation, and neutrophil chemotaxis.12Given periodontitis induced localized inflammation and diabetes mellitus associated systemic inflammatory involvement, ORM serves as a crucial biomarker, providing valuable insights into immune dysregulation and disease progression.

Hence, this study aims to evaluate Psidium guajava leaf extract as an adjunct to nonsurgical periodontal therapy in patients with periodontitis and diabetes mellitus, hypothesizing that it may enhance clinical outcomes by mitigating inflammation and regulating the inflammatory marker orosomucoid in gingival crevicular fluid.

Table 1: Comparison of variables before and after therapy in the SRP group

VARIABLES		GROUP 1 (BASELINE) n = 20	GROUP 1A (SRP) n = 20	Effect Size	95% Confidence Interval	r VALUE	p VALUE
AGE	Mean ± SD	42.80 ± 2.700					
GENDER		Female : 8, male : 12					
PI	Mean ± SD	2.670 ± .6019	1.730 ± .3653	1.89	0.62 – 1.26	.090	**0.002**
GI	Mean ± SD	2.210 ± .3957	1.670 ± .3093	1.52	0.31 – 0.77	.275	**0.003**
BOP	Mean ± SD	2.610 ± .2644	1.520 ± .1874	4.76	094 – 1.24	-.139	**<0.001**
PPD	Mean ± SD	5.610 ± .5507	3.230 ± .3889	4.99	2.07 – 2.69	.590	**<0.001**
CAL	Mean ± SD	4.510 ± .5384	2.420 ± .3259	4.70	1.81 – 2.37	.632	**<0.001**
HbA1c	Mean ± SD	8.970 ± 1.345	7.780 ± 1.190	0.94	0.38 – 2.00	.943	**<0.001**
ORM	Mean ± SD	2.490 ± .6284	1.740 ± .3944	1.43	0.41 – 1.09	.390	**0.003**

*p-Value ≤ 0.01: Statistically significant, SD –Standard Deviation, r- correlation coefficient, PI – Plaque index, GI – Gingival index, BOP – Bleeding on probing, PPD – Probing Pocket Depth, CAL – Clinical Attachment Loss, HbA1c-Glycosylated haemoglobin, ORM – Orosomucoid.

Materials and Methods

The sample size was calculated using G*Power software, assuming a clinically significant effect size of 0.8. With an alpha error probability of 0.05, a power of 80%, and an equal allocation ratio of 1:1, the final sample size was determined to be 20 participants per group. Prior to the commencement of the study, ethical approval was obtained from the Institutional Ethics Committee (TMDCH/No. 106/2023/2/IEC), and informed consent was secured from all participants

A total of 40 patients who visited the Outpatient Department (OPD) of the Department of Periodontology were screened for study enrollment. Patients aged between 25 to 56 years with a diagnosis of periodontitis and diabetes mellitus were included. Participants were randomized using a lottery-based odd-even allocation method, wherein participants drawing odd numbers were assigned to Group I and those drawing even numbers were assigned to Group II.

Inclusion and Exclusion Parameters of the Study Groups

Group 1 and Group 2 included patients diagnosed with Stage 2 or Stage 3, Grade B periodontitis, characterized by an interdental Clinical Attachment Loss (CAL) of ≥5 mm. Hemoglobin A1C (HbA1c) levels were 6.5% or higher.

Group 1 will receive Scaling and Root Planing (SRP) as periodontal therapy. Baseline and post-operative values will be categorized as Group 1 and 1A, respectively.

Group 2 will receive SRP along with a Psidium guajava leaf extract chip. Baseline and post-treatment values will be categorized as Group 2 and 2A, respectively.

The exclusion criteria encompassed individuals with a history of periodontal surgeries or procedures within the past six months, those undergoing antibiotic therapy, pregnant individuals, smokers, alcohol consumers, and patients with systemic conditions or diseases

Clinical Parameters

The assessment parameters included the Plaque Index (Silness and Loe, 1964), Gingival Index (Loe and Silness, 1963), Bleeding on Probing (BOP), Probing Pocket Depth (PPD), and Clinical Attachment Level (CAL), all measured using a williams periodontal probe. Additionally, HbA1c levels were documented to evaluate systemic glycaemic status.

Clinical Procedure

Periodontal films were developed using the solvent casting technique. Chitosan (2% w/v) was dissolved in 1% aqueous acetic acid, left for 24 hours, and filtered. Copolymers HPMC K4M and sodium CMC (10%, 20%, and 30% w/w of chitosan) were added and stirred until dissolved. Propylene glycol was introduced as a plasticizer, followed by guava extract. After eliminating air bubbles, the solution was poured into aluminium-lined Petri dishes and dried for 24 hours. The dried films were cut, wrapped in aluminium foil, and stored in a desiccators for further analysis as seen in Fig 1.

Group 1 underwent meticulous scaling and root planing (SRP), while Group 2 received SRP supplemented with the insertion of a Psidium guajava-derived chip into the pathologically deepened periodontal pocket, secured with a periodontal dressing. Gingival crevicular fluid (GCF) samples were aseptically collected at baseline and one month post-therapy using micro capillary tubes. Orosomucoid levels in GCF were quantified using a highly sensitive ELISA molecular assay, utilizing a commercially available kit from Hangzhou

Table 2:Comparison of variables before and after therapy in the SRP group with guava leaf extract chip

VARIABLES		GROUP 2 (BASELINE) n = 20	GROUP 2A (SRP +CHIP) n = 20	Effect Size	95% Confidence Interval	r VALUE	p VALUE
AGE	Mean ± SD	38.90 ± 3.107					
GENDER		Females: 8, Male: 12					
PI	Mean ± SD	2.280 ± .2440	1.280 ± .2150	4.35	0.85 – 1.15	.457	**<0.001**
GI	Mean ± SD	2.800 ± .2539	1.400 ± .1414	6.79	1.24 – 1.56	.248	**<0.001**
BOP	Mean ± SD	2.560 ± .2366	1.590 ± .1449	4.95	0.84 -1.10	.700	**<0.001**
PPD	Mean ± SD	4.410 ± .5801	2.290 ± .4630	4.03	1.76 – 2.48	.062	**<0.001**
CAL	Mean ± SD	4.030 ± .7166	2.130 ± .5458	2.98	1.48 – 2.32	.799	**<0.001**
HbA1c	Mean ± SD	9.130 ± .6783	6.690 ± .5322	4.00	2.04 – 2.84	.963	**<0.001**
ORM	Mean ± SD	2.745 ± .7099	.6209 ± .3701	3.80	1.61 to 2.64	.647	**<0.001**

*p-Value ≤ 0.01: Statistically significant, SD –Standard Deviation, r- correlation coefficient, PI – Plaque Index, GI – Gingival Index, BOP – Bleeding on Probing, PPD – Probing Pocket Depth, CAL – Clinical Attachment Loss, HbA1c-Glycosylated haemoglobin, ORM-Orosomucoid.

Eastbiopharm Company, Zhejiang, China. The results were expressed in nanograms per milliliter (ng/mL) as seen in Fig. 2 and Fig. 3.

Statistical Analysis:

Statistical analysis was conducted using IBM SPSS Statistics (Version 26.0). Descriptive statistics, including mean and standard deviation, were calculated. Data normality was confirmed using the Kolmogorov-Smirnov test, allowing for parametric tests. Paired samples t-tests compared baseline and post-treatment values, while Pearson's correlation assessed paired sample relationships. Group comparisons utilized independent samples t-tests, with significance set at $p < 0.05$

Results

A comparative evaluation of baseline values in Group 1 with post-treatment values in Group 1A (scaling and root planing alone) exhibited a statistically significant enhancement across all the clinical parameters ($p \leq 0.001$), along with a very strong positive correlation with HbA1c ($r = 0.943$) as shown in Table 1.

Similarly, participants in Group 2 demonstrated substantial post-treatment improvements in Group 2A (scaling and root planing with guava chip insertion) when compared with the baseline values, with significant amelioration of clinical parameters ($p \leq 0.001$) as shown in Table 2. A very strong positive correlation was observed for HbA1c ($r = 0.963$), a strong positive correlation for clinical attachment loss ($r = 0.799$), and a moderate-to-strong positive correlation for orosomucoid levels ($r = 0.647$).

Additionally, intergroup comparison between Group 1A (SRP alone) and Group 2A (SRP with guava chip insertion) revealed statistically significant differences in the gingival index, HbA1c, and orosomucoid levels ($p < 0.001$), whereas the remaining parameters did not demonstrate statistical significance, as shown in Table 3 and Fig. 4.

These findings underscore the potential of incorporating guava chips as an adjunct to nonsurgical periodontal therapy. By significantly reducing gingival inflammation, lowering HbA1c levels, and modulating orosomucoid levels, guava chips may help regulate periodontal inflammation and improve overall treatment outcomes.

Discussion

This study incorporated guava extract into a novel localized drug delivery system to investigate its impact on periodontal inflammation. A comparative assessment of baseline clinical parameters in Group 1 (pre-treatment) and post-treatment values in Group 1A (SRP alone) exhibited statistically significant enhancements ($p \leq 0.001$). These results highlight the effectiveness of periodontal therapy. The strong correlation observed with HbA1c, reinforcing the systemic benefits of periodontal treatment by improving the glycaemic control.

These results correspond with the findings of Kiran et alwho documented substantial improvements in periodontal health parameters and a notable decline in HbA1c levels three months post-intervention.[13] The study concluded that nonsurgical periodontal therapy plays a pivotal role in enhancing metabolic regulation in diabetic individuals. Furthermore, a Cochrane review by Simpson T.C reported an approximate 0.4% reduction in HbA1c following nonsurgical periodontal therapy, reinforcing its significance in glycemic modulation.[14] Nonsurgical periodontal therapy, primarily targeting microbial reduction, remains an effective strategy for optimizing clinical periodontal outcomes.

In this study, a comparative analysis of baseline clinical parameters, HbA1c levels, and orosomucoid concentrations in Group 2 patients with post-treatment values in Group 2A (SRP with Guava chip) demonstrated statistically significant enhancements across all measured variables ($p \leq 0.001$). A strong correlation was observed in HbA1c, Clinical attachment loss suggesting that SRP along with chip not only improves periodontal parameters but significantly impacts

Table 3: Comparison of variables between SRP and SRP + Chip treatments

		Mean Diff.	Std. error	95% Confidence Interval		p VALUE
				LB	UB	
PI	Group 1A VS Group 2A	.9400	.21354	.4569	1.4231	0.089
GI	Group 1A VS Group 2A	-.86000*	.14933	-1.2622	-.4578	**<0.001**
BOP	Group 1A VS Group 2A	.12000	.13447	-.2422	.4822	0.809
PPD	Group 1A VS Group 2A	.26000	.25303	-.4215	.9415	0.735
CAL	Group 1A VS Group 2A	.19000	.19415	-.3329	.7129	0.762
HbA1C	Group 1A VS Group 2A	-1.25000*	.27136	-1.9808	.963	**<0.001**
ORM	Group 1A VS Group 2A	-1.37390*	.31998	-2.2357	-.5121	**0.001**

*p-Value ≤ 0.01: Statistically significant, p-value > 0.05: Non-significant, SD - Standard deviation, LB-Lower bound, UB- Upper bound, PI -Plaque Index, GI -Gingival Index, BOP-Bleeding on Probing, PPD – Probing Pocket Depth, CAL -Clinical Attachment Loss, ORM -Orosomucoid.

systemic glycemic control. Additionally Orosomucoid levels showed positive correlation indicating regulation of local inflammation. These observations are consistent with the findings of Ongoz Dede, F. (2018), who reported significantly increased orosomucoid concentrations in the saliva of chronic periodontitis patients compared to healthy individuals.[15]

To further substantiate these results, a comparison was made with analogous studies investigating the efficacy of other herbal adjuncts in periodontal therapy. Warad et al. assessed the therapeutic potential of locally administered 2% lemongrass essential oil alongside SRP for chronic periodontitis, while Tewari et al. explored the subgingival application of Emblica officinalis (Amla) sustained-release gel as an SRP adjunct.[16,17] These studies underscore the increasing interest in phytotherapeutic agents as complementary interventions for periodontal disease and provide a comparative foundation for our findings.

Following periodontal therapy and the adjunctive use of a guava leaf extract chip, the present study observed a statistically significant reduction in the inflammatory marker orosomucoidand HbA1c levels. These findings align with previous studies conducted under similar conditions. Deguchi and Miyazaki reported that guava leaf infusion effectively reduced postprandial glycaemia and improved hyperinsulinemia in murine models.[18] Additionally, Dutta and Das demonstrated the significant anti-inflammatory properties of ethanol extracts derived from guava leaves in experimental models.[19] Furthermore, El-Beblawy identified a notable increase in serum and urinary orosomucoid levels among children and adolescents with type 1 diabetes, highlighting its relevance as a biomarker.[20]

Although the observed reduction in HbA1c may seem modest, its clinical significance is substantial, as even a 1% decrease in HbA1c has been associated with a significantly lower risk of diabetes-related complications. The impact of periodontal therapy on glycaemic control is often reflected in improvements in periodontal inflammation parameters.

In the present study, a comparative analysis between Group 1A (SRP alone) and Group 2A (SRP with the adjunctive application of a guava chip) demonstrated statistically significant differences in the gingival index, HbA1c, and orosomucoid levels (p = 0.000, 0.001, and 0.000, respectively).

Fig 1:(A-F) Formulation and Preparation of Psidium guajava leaf extract-based chip

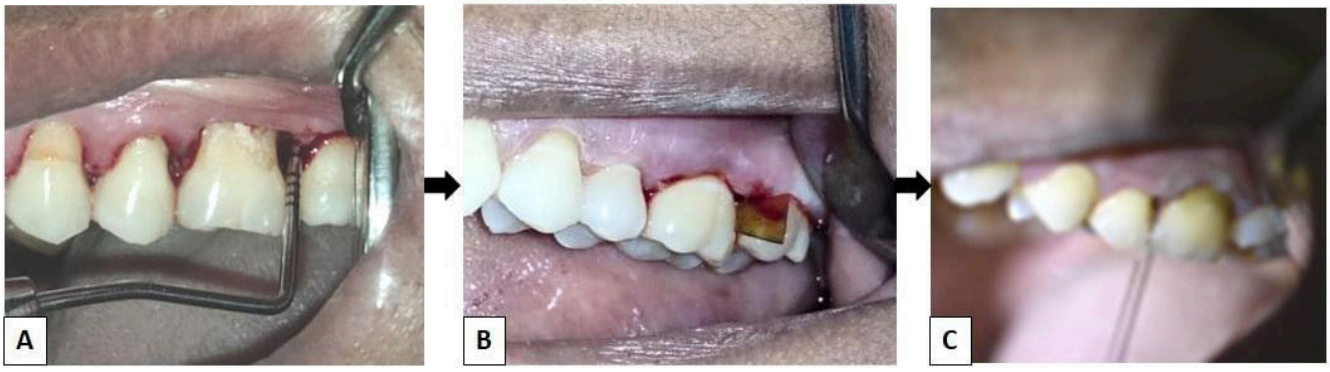

Fig. 2:(A-C) Deepest periodontal probing pocket depth, Placement of Guava leaf extract chip, Collection of GCF

SRP with the guava chip showed significantly better outcomes in reducing gingival inflammation (GI), improving glycaemic control (HbA1c) and lowering orosomucoid levels in GCF, there by suggesting periodontal therapy along with gauva leaf extract may provide added benefits in regulating local inflammation and systemic glycaemic control.

These results align with the findings of Manohar Sharma et al. (2021), who investigated the efficacy of a 3% Psidium guajava formulation as a localized drug delivery system for managing chronic periodontitis using saliva samples.21 Their study reported substantial improvements across various clinical parameters, reinforcing the therapeutic potential of guava-based adjuncts in periodontal treatment.

Psidium guajava (guava) is a potent phytotherapeutic agent with anti-inflammatory, antimicrobial, antioxidant, and antihyperglycemic properties. Its phenolic compounds, including quercetin and guaijaverin, contribute to inflammation reduction by inhibiting prostaglandins, kinins, and histamines.[22] The observed decrease in orosomucoid levels post-treatment highlights guava's therapeutic potential, attributed to its rich composition of polyphenols, triterpenoids, and bioactive molecules that effectively modulate inflammatory responses. Beyond its anti-inflammatory effects, guava is rich in vitamin C (ascorbic acid), which is essential for fibroblast differentiation, extracellular matrix modulation, and collagen synthesis through procollagen gene regulation. When combined with bioflavonoids, vitamin c accelerates wound healing, potentially accounting for the significant clinical improvements observed in this study.[23]

To the best of our knowledge, no prior research has explored the application of Psidium guajava (guava) in the form of a localized drug delivery chip for the management of chronic periodontitis in diabetic patients, underscoring the novelty and clinical significance of this investigation.

Furthermore, a large cohort study demonstrated that elevated orosomucoid levels are associated with the onset of diabetes mellitus in middle-aged adults.[24] More recently, an animal study suggested that orosomucoid may contribute to reduced neutrophil migration and increased susceptibility to sepsis in diabetic mice.[25] Given these findings, diabetes may act as a confounding factor in the relationship between elevated orosomucoid levels and periodontitis, particularly in obese patients with impaired neutrophil function.[26,27]

Orosomucoid (ORM) serves as a robust and independent biomarker for assessing disease activity, primarily due to its sensitivity in reflecting the inflammatory milieu of periodontal disease. Its immunomodulatory capacity arises from interactions with lymphocytes and pro-inflammatory cytokines. ORM levels escalate three- to fourfold post-inflammation, underscoring its significance in chronic inflammatory pathophysiology. Additionally, neutrophils and monocytes synthesize ORM, amplifying its systemic elevation in conditions such as sepsis.

The findings of this study highlight the role of orosomucoid (ORM) as a key biomarker in periodontal inflammation. The observed reduction in ORM levels following treatment suggests a modulation of the inflammatory response, reinforcing its utility in assessing disease activity. ORM's association

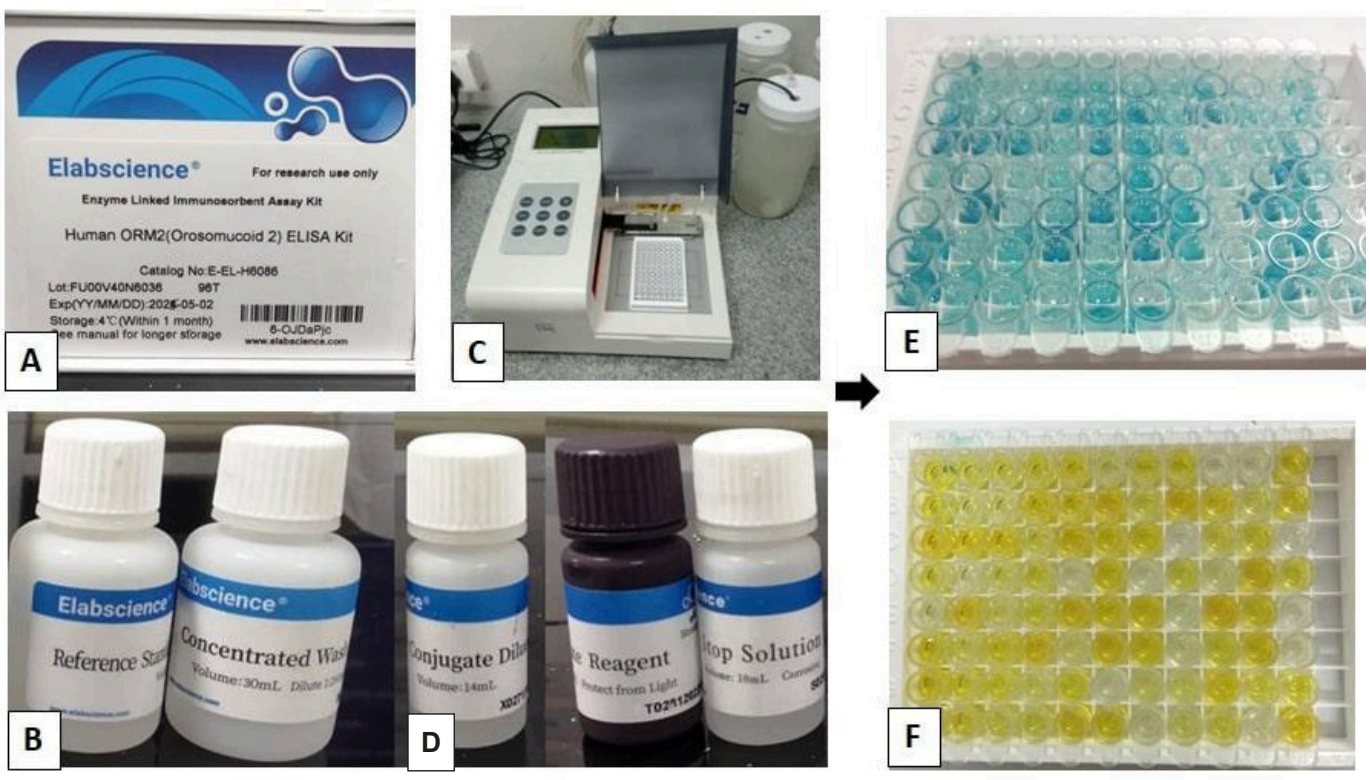

Fig. 3: Assessment of orosomucoid levels through enzyme-linked immunosorbent assay (ELISA)

with lymphocytes and pro-inflammatory cytokines further supports its involvement in periodontal pathophysiology. Given that ORM levels typically rise three- to fourfold during inflammation, its decline post-treatment indicates a positive therapeutic effect.[25] Additionally, as neutrophils and monocytes contribute to its synthesis, the reduction in ORM may also reflect improved immune regulation, aligning with the overall clinical improvements observed in this study.[28]

A study by Rangé et al. observed that plasma ORM levels were significantly elevated in patients with severe periodontitis compared to those with mild to moderate periodontitis in obese individuals.[29] The researchers suggested that the severity of periodontitis is associated with increased ORM levels in obese patients. The importance of effective periodontal therapy is particularly pronounced in individuals with diabetes, as periodontitis is known to exacerbate glycemic dysregulation and contribute to diabetes-related complications. Notably, periodontal treatment has been associated with measurable improvements in HbA1c levels.

Thus, periodontal therapy not only mitigates local inflammation but also reduces systemic inflammatory mediators implicated in insulin resistance, thereby enhancing glycemic control when complemented with phytotherapeutic interventions. The adjunctive use of phytotherapy, such as guava extract, may further potentiate these benefits by exerting anti-inflammatory, antimicrobial, and antioxidative effects, contributing to improved periodontal and systemic health outcomes.

However, this study has certain limitations. The relatively small sample size may constrain the broader applicability of the findings. Additionally, the precise mechanisms by which guava extract influences orosomucoid levels and interacts with periodontal pathogens were not extensively elucidated. These limitations underscore the necessity for further research to validate and expand upon these findings.

The bidirectional relationship between diabetes and periodontal disease supports the concept of a reciprocal interaction. Diabetes contributes to periodontal disease susceptibility and progression both directly by inducing systemic and localized inflammation and indirectly by impairing immune cell function and disrupting tissue homeostasis thereby increasing vulnerability to periodontal destruction.

Conclusion

Guava has been revered for its medicinal attributes since antiquity, exhibiting a vast spectrum of pharmacological properties, including antimicrobial, antidiarrheal, antiparasitic, antitussive, antigenotoxic, antimutagenic, antiallergic, anthelmintic, hepatoprotective, and antioxidant activities. The present study furnishes preliminary evidence underscoring the potent anti-inflammatory efficacy of guava leaf extract. Its integration as an adjunct to conventional pharmacotherapeutics presents a cost-effective and pragmatic alternative to synthetic drugs. Furthermore, its therapeutic potential in mitigating periodontitis in individuals with diabetes mellitus is

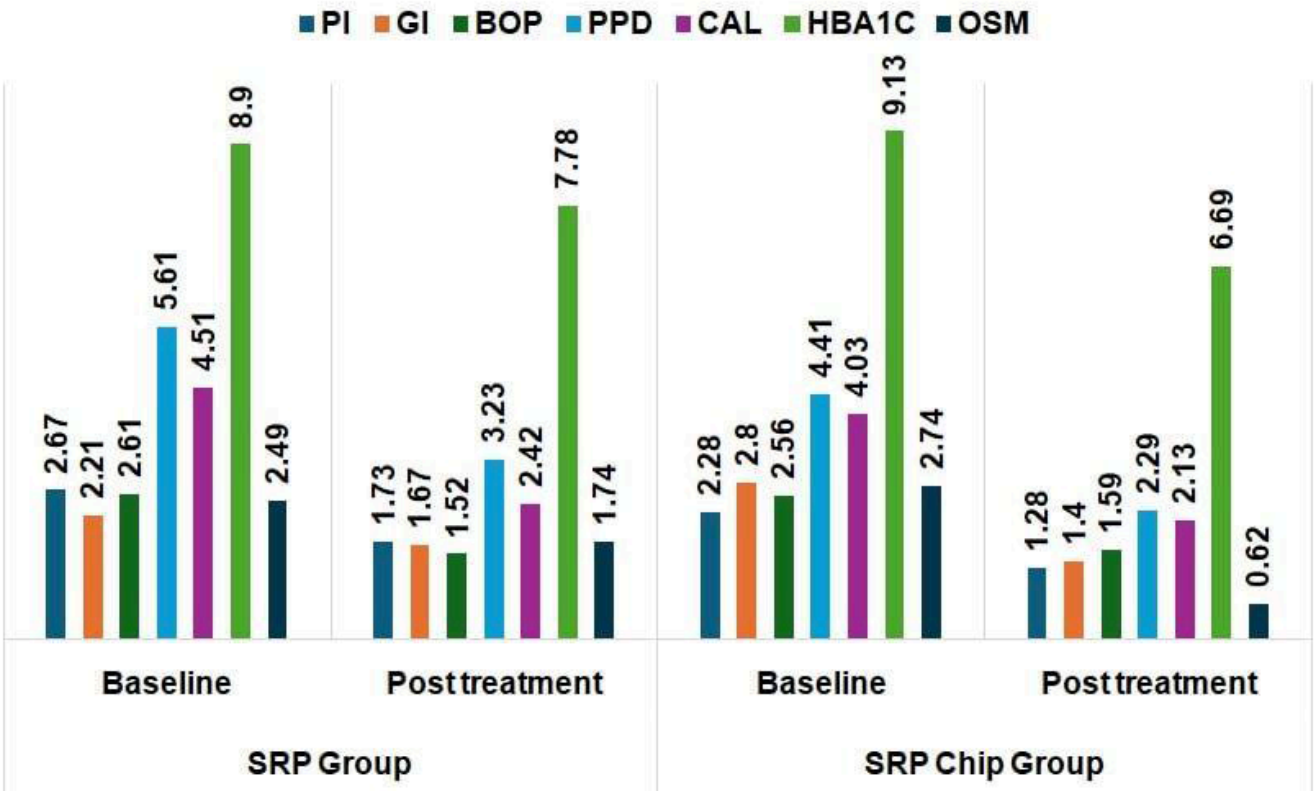

Fig. 4: Comparison of variables in the study groups

particularly noteworthy, as it modulates inflammatory cascades by regulating orosomucoid levels in gingival crevicular fluid, thereby contributing to periodontal and systemic homeostasis.

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