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EFFECT OF A SINGLE APPLICATION OF LOW-LEVEL LASER THERAPY ON PAIN CAUSED BY BONDING AND BANDING IN ORTHODONTIC PATIENTS

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Introduction: In the field of dentistry fixed orthodontic treatment improves dentofacial aesthetics and also performance of mastication, like any other treatment it is also correlated with distress and pain. Studies about the ratio of patients with pain encounter during fix orthodontic treatment have indicated estimations varying from 70% for the Caucasian population and 95% for the Asian population. It has been testified that greater than 90% of patients with fixed orthodontic treatment encounter altering intensities of pain after the fixative of elastomeric separators, application of brackets, primary wire placing and activations. After appliance setting, patients report of pressure, tension soreness of the teeth and pain in supportive periodontal tissues. There are different studies showed that one of the restraining factors for obtaining orthodontic treatment with fixed appliances is the individual's concern for the associated pain and discomfort. Clinicians are always looking for some newer, safer and reliable approaches, like low-level laser therapy (LLLT) to diminish pain from orthodontic appliances and it has been established through some studies that LLLT decreases pain during orthodontic treatment. In view of the easiness of patients, many investigators have tried a single dose of LLLT with different designs of studies including case controlled, split mouth studies etc., and they observed considerable results regarding pain reduction related with initial visits of orthodontic treatment. Hardly any author has investigated the analgaesic effect of single dose of low-level laser therapy on pain associated with initial visit of fixed orthodontic treatment and never been tested with laser assisted bleaching arch tray.

Objective: The purpose of this research was to evaluate the effect of a single dose of LLLT assisted arch tray on pain caused by the placement of orthodontic appliances in initial phase of fixed orthodontic treatment.

Methods: For this study, 24 patients (12 male and 12 female, aged 18 years old–30 years old, mean age = 23 years old) participated, comprising 10 subjects aged 25 years old or above, and 14 aged under 20 years old. These patients were listed for fix orthodontic treatment at the Orthodontic clinics, Dental department of Aga Khan Hospital for Women Karimabad, a secondary hospital of Aga Khan University Hospital Karachi Sindh Pakistan. Immediate bonding of 0.018 Roth reference brackets* were performed for all applicants. Brackets were positioned by the same orthodontist specialist who was also co researcher of this study from the premolars to the premolars for upper and lower jaws both. Nickel-titanium (NiTi) alloy arch wire of 0.012 was applied with elastic O-rings as an initial wire in all cases. Comprehensive oral hygiene instructions were conveyed to both groups and LLLT in arch form was applied on anterior segment of both jaws in one group of patients. Patients were requested to fulfill a questionnaire on the following visit; the questionnaire was related with level of pain felt soon after placement (T₁), 1 day (T₂), after 2 days (T₃), following 5 days (T₄) and after 1 week (T₅) of placement of the appliance.

Results: The intensity of pain in the experimental group was lesser than in the controlled group. There was a substantial difference ($P > 0.05$) amongst the experimental and the controlled groups on pain perception by the patients after application of brackets for initial one week. The great amount of pain was allied with pain of brackets application in the controlled group. While the LLLT in arch form reduced the pain sensitivity on brackets application force in the experimental group. Almost all participants had highest amount of pain at day first and day second after the application of brackets, and it subsided considerably on the day third in about both groups; though, the pain intensity in the experimental group decreased more steadily.

Conclusion: With the parameter settings applied in this study, single dose of LLLT in arch form of application subsidised the pain resulted from application of orthodontic brackets.

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MODELING K-FACTORS ANALYSIS IN DESIGN OF EXPERIMENT (DOE) TOWARDS REGRESSION APPROACH USING MULTI-LAYER FEED-FORWARD NEURAL NETWORK (MLFF): ITS' APPLICATION IN BIOSTATISTICS

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Design of experiments (DOE) is one of the well-known and widely used statistical methodologies. The results of this DOE provide a very valuable result especially when a researcher studying the relationship between variables. A large number of studies that have been carried out today are hoping for a more accurate result. Indeed, the number of studies involving the development of scientific research methodology is increasing over time. This study aims to develop the best method for data analysis, especially involving a combination of DOE, bootstrap, and linear regression as well as a multi-layer feed-forward neural network (MLFF) through the R programming language. The thesis emphasises the development of an accurate and valid regression model that involves several combinations of key methods. Based on the results obtained, it can be concluded that this developed methodology shows results encouraging for modeling techniques. In conclusion, this method can be used effectively, especially when performing regression modeling on experimental design.

Supervisor:
Associate Professor Ts. Dr. Wan Muhamad Amir W Ahmad

THE ASSESSMENT OF INTERLEUKIN-6, PROTEIN INDUCED BY VITAMIN K ANTAGONIST II, AND ALPHA-FETOPROTEIN AMONG HEPATOCELLULAR CARCINOMA PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Hepatocellular carcinoma (HCC) is a primary liver cancer that has a poor prognosis and a high prevalence among the Malaysians. At present, ultrasonography and serum Alpha-fetoprotein (AFP) are the only tools for HCC screening in this country. Serum interleukin-6 (IL-6) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) are two potential serum biomarkers that were

shown to be elevated in HCC patients. However, there had been insufficient research on them in our population. This study aimed to assess the serum IL-6 and PIVKA-II levels among HCC subjects in Hospital USM, before and after treatment, as well compare their levels to those of serum AFP. Twenty six HCC subjects (Group 1) and thirty four healthy subjects (Group 2) were recruited. For Group 1, blood samples were collected and radiological assessments of their HCC lesions were done at the first visit and 6 weeks after their local treatment. For Group 2, only blood samples were only collected once. This study found that serum IL-6, PIVKA-II and AFP had higher median levels in HCC subjects than healthy subjects ($P < 0.001$). IL-6 was not significantly correlated with radiological response post treatment ($P = 0.822$). When comparing pre- and post- treatment values, serum IL-6 levels did not change significantly ($P = 0.328$), whereas serum PIVKA-II levels were most significantly different ($P < 0.001$) followed by serum AFP levels ($P = 0.007$). In HCC diagnosis, PIVKA-II had the higher sensitivity and specificity (Sn: 92.30%, Sp: 94.11%) followed by serum IL-6 (Sn: 84.62%, Sp: 70.59%) and AFP (Sn: 73.08%, Sp: 97.06%). Furthermore, the combination of all three serum biomarkers demonstrated the best diagnostic performance in HCC diagnosis (AUC = 0.999). Conclusively, serum IL-6 and PIVKA-II have potential uses in HCC diagnosis as well as HCC treatment monitoring, especially when used in combination with serum AFP.

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A LONGITUDINAL QUALITATIVE STUDY ON LIVED EXPERIENCE OF ORAL CANCER PATIENTS DURING COVID-19 PANDEMIC IN KHYBER PAKHTUNKHWA PAKISTAN

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Introduction: Oral cancer health experiences are profound and complex for patients even at the best of times. There is, however, little knowledge of how oral cancer patient's health experiences may alter and develop in response to the COVID-19 pandemic's changing environment.

Objectives: This study explored the physical, social and psychological experiences of oral cancer patients at diagnosis, 6 months after diagnosis and 1 year after diagnosis, with a particular focus on how experiences change through the different periods of time during the COVID-19 pandemic.

Methods: Patients diagnosed with oral cancer at Khyber College of Dentistry, Peshawar, Pakistan were included in the study. The participants were selected using a maximum variation purposive sampling method to participate in this study. A longitudinal qualitative design was employed using the principles of phenomenological inquiry. Three semi-structured interviews were conducted as follows: at diagnosis (T1), 6 months after diagnosis (T2) and 12 months after diagnosis (T3). The sample at T1 and T2 comprised 17 participants. The sample at T3 comprised of a total 12 participants. The interviews were conducted in Pashto, the local language of Khyber Pakhtunkhwa. The audio-recorded interviews were transcribed *ad verbatim* in English and thematically analysed. Data was organised using ATLAS.ti software version 8.0.

Results: Eight major broad-level themes were derived at T1: i) pain and generalised physical weakness, ii) shock at diagnosis, iii) psychological distress of the COVID-19 pandemic, iv) faith and religion, v) double hit loss of employment, vi) social isolation, vii) social support from caregivers and viii) lack of support from health care professionals. At T2, five major broad-level themes were derived: i) physical impairment and limitations, ii) psychological vulnerability, iii) reliance on God for protection, iv) availability of social support systems and v) financial decline. Finally, four major broad-level themes were derived at T3: i) the new normal, ii) the sum of fears, iii) belief in traditional healing practices, and iv) striving towards normalcy in social life.

Conclusion: This longitudinal qualitative study provides insight into the complexities of living with oral cancer during the pandemic. The narratives in the study highlight conventional physical experiences while heightened psycho-social concerns at diagnosis. Patients social support slightly improved 6 months after diagnosis, but increased financial burdens, psychological distress, and physical symptoms continued. Finally, after twelve months, patients attempted to recover physically and gain social normalcy, but unwavering psychological concerns about the recurrence of oral cancer and the COVID-19 pandemic lingered. The duality of the common oral cancer experiences and additional pandemic-inflicted experiences were evident in all three phases which affected the physical, psychological and social well-being of oral cancer patients in Pakistan.

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EFFECT OF SINTERING TEMPERATURE ON MECHANICAL BEHAVIOUR AND BIOACTIVITY OF CALCIA-STABILISED ZIRCONIA DERIVED COCKLE SHELLS BIO-CERAMIC

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The original experimental research carried out for this study by previous researcher was to investigate the synthesised of calcium oxide derived from cockle shells to be used as stabilizer for zirconia bioceramic at different temperatures. However, this research was continued by improved the production of calcium oxide derived from cockle shells using an improved protocol and determine its purity. Further, the improved data analysis of Ca-SZ bioceramic at different sintering temperatures were compared to the commercialised CEREC Sirona dental block. Hence, the aim of this study is to investigate the effect of sintering temperature on structural, morphological, mechanical, and biological properties of calcia-stabilised zirconia derived cockle shells bioceramic. To achieve this objective, three sintering temperatures at 1200 °C, 1300 °C and 1400 °C were selected in order to understand the structural, morphological and mechanical properties of Ca-SZ bioceramic after incorporation of 8 wt% of nano-CaO powders derived from cockle shells. Moreover, to give better comparative results, CEREC Sirona was sintered at temperature 1510 °C followed the protocol provided by Sirona, the Dental Company. In this experimental work, the diluted cockle shells powder was mixed with calcium chloride (CaCl₂) and potassium carbonate (KCO₃), using mechanochemical synthesis process. Then, nano-CaCO₃ powder underwent calcination process at a temperature range of 300 °C–550 °C to obtain nano-CaO powders. Nano-CaO powder derived from cockle shells were characterised using X-Ray Diffraction (XRD) analysis, Field Emission Scanning Electron Microscopy (FESEM) and Transmission Electron Microscope (TEM) to ensure high purity of nano-CaO powder was obtained in fabricating Calcia-Stabilised Zirconia (Ca-SZ). FESEM and TEM analyses show that nano-CaCO₃ produced hexagonal shape crystals while nano-CaO display spherical shape with crystal-like structure. Next, Ca-SZ bioceramic derived cockle shell powder obtained at different sintering temperature were then compacted and characterised using FESEM and XRD. Ca-SZ sintered at 1400 °C showed the highest mechanical properties and better in in-vitro test using SBF solution compared to other sintered specimens due to the pore size reduced within temperature rise. However, Ca-SZ sintered at 1400 °C produced lower mechanical strengths when compared to commercialised CEREC Sirona. Therefore, these findings revealed that by adjusting the previous protocol, improved, pure nano-CaO may be synthesized using natural Ca source from cockle shells.

Additionally, the fabricated Ca-SZ has a potential in biological properties and also showed a significantly lower mechanical properties compared with CEREC Sirona when sintered at 1400 °C which may be easier for machining and has a potential to be commercialised soon which helps in study for dental treatment.

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MOLECULAR CHARACTERISATION OF ALPHA-THALASSAEMIA IN PATIENTS INVESTIGATED FOR HYPOCHROMIC MICROCYTIC INDICES IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Alpha (α)-thalassaemia is a common genetic disorder that affects 5% of the worldwide population. Deletional or non-deletional mutations of one or both *HBA1* and *HBA2* on chromosome 16 cause a reduction/abnormal in the production of α globin chains, a component of haemoglobin (Hb) which are required for the formation of red blood cells (RBC). Thus, reduced Hb leads to anaemia. Many genetic mutations in α -thalassaemia have been discovered, which produced wide spectrum of clinical manifestation, ranging from asymptomatic to lethal. This study focused on the characterisation of RBC parameters and molecular based on α -thalassaemia mutations to determine the prevalence and to describe the RBC parameters based on the mutations detected. A cross-sectional study involving 136 suspected α -thalassaemia patients was collected. The DNA extracted from blood samples was subjected to the multiplex GAP-polymerase chain reaction, multiplex amplification refractory mutation system polymerase chain reaction (MARMS-PCR), and duplex-polymerase chain reaction to detect common deletional and non-deletional α mutations, respectively. Multiplex ligation dependent probe amplification and Sanger sequencing were performed to detect rare mutations in patients that do not carry any common mutations. The prevalence of α -thalassaemia in this study was 47.1%. Thirty-nine and 1.4 percent of patients were found to have heterozygous and homozygous α -thalassaemia mutations, respectively, with 6.6 percent being compound heterozygous. Among the patients, the following genotypes were found: $-\alpha^{3.7}/\alpha\alpha$ (15.4%), $-\alpha^{4.2}/\alpha\alpha$ (3.7%), $--^{SEA}/\alpha\alpha$ (7.4%), $\alpha^{CS}\alpha/\alpha\alpha$ (10.3%), $\alpha^{Adana}\alpha/\alpha\alpha$ (0.7%), $\alpha^{Quong\ Size}\alpha/\alpha\alpha$ (1.5%), $-\alpha^{3.7}/-\alpha^{3.7}$ (0.7%), $\alpha^{CS}\alpha/\alpha^{CS}\alpha$ (0.7%), $-\alpha^{4.2}/\alpha^{CS}\alpha$ (0.7%), $-SEA/\alpha^{CS}\alpha$ (1.5%),

$-\alpha^{3.7}/\alpha^{Quong\ Size}\alpha$ (0.7%), $-\alpha^{3.7}/\alpha^{Adana}\alpha$ (0.7%), $--^{SEA}/-\alpha^{3.7}$ (2.2%) and $\alpha^{CS}\alpha/\alpha^{Adana}\alpha$ (0.7%). Statistical analysis of RBC parameters according to the mutations was performed. A few indicators, such as Hb ($P = 0.020$), mean corpuscular volume ($P = 0.008$), mean corpuscular haemoglobin ($P = 0.018$), RBC ($P = 0.029$) and haematocrit ($P = 0.049$), showed significant changes among patients with deletional mutations but there were no significant differences between patients with non-deletional mutations. Patients with single gene deletional and non-deletional mutations shows only significant differences for HbA₂ ($P = 0.028$). A wide range of RBC parameters were observed among the patients, including those with the same genotypes. Thus, based on RBC parameters alone, they are not sufficient to describe the specific mutations of α -thalassaemia.

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BACTERIAL LEAKAGE AND MARGINAL ADAPTATION OF THREE BIO-CERAMICS PULP DRESSING MATERIAL

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This study aims to evaluate the sealing ability and marginal adaptation of three different bioceramics pulp dressing materials using a bacterial leakage test and scanning electron microscope (SEM). Fifty-five recently extracted lower first premolars were randomly divided into five groups, with three experimental groups ($n = 15$), a positive control group ($n = 5$) and a negative control group ($n = 5$). The samples were instrumented with a modified coronal pulpotomy procedure except for the negative control group ($n = 5$). Different types of bioceramics dressing material were placed in the cavity 3 mm thickness in group 1 (Biodentine), group 2 (MTA) and group 3 (ProRoot MTA). There was no dressing material placed in the positive control group. Samples were placed in an incubator at 37 °C, 100% humidity, for 24 h to allow the material to be set, after the placement of the composite restoration. Two layers of nail varnish were applied, and the 3 mm root tip was removed. The bacterial leakage test was performed using *Enterococcus faecalis*, and one sample from each experimental group was sliced and examined under SEM for marginal adaptation. Data analysis was conducted under the One-way ANOVA test, completed by Tukey's post hoc test. The groups observed a significant difference in sealing ability and marginal adaptation ($P < 0.05$), wherein Biodentine showed bacterial leakage on day 6 (7%), and on day 14 (80%), MTA showed on day 9 (14%) and on day 14 (40%), ProRoot showed on day 11 (7%) and on day 14 (33%). From SEM, ProRoot MTA demonstrated the least gap between the dressing material and significantly higher penetration in dentinal tubules.

ProRoot MTA demonstrated better sealing ability and marginal adaptation compared to other groups. The finding indicates that ProRoot MTA would be the best pulp dressing material for the clinical setting.

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A CLINICAL STUDY ON THE EFFECTS OF TREATING TEMPOROMANDIBULAR DISORDER (TMD) BY LOW LEVEL LASER THERAPY (LLLTT), CONSERVATIVE AND COMBINATION TREATMENTS

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Temporomandibular disorders (TMD) are a common term for a group of musculoskeletal diseases that are associated with pain and/or malfunction in the chewing muscles. They are prevalent among Asians and Malaysians. Treatment modalities involving conservative and level laser therapy (LLLTT) have not been widely investigated, although their potential exists. The aim of this study was to compare the effects of treating TMD by LLLTT, standard conservative treatment (home based therapy) and the combination treatments. A total of 32 patients aged 18 years old and above with TMD were enrolled in three different groups: 10 (conservative), 11 (LLLTT), and 11 (combined treatments). Purposive sampling method was applied. A proforma for the patient's history and examination and validated translated questionnaires of Mal-RDC/TMD were used. Pain was measured by visual analogue score (VAS). Patients in LLLTT only group and combined treatment group were treated with 5 sessions of low-level laser every other day for a duration of 10 days. Patients in conservative treatment group and combined treatment group received standard conservative TMD treatment (diet and stress counseling, jaw exercises, physical therapy). Blood samples were collected from all groups following universal precautions for venipunctures in comparing hs-CRP, IL-6, IL-8. Descriptive analysis and Repeated measures ANOVA were used for data analysis. Between the three groups (LLLTT, conservative and combined treatment), there was a statistically significant difference in the mean levels of IL-6 ($P = 0.037$) and IL-8 ($P = 0.001$). From baseline to post-treatment, the level of anxiety amongst the patients dramatically lowered, although the group did not differ significantly. From baseline to post-treatment, the mean depression index score decreased because of the treatment. There was no significant difference between all treatment groups in terms of jaw disabilities following therapy ($P = 0.244$). Chronic pain intensity score, NSPSE ($P = 0.009$)

score and NSPSI ($P < 0.001$) significantly decreased from baseline to post treatment, but not significant between the groups. Mean lateral excursion, maximum assisted and unassisted mouth opening all showed significant difference ($P < 0.001$) before and after the treatment. The mean of VAS significantly ($P < 0.001$) decreased from baseline to 12 weeks and between three groups ($P < 0.010$). A significant change was noticed in IL-6 and IL-8. Among the groups with three different treatment modalities, LLLTT and combination (LLLTT + conservative) treatment approaches were found to be better than the conservative treatment alone.

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3D MORPHOMETRIC EVALUATION OF PALATAL RUGAE AMONG MALAYSIAN MALAY POPULATION

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Palatal rugae pattern may have a promising and interesting future for human identification purpose. Previous studies showed that palatal rugae pattern has a lot of morphological and dimensional characteristics that are different from a person to another even among the identical twins. In fact, palatal rugae are anatomically located in a well-protected place, behind boons, teeth, cheeks and lips, which provides a good alternative option for human identification in mass disasters and accidents. This study aimed to evaluate the variability and uniqueness of palatal rugae among Malaysian Malays using 3D dental models. A 3D Next Engine Laser scanner (USA) was used to digitise plaster dental casts of 130 Malaysian Malay patients (65 males and 65 females) obtained from the archive of Orthodontic Clinic, Hospital Universiti Sains Malaysia. The resulting 3D models were highlighted using Paint 3D software (USA) for the purpose of rugae shape assessment. Rugae size category and direction were assessed using 3Matic research software (Belgium). The classification method of Thomas and Kotze as described by Kapali et al. was adopted. Palatal rugae uniqueness was performed by superimposing 42 pairs of digital models (21 models were duplicated from the same patients and 21 models were randomly selected from the group). The 42 superimposition sets were examined for palatal rugae surface fitting by a single blinded evaluator. Prevalence of palatal rugae was presented in percentages while mean and standard deviation were presented for number of rugae. Chi-square analyses

were used to evaluate the association between sex and prevalence of palatal rugae variables. Independent *t*-test was used to compare sex difference in number of palatal rugae. Correct/wrong decision of superimposition was presented in percentages. *P*-value < 0.05 was considered statistically significant. Total number of rugae was 1,359 (673 in males and 686 in females). Wavy shape was the predominant rugae among the sample, followed by curve shape and straight shape, respectively. The predominant rugae size category was the primary size. Forwardly directed rugae were the most prevalent rugae among the sample. There was no significant difference regarding rugae features between males and females except for the rugae direction in the left side of the palate, as the backward rugae direction was more prevalent among the females (*P* = 0.001). Palatal rugae pattern was unique. No two individuals have the same pattern. Wavy shape, Primary size and forward direction were the most prevalent among Malaysian Malays. Palatal rugae is unique thus could be used for human identification in the case where pre-mortem and post-mortem records are available.

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DEVELOPMENT OF A NOVEL BIOCERAMIC ROOT CANAL SEALER AND ITS EFFECT ON THE DISLODGEMENT RESISTANCE AND DENTINAL TUBULE PENETRATION

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Introduction: Root canal treatment aims to remove microorganisms from infected teeth and promote periapical healing. Bioceramic-based sealers have been developed to improve the sealing of root canals, but their bond strength and tubule penetration capabilities are still a matter of debate.

Objectives: The present study aimed to fabricate and characterise novel algin-incorporated bioactive glass 58S calcium-silicate root canal sealer (Bio-G) and evaluate its effect on the dislodgement resistance and dentinal tubule penetration to root dentinal walls in comparison to commercially available bioceramic-based sealers (BioRoot RCS and iRoot SP).

Methods: Three groups of bioactive glass (BG) 58S powders were synthesised using sol-gel method and characterised using SEM, HRTEM and FTIR for optimisation: BG-1 (no ammonia), BG-2 (3 mL of ammonia), and BG-3 (5 mL of ammonia). Optimised BG-3 was used to fabricate the powder form of experimental Bio-G sealer with the addition of calcium silicate, zirconia dioxide, calcium carbonate and alginic acid powder. Meanwhile, the liquid form composed of 5% calcium chloride solution.

The experimental 0%–5% algin Bio-G sealers were then compared with BioRoot RCS and iRoot SP. Standardised disc specimens of mixed sealer materials (*n* = 5 per group) were prepared and placed in an incubator to allow setting before characterising under SEM, HRTEM, EDS, FTIR and XRD. Next, 176 mandibular premolars were randomly assigned (*n* = 16 per group): control, gutta-percha + 0%–5% algin Bio-G, gutta-percha + BioRoot RCS, and gutta-percha + iRoot SP groups, with the exclusion of the control group in adhesive pattern and dentinal tubule penetration tests. They were instrumented, obturated and placed in an incubator to allow sealer set. For the dentinal tubule penetration test, sealers were mixed with 0.1% of rhodamine B dye. Subsequently, teeth were cut into a 1-mm-thick cross-section at 5-mm and 10-mm levels from the root apex, respectively. Push-out bond strength, adhesive pattern and dentinal tubule penetration tests were performed.

Results: Experimental Bio-G sealer revealed irregular micro-sized particles with a higher content of oxygen, silicon, and calcium, as well as trace of aluminium and chloride. Meanwhile, FTIR and XRD findings suggested that all sealers predominantly contained calcium silicate hydrate, calcium carbonate, and zirconium dioxide, while calcium aluminium silicate oxide was detected in 0%–5% algin Bio-G. The 5% algin Bio-G showed the highest mean push-out bond strength (*P* < 0.05) with more favourable adhesion pattern, while iRoot SP showed the greatest sealer penetration (*P* < 0.05). In addition, no significant association was noted between the dislodgement resistance and dentinal tubule penetration (*P* > 0.05).

Conclusion: Novel Bio-G sealer demonstrated desirable particle size distribution and acceptable degree of purity. Algin-incorporated Bio-G showed favourable adhesive pattern with comparable dislodgement resistance and dentinal tubule penetration values to commercialised bioceramic-based sealers.

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CYTOTOXIC AND MOLECULAR EFFECTS OF BETEL QUID AND ARECA NUT EXTRACTS ON SELECTED ORAL EPITHELIAL CELL LINES

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The habit of betel quid chewing is widely prevalent in many parts of Asia. Betel quid comprises areca nut, betel leaf, lime, and other potential constituents such as tobacco and essences. The main ingredient of betel quid

is areca nut. Many epidemiological studies link betel quid and areca nut chewing to oral cancer. Therefore, this study aimed to investigate the effect of areca nut and betel quid on mouth-ordinary-epithelium1 (MOE1) and human oral squamous carcinoma (HSC-2). Phytochemical compounds were identified using GC–MS. MOE1 and HSC-2 cells were treated with high concentrations (25%–100%) and low concentrations (0.0122%–25%) and subjected to MTT assay. The cell and nuclei morphological changes were observed under inverted phase contrast and fluorescence microscopes. Following microarray analysis, the gene expression data was subjected to bioinformatic analysis. Microarray data was validated by analysing the expression of six selected genes through real-time reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Arecoline was identified as the major chemical compound in areca nut alkaloids, while phenol, 2 methoxy4 (1propenyl) was the major chemical compound in betel quid phenolics. MOE1 treated with areca nut decreased in viability starting from 0.0244% until 1.56%. However, at concentrations 6.25% and above, the cells viability increased. With betel quid treatment, MOE1, cell viability started to decrease at extract concentration of 0.78% (24 h) and 3.125% (48 h and 72 h). However, at concentration 50% and 100%, the cell viability increased significantly. Areca nut treatment on HSC-2 decreased the cell viability tremendously at all concentrations and treatment time. Betel quid concentration from 6.25% to 25% decreased HSC-2 viability significantly at all treatment duration. Based on the cytotoxicity data, two concentrations

were selected, which were 0.0976% for areca nut and 6.25% for betel quid for the subsequent experiments. Microscopy findings indicated that the extracts caused noticeable morphological changes such as cell shrinkage and ballooning, nuclei condensation, and fragmentation. The microarray gene expression analysis revealed that the total number of DEGs in MOE1 treated with areca nut and betel quid compared to controls was 3,038 and 1,985, respectively, while in HSC-2, it was 4,413 and 1,110, respectively. The shared upregulated DEGs of areca nut treatment were *CLDN4*, *PIMI1*, and *HBEGF*. KEGG analysis suggested the genes are associated with few main pathways, including the ErbB signalling pathway. The shared upregulated DEGs for betel quid treatment are *HMOX-1*, *GCLM*, and *EGLN3*. Its KEGG analysis suggested an association with a few pathways, mainly ferroptosis. RT-qPCR results of selected genes validated the microarray gene expression. In conclusion, areca and betel quid showed different effects on normal and malignant epithelial cells, whereby cell survival mechanism might play an important role in cells treated with betel quid compared to the areca nut treatment.

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