Manuscript (66).docx

WORD COUNT 4040
TIME SUBMITTED 02-NOV-2022 02:41PM
PAPER ID 92202675

Title: Evaluating the efficacy of Centella asiatica on enhancement of oral health status in hyperglycemic patients - A Randomized clinical trial

Short title: Efficacy of Centella Asiatica in hyperglycemic patients

Aim: The aim of the study was to evaluate the oral secretagogue, anti-microbial and immunomodulatory properties of *Centella asiatica* in patients with type II diabetes mellitus.

Materials and methods: In-vivo and In- vitro assessment was conducted for a period of 3 months. A before and after trial for a period of 3 months of intervention was performed involving 20 participants. Unstimulated Saliva and gingival crevicular fluid (GCF) samples was collected from all the participants before and after the intervention period. The effectiveness of Centella asiatica was estimated by evaluating the pre and post intervention values of salivary flow rate, salivary pH , S.mutans count, GCF flow rate, neutrophils count and alpha 1 defensin levels.

Results: This clinico-interventional study inferred that after the usage of aqueous extract of Centella asiatica mouth wash, there was a high statistically significant improvement in the GCF flow rate, GCF neutrophil count and alpha 1 defensin levels from baseline to 90thday (after 3 months) (P=0.001). The salivary flow rate, salivary pH and S.mutans colony count showed no statistically significant difference.

Conclusion: The outcome of the current study enlightens the utility of ethnomedicinal plants and their usage, it is also helpful in enhancement of oral health status in hyperglycemic conditions. The current study concluded that rinsing twice with aqueous extract of ***Centella asiatica*** as mouth rinse for a period of 3 months has an immunomodulatory action.

Clinical significance: Centella asiatica mouthwash can be used as an immunomodulatory agent.

Keywords: Alpha 1 defensin levels, Centella asiatica ,Diabetes mellitus, Gingival crevicular fluid (GCF), Saliva

1.Introduction:

Diabetes mellitus (DM) is a significant global health issue and regarded as a Global Epidemic with more number of individuals affected worldwide. In a survey conducted by Kaveeshwar in the year 2014, India currently has 61 million people with diabetes and will soon become the Diabetic Capital of the world.(Kaveeshwar and Cornwall 2014) The Asian-Indian Phenotype of diabetes is defined by a younger age of development, decreased body mass index, and greater insulin resistant in Asian Indians.(Mohan et al. 2007)

In addition to many of the systemic complications, DM causes significant oral manifestations that occur more often than in normal patients, such as gingivitis, periodontal diseases, decreased salivary flow rate and decreased oral pH. Moreover, the severity of diabetic complications is directly proportional to the duration and degree of hyperglycaemia.(Kripal K. 2017) The potential pathways that could be linked to these oral complications include elevated collagenase enzyme activity, neuropathy, impaired neutrophil function, inadequate collagen synthesis and microangiopathy.

Recently, harmonizing alternative medicine has become more popular due to the natural way of curing various maladies. Traditional herbal products are an ancient treatment technique and are gaining importance in the research world and plant based drugs have been in existence ever since the inception of mankind. Phytochemicals have been shown to possess excellent activity against a variety of diseases. This, combined with the reduced to nil side effects makes them an excellent alternative to allopathic system of medicine. Several plant products have been shown to possess anti-inflammatory, anti-oxidant, immunomodulatory and anti-microbial properties.(Biswas et al. 2021)

Centella asiatica* (CA)**, a perennial, clonal herbaceous creeper with its regional name ***Gotu kola belongs to the family *Umbellifere (Apiceae)*. This particular herb belongs to Kingdom- plantae, Division- Magnoliophyta, Class- Mangoliospida, Order- Apiales, Family - Apiaceae, Genus- Centella and Species- asiatica. It has proven to possess anti-degenerative potential and it has been utilised as a medicinal drug in the treatment of "Alzheimer's disease" and in memory enhancement.(Chandrika and

Prasad Kumarab 2015) It is also used to treat diabetes mellitus, improve wound healing, and improve venous insufficiency. In a recent (Prakash, Jaiswal, and Srivastava 2017)t study, it was found that it has an potency to improve the oral hygiene in poorly controlled diabetes mellitus by increasing the collagen synthetase activity and hastens the immunomodulatory mechanism. The other multifarious properties of this herb are it is used as a topical therapy for ulcers and wounds. It has various medicinal benefits like anti-oxidant activity, anti-inflammatory, wound healing, chronic venous insufficiency, anxiolytic property, for Alzheimer's disease, for treating diabetes and it is also used to treat ulcers and varicose veins.(Prakash, Jaiswal, and Srivastava 2017)

The main aim of this study is to evaluate the secretagogue, the antimicrobial and immunomodulatory properties of Centella asiatica (CA) and to determine its efficacy on improving the oral health status in patients with type 2 diabetes mellitus. The objectives of the current study is that , to evaluate the efficacy of Centella asiatica on salivary flow rate, salivary pH and bacterial colony count in patients with poorly uncontrolled type II diabetes mellitus and to evaluate the efficacy of Centella asiatica on gingival crevicular fluid flow rate, gingival crevicular fluid neutrophil count, gingival crevicular fluid alpha 1 defensin level in patients with type II diabetes mellitus.

2.Materials and Methods:

A single group randomized controlled interventional (pre and post- intervention) study was conducted among patients with poor oral health status in hyperglycemic participants. However, a control group was not included in the current study as a healthy population (without periodontitis, gingivitis) in a similar age group as that of the study population could not be identified. The ethical clearance was given by the Institutional Review Board, SRM University, Chennai, India (Ref no: SRMDC/IRB/2019/MDS/No.601). Before the intervention, all the recruited participants were explained about the study and informed consent was obtained. This study was conducted at SRM dental college. The participants were included as per the following **inclusion criteria**: Participants with history of poorly controlled type 2 diabetes mellitus for past 5years, participants between the ages of 35 and 70,

of any gender, type 2 diabetes mellitus participants with Russell's periodontal index grade 3 [Periodontal pocket- 4 to 5mm depth] and Decayed, Missing due to caries and Filled teeth (DMFT) index moderate category [WHO moderate (2.7-4.4)]. The **exclusion criteria** were: History of any oral topical therapy, presence of any systemic illness other than type 2 diabetes mellitus and presence of adverse oral habits. Using the sample size calculator (G*Power version 3.1.9.2), a minimum sample size of 10 was calculated. In addition, 10 more were added to compensate for any drop outs and hence, the total sample was 20. The study participants were poorly uncontrolled type 2 diabetes mellitus patients who were recruited as per the above-mentioned criteria.

2.1. Preparation of Centella asiatica Extract:

Centella asiatica leaves were shade dried and was milled to fine powder. To prepare the aqueous extract, 75g of Centella asiatica powder (12.5 µg/ml concentration) were dissolved in 500 ml of distilled water and boiled at 50°C for 20 minutes and the mixture were placed at room temperature for 24 hours on shaker at 150 rpm. Initially the solution were strained using muslin cloth and it was filtered under aseptic conditions using Whatman filter paper No.1. Finally, 50 ml aqueous preparation were collected in a sterile beaker and stored at 4°C for further use. The final pH of Centella asiatica extract ranged between 5-6 and it was recorded. The aqueous extract was stored for a period of 15 days, after which fresh extracts were prepared and given to the recruited participants

2.2.In-Vitro Assay for Cytotoxic activity:

The human epidermal keratinocyte cell lines were obtained from National center for cell lines, Pune, India was used in this study. In order to evaluate the cytotoxicity of Centella asiatica aqueous extract, the viable human epidermal keratinocyte cell lines were seeded in 96-well microplates (1 x 10^6 cells/mL) and it was incubated at 37°C for 24 hour time period with 5% CO_2 incubator and it was allowed to grow at 90% confluence. At end of the incubation, the medium was replaced and the keratinocytes cells were treated with aqueous extracts of Centella asiatica were added to each well at different concentrations of 100, 50, 75, 25 and 12.5 μg/mL. This cytotoxic 3,4,5-dimethylthiazol-2-yl-

2,5-diphenyl tetrazolium bromide (MTT) assay cell culture experiment to evaluate the aqueous extract of *Centella asiatica* against oral keratinocyte cell line were run in duplicates.

MTT assay generally evaluates the cytotoxicity of potential medicinal agents and other toxic agents by measuring the metabolic activity of the cell post the exposure of the drugs, other agents, etc. On evaluating the cytotoxicity test results, it was inferred that 99% of cell viability was seen at 12.5 µg/ml concentrations as shown in table 1. Therefore, 12.5 µg/ml concentration was used in the current study for the preparation of aqueous extract of Centella asiatica mouth rinse and same concentration can be used in future studies.

2.3. Clinical intervention:

Unstimulated saliva and Gingival crevicular fluid were collected from the participants with the help of Eppendorf and calibrated centrifuge collection tubes (Sigma–Aldrich; St. Louis, MO, USA). The samples were collected at the baseline (First day) and during the post-intervention period (after a period of 3 months). The collected samples were centrifuged and stored at -80°C for further in- vitro assessment.

2.4. Clinical procedure:

Baseline parameters (salivary flow rate, salivary pH, S.mutans count, Gingival crevicular fluid (GCF) flow rate and GCF alpha 1 defensin count) were collected from the recruited 20 participants. All the participants were provided 12% Centella asiatica mouth wash and they were instructed to rinse 10 ml of 12% aqueous concentration of Centella asiatica mouth rinse for 30 seconds twice daily after tooth brushing. For analysing the secretagogue activity, salivary flow rate was evaluated using the calibrated collection tube and Salivary pH was evaluated with the help of Eutech pH meter (pH 2700), standardization were done with standard buffer and pH electrode were dipped in 1 ml of saliva to measure salivary pH. Spread plate technique was employed for assessing the anti-microbial activity testing against streptococcus mutans by counting the viable bacterial colony, forming after 48 hours which was taken account using a Colony counter. GCF flow rate were evaluated with the help of calibrated microcapillary pipette. For analysis of GCF neutrophil count , a thin smear was prepared and

stained using Leishman's stain and the number of neutrophils per hundred cells were counted in a field. The GCF alpha 1 defensin levels were assessed using ELISA kit (Human alpha 1 defensin (defa1) ELISA,96- well plates; Ls Bio, Anyang, South Korea) with 450nm wavelength.

During the study period it was ensured that all the participants followed their routine toothbrushing method and administration of Centella asiatica mouth rinse twice daily after tooth brushing. After the post-intervention period (3 months), all the previously mentioned six parameters were collected and evaluated. All the readings were recorded and tabulated.

2.5. Statistical analysis:

The collected data were analysed using Statistical package for social sciences (SPSS) 22 software. Unpaired/Independent sample t test was used to compare the mean values recorded for all the variables included in the study. The data was summarized using mean, standard deviation and percentage. P-value <0.05 is considered to be statistically significant.

3.Results:

On in-vitro analysis of cytotoxic MTT assay it showed that **12.5 µg/ml concentrations** showed cell viability of 99%. Hence, this concentration are used in the current study for Centella asiatica extract to avoid any deleterious effects.

(Table1,Figure 1a,b)

3.1. Study Characteristics:

The present study included 20 patients (11 males and 9 females) with the males having the mean age of 54.5 years. Females having the mean age of 47.8 years.

3.2. Secretagogue activity:

The mean salivary flow rate at the base line were 0.415 and after post- intervention period were 1.105.The mean salivary pH at the base line were 5.74 and after post- intervention period were 5.63. Statistical analysis using unpaired t- test for salivary flow rate (P=0.215) and salivary pH (P=0.188)

showed that there was no significant difference found between baseline and during the follow-up period (P >0.05).However, clinically there was mild reduction in the salivary flow rate and salivary pH between the baseline and in the post-intervention period but it was not statistically significant.(Table 2)

3.3. Anti-Microbial activity:

The mean S.mutans colony count at the base line were 665.3 and after post- intervention period were 662.7. Statistical analysis using unpaired t- test showed that there was no significant difference found between baseline and follow-up period (P=0.330) (P >0.05).However, clinically there was very minimal reduction in the S.mutans colony count between the baseline and in the post-intervention period but it was not statistically significant.(Table 3, Figure 2a,b)

3.4. Immunomodulatory activity:

The mean GCF flow rate at the base line were 3.66 and after post- intervention period were 2.79. The mean GCF neutrophil count at the base line were 52.35 and after post- intervention period were 42.20. The mean GCF alpha 1 defensin levels at the base line were 1.06 and after post-intervention period were 1.31. Statistical analysis using unpaired t- test showed that there was highly significant difference found between baseline and follow-up period ($P \leq 0.001$), indicating that aqueous extract of Centella asiatica mouth wash could be administered as an effective immunomodulatory agent, thus decreasing the gingival and periodontal inflammation. (Table 4)

4. Discussion:

Diabetes mellitus (DM) is currently a major health concern for people all over the world and the relationship between oral health and Type 2 diabetes mellitus (T2DM) has been described as a new epidemic with both existing in a synergistic relationship.(Standl et al. 2019) Chronic hyperglycaemia results in various complications such as neuropathy and microangiopathy involving multiple organ systems. In poorly controlled states, oral complications are discernibly evident, hence sustentation of blood glucose levels is essential.(Borgnakke 2019)

Oral manifestations include dry mouth (xerostomia), dental and root caries, periapical pathology, gingival inflammation, periodontal pathology, oral Candidal infection, altered taste sensation, fissured tongue, glossodynia, wandering rash of the tongue, recurrent aphthous ulcers and stomatitis.(Rohani 2019)

Over the years, numerous treatment modalities for the maintenance of oral hygiene in type 2 DM patients have been proposed; the most commonly followed therapeutics are oral prophylaxis, restoration, and root planning. For the management of xerostomia in type 2 diabetes, administration of pilocarpine and other cholinergic drugs are used. Recent studies have identified that uncontrolled type 2 DM can be treated solely by non-surgical periodontal therapy without the administration of anti-diabetic drugs . A 6-month follow up and subsequent HbA1c evaluation of these study participants exhibited significant modulation of both the periodontal and hyperglycaemic status of the patient.(Mauri-Obradors et al. 2018)

Numerous researches are going on utilizing naturally available herbal extracts in an attempt to improve oral hygiene. The use of ethnomedicinal plants and plant-derived components called, ***Phytochemicals*** are key alternate medicines available in our country from time immemorial. Ever since ancient times, phytochemicals have been the source of medicines due to their elemental role in disease management. Many recent studies have proved that most of the herbal extract has got medicinal effects like secretagogue, antimicrobial, immunomodulatory, antioxidant and anticancer properties. There are numerous literature reports related to the use of ethnomedicines in symptom alleviation of xerostomia, gingivitis, periodontitis occurring due to various aetiologies such as Sjögren syndrome, metabolic disorders, depression and drug-induced conditions.(Behl T et al. 2021)

To alleviate the symptoms of xerostomia **Murakami et al**(Murakami et al. 2019) **conducted a study** in Japanese population, with the help of fruits like **Pineapple extract** and it was found that there was an increase in the salivary flow rate due to the presence of ceramide and increase in turnover of cells. Similarly to diminish the bacterial count there are many herbal formulations have been established for antibacterial activity in the recent studies. This includes a study conducted by **P Mahalaksmi et al**(Mahalakshmi et al. n.d.) which proved that herbs like **Pistacia lentiscus and Solanum nigrum** exhibited significant antimicrobial efficacy against Streptococcus, Lactobacillus and Actinomyces species.(Murakami et al. 2019) For anti-fungal activity, a study conducted **Lekshmy et al**(Jayan et al.

n.d.) with herbal compounds like Coriandrum sativum, Mentha piperita and Punica granatum showed significant antifungal activity against Candida galbrata species.

In 2021 Kyoung et al(Park 2021) conducted a review to assess the potent effects of Centella asiatica on skin diseases and it was inferred that Centella asiatica has a major role in the management of skin disorders, this is mainly due to the presence of phytochemicals like triterpene and its therapeutic effects against various dermatological disorders by regulating the MAPK, STAT and WNT signaling pathways.

In 2021 Elza et al(Iskandar E, Theodorus T, Tribowo A, Erna R 2012) conducted a study to analyze the efficacy of Centella asiatica extracts on postoperative wound healing and it was inferred that Centella asiatica has a pivotal role as a postoperative wound healing activity by inhibiting the inflammatory responses which simultaneously promotes the wound proliferation and remodeling activity.

Even though there are many therapeutic management techniques indicated for improving the oral health status in type 2 DM affected individuals, these therapies tend to inculcate numerous complications with chronic use. With these above facts and considering the potential role of herbal extracts in improving the oral health status, the current study was done to evaluate the oral secretagogue, anti-microbial, and immunomodulatory effects of Centella asiatica in patients with type 2 diabetes mellitus patients. To our knowledge, this is the first study to evaluate the efficacy of Centella asiatica on enhancing the oral health status in patients with type 2 diabetes mellitus. Centella asiatica was chosen as it is easily available and they are consumed daily in many parts of India and the oral use of Gotu kola has many medicinal benefits like alleviating the symptoms of delayed wound healing and immunomodulatory activity.

Centella asiatica is mainly derived from the chemical components like flavonoids and terpenes which are derived from phenylpropane and acetate. The other components of *Centella asiatica* includes the triterpene acids, asiatic acid, madecassic acid and asiaticosides. Among these chemical constituents, Phenolic agents has the most predominant and medicinal effects, it acts as an *anti-oxidant property*. (Ogunka-Nnoka CU et.al)

In-vitro testing of any drug should always involve the evaluation of cytotoxicity assessment using MTT assay. Hence, the cell viability assay was performed to evaluate for the effects of the test herbal extracts utilized in the study against the oral keratinocytes. Oral keratinocyte cell lines are the epithelial cells, which come in direct contact with any oral preparations. The herbal extract namely ***Centella asiatica*** were tested against the NHEK cell lines to assess its effect on these cells. This primarily was performed to determine the safety of these extracts, although termed natural or herbal, may produce deleterious cytotoxic effects. All the test sample results showed that the cell viability were falling within the range of **98-99%,** which indicated that these herbal extracts are safe to be used in humans.

On analysing the study results of secretagogue activity, it showed that no significant increase in the salivary flow rate (P=0.215) and salivary pH (P=0.188) after administration of aqueous extract of Centella asiatica. Although, the results were statistically insignificant, clinically there was mild improvement in the salivary flow rate and salivary pH after the usage of aqueous extracts of ***Centella asiatica.***

On analysing the study results of anti-microbial activity ,it showed that clinically there was very minimal reduction in the S.Mutans count after usage of the herbal product. However, this reduction was not statistically significant (P= 0.330),

On analysing the study results of immunomodulatory activity , it showed that GCF flow rate, GCF neutrophil count and alpha-1 defensin levels was substantially reduced after usage of Centella asiatica and found to be statistically significant ($P \leq 0.001$). Further, it proved that aqueous extract of Centella asiatica could be administered as an effective immunomodulatory agent, thus decreasing the gingival and periodontal inflammation.

The results of the present study was similar to study conducted by **Talat Mohammadi et al**(Mohammadi T, Shivamurthy Ravindra D, Vivekananda MR, Dasappa Shivaprasad D 2018) who evaluated the clinical efficacy of Centella asiatica in the reduction of periodontitis and gingivitis and it showed significant improvement in reducing gingival inflammation and periodontitis. This study was done using the alcoholic extract of Centella asiatica mouthwash as an adjunct to scaling, suggesting

that Centella asiatica mouthwash can be used as herbal formulation for the treatment of chemical plaque control.

Noah Samuels et al(Samuels et al. 2012)**,** showed Centella asiatica mouth wash was safe and effective in treating and preventing gingival inflammation along with adjuvant mechanical plaque control. This study was done by placing the transmucosal herbal periodontal patch for 3 days in adjunct to mechanical control.

The mechanism behind the immunomodulatory activity of *Centella asiatica* is due to the interactions of active components of *Centella asiatica* and their growth factors. The primary active components like pectin, saponins and triterpenoids showed the immunomodulatory activity by enhancing the wound healing process and also substantially reduces the severity of gingivitis and periodontitis.

Overall, the study results showed that the aqueous extracts of Centella asiatica were well tolerable by all the participants. Centella asiatica can also be used as an ***immunomodulator,*** which can be used as an adjunct in the management of gingival and periodontal inflammation. Although, the study showed the potential of these herbal products in improving the overall oral health status, it is not without their own limitations. Firstly, the trial was conducted with a smaller sample size and the period of follow up was shorter than those suggested for such interventional studies.

5.Conclusion:

This interventional study concluded that Centella asiatica is effective as an immunomodulatory agent. Hence, the current study enlightens the robust potency of herbal medicines which realms, on enhancing the oral health status in type 2 diabetes. However, the future directions of the current study are to clearly comprehend the mechanisms behind its mode of action further molecular studies with larger small size and longer follow-up period are recommended.

Disclosure of Funding: None

Disclosure of any Conflict of interest: "The authors declare no conflict of interest."

Figure legends:

Figure 1: Microscopic images of *Centella asiatica* against oral keratinocyte cell line in control (1a) and after 24 hour exposure with 12.5 μg/mL concentrations (1b)

Figure 2: Streptococcus mutans colony count using agar plate method. 2a representing the pre-interventional period (at baseline or first day) and 2b representing the post-interventional period (after period of 3 months)

Table legends:

Table 1: Assessment of cytotoxicity of Centella asiatica against oral keratinocyte cell line

Table 2: Comparison of mean salivary flow rate and salivary pH before and after the intervention

Table 3: Comparison of S.mutans count before and after the intervention

Table 4: Comparison of GCF flow rate, GCF neutrophil count and alpha 1 defensin levels before and after the intervention

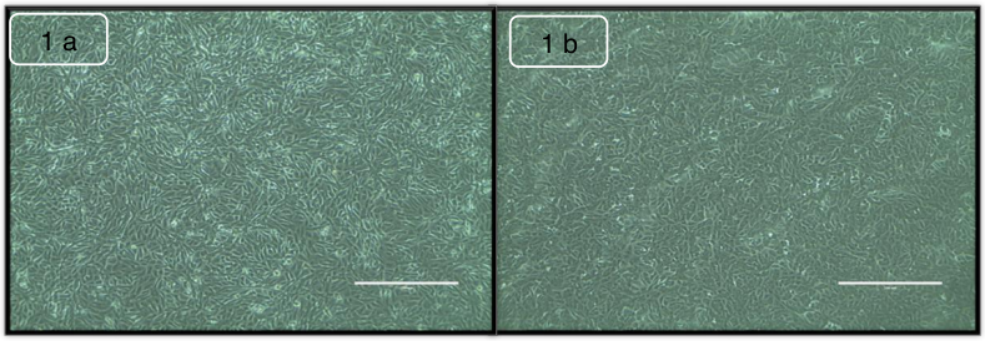

Fig 1: Microscopic images of *Centella asiatica* against oral keratinocyte cell line in control (1a) and after 24 hour exposure with 12.5 μg/mL concentrations (1b)

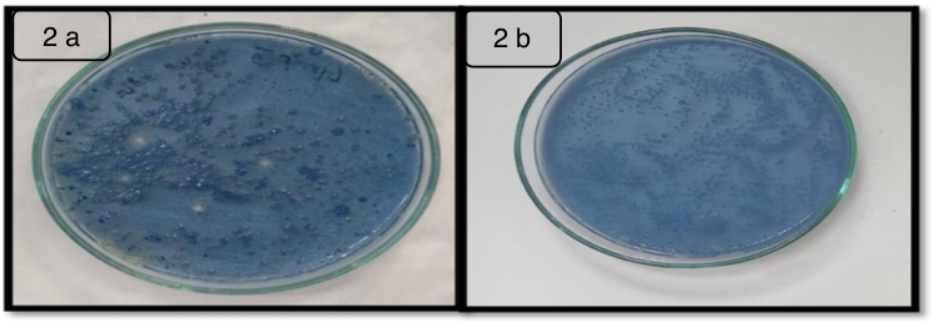

Fig 2: Streptococcus mutans colony count using agar plate method. 2a representing the pre-interventional period (at baseline or first day) and 2b representing the post-interventional period (after period of 3 months)

Table 1: Assessment of cytotoxicity of Centella asiatica against oral keratinocyte cell line

Concentrations (μg)	Absorbance (nm)		Average (nm)	Cell Viability (%)
	I	II		
Control	0.88	0.894	0.887	100
12.5	0.879	0.89	0.8845	99.71
25	0.876	0.87	0.873	98.42
50	0.858	0.87	0.864	97.40
75	0.837	0.852	0.8445	95.20
100	0.8	0.808	0.804	90.64

Table 2: Comparison of mean salivary flow rate and salivary pH before and after the intervention

Variables	Interventions	Mean	Std. deviation	P-Value
Salivary flow rate	Pre-Intervention	0.415	.230	0.215* (P>0.05)
	Post-Intervention	1.105	.318	
Salivary pH	Pre-Intervention	5.74	.434	0.188* (P>0.05)
	Post-Intervention	5.63	.455	

- P<0.05 Statistically significant
- P >0.05 Statistically insignificant
- No significant difference in salivary flow rate and salivary pH.

Table 3: Comparison of S.mutans count before and after the intervention

Variables	Interventions	Mean	Std. deviation	P-Value
Streptococcus mutans count	Pre-Intervention	665.3	212.25	0.330* (P>0.05)
	Post-Intervention	662.7	212.29	

- P<0.05 Statistically significant
- P>0.05 Statistically insignificant
- No significant difference in S. mutans count

Table 4: Comparison of GCF flow rate, GCF neutrophil count and alpha 1 defensin levels before and after the intervention

Variables	Interventions	Mean	Std. deviation	P-Value
GCF flow rate	Pre-Intervention	3.665	1.14	P<0.001*
	Post-Intervention	2.795	0.25	
GCF neutrophil count	Pre-Intervention	52.35	9.66	P<0.001*
	Post-Intervention	42.20	8.98	
GCF alpha 1 defensin count	Pre-Intervention	1.069	.304	P<0.001*
	Post-Intervention	1.313	.269	

- P<0.05 Statistically significant
- P>0.05 Statistically insignificant
- Significant difference in GCF flow rate, GCF neutrophil count and alpha 1 defensin levels.

Manuscript (66).docx

ORIGINALITY REPORT

8%
SIMILARITY INDEX

PRIMARY SOURCES

1	Pannerselvam Balashanmugam, Prabhu Durai, Manickam Dakshinamoorthi Balakumaran, Pudupalayam Thangavelu Kalaichelvan. "Phytosynthesized gold nanoparticles from C. roxburghii DC. leaf and their toxic effects on normal and cancer cell lines", Journal of Photochemistry and Photobiology B: Biology, 2016 Crossref	43 words — 1%
2	Arya Mitra Loka, Deepa Ponnaiyan, Harinath Parthasarathy, Anupama Tadepalli, Dhayanand John Victor. " Association of the rs4647602 Gene Polymorphism with Periodontitis in South Indians of Tamil Ethnicity ", Genetic Testing and Molecular Biomarkers, 2022 Crossref	26 words — 1%
3	www.allresearchjournal.com Internet	26 words — 1%
4	effiloop.com Internet	24 words — 1%
5	www.ecorfan.org Internet	21 words — 1%
6	www.pharmaresearchlibrary.com Internet	21 words — 1%

7	J. N. Smith. "Pharmacokinetics of the chlorpyrifos metabolite 3,5,6-trichloro-2-pyridinol (TCPy) in rat saliva", Toxicological Sciences, 11/17/2009 Crossref	20 words — 1%
8	journal.waocp.org Internet	18 words — < 1%
9	www.hindawi.com Internet	15 words — < 1%
10	www.science.gov Internet	12 words — < 1%
11	Ashwin Rao, Nikhil Kumar, Anupama Nayak P. "Effect of Different Commercially Available Biscuits on Salivary pH, Flow Rate and Oral Clearance Rate Among Children", World Journal of Dentistry, 2019 Crossref	11 words — < 1%
12	Priyanka Mohapatra, Asit Ray, I. Sriram Sandeep, Sanghamitra Nayak, Sujata Mohanty. "Chapter 4 Tissue-Culture-Mediated Biotechnological Intervention in Centella asiatica: A Potential Antidiabetic Plant", Springer Science and Business Media LLC, 2021 Crossref	11 words — < 1%
13	tampub.uta.fi Internet	11 words — < 1%
14	connect.myesr.org Internet	10 words — < 1%
15	www.journalofosseointegration.eu Internet	10 words — < 1%
16	www.omicsonline.org	

Internet

10 words — < 1%

17 www.phcog.com
Internet

10 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 10 WORDS