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A Comparative Study of Cytotoxicity in Dental Composite Resins

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Abstract

Background: Resin-based dental restorative materials release residual monomers that may affect the vitality of pulp cells and gingival tissue. Aim of the study: The purpose of this study was to evaluate and compare the cytotoxic effect of the resin composite on human dermal fibroblast normal (HdFn) cells. Materials and methods: In this study we evaluate and compare the cytotoxicity of six light-cured restorative materials, respectively (Activa Bioactive_restorative, Beautifil II, G-aenial (anterior), Kluzer, Palfique Omnichroma, and Briliant EverGlow). We light-cured samples of the materials and directly placed them in contact with cells for 24, 72, and 168 hours. Human dermal fibroblast normal (HdFn) cell lines were seeded in 96-well (1×10^4) plates and incubated for 24 h at 37°C with the obtained extraction medium. Cytotoxicity tests assess the cell number and growth before and after exposure to that material. We commonly perform the cytotoxic assays using 3-(dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT). The percentage of viable cells in each well (MTT test) was calculated relative to control cells, which were set to 100%. Results: All the composite materials tested caused a decrease in cell number and growth after 1 week (168 h). Conclusions: The different cytotoxic effects of dental composites should be considered when selecting an appropriate resin-based dental restorative material for operative restoration.

Introduction:

Conservative dentistry extensively uses composite resins as restorative materials due to their ideal mechanical properties and desirable aesthetics (1, 2). However, their use requires specific focus on the safety of the components used (3-5). In the past two decades, researchers have developed resin composites to minimize cytotoxicity, minimize polymerization shrinkage, and enhance aesthetics (3, 4). The chemistry of the biopolymers used to make composites plays a crucial role in ensuring their biocompatibility (5). Innovative resin composites consist of a polymerizable organic resin matrix and a particulate ceramic reinforcing filler. A silane coupling agent connects these two main components (6). The polymerizable organic resin matrix is the main focus of biocompatibility attention. Because of the possibility of unbound monomer release, the resin matrix is the sole unstable element in composite resins. According to one research (5), throughout the polymerization process, 15–50% of the methacrylic groups in the organic matrix stayed free as monomers (7). The quantity of organic resin matrix has diminished over time. Hybrid polymers have given way to organically modified ceramic materials (ormocers) as composite resins. When compared to traditional composites, recent research on ormocers has revealed unsatisfactory clinical results over an extended period of time (8,9). Recently, manufacturers introduced nano-hybrid ormocers in order to maintain high standards in the physicochemical properties of the materials (3, 4, 10). According to the composition data provided, the resin matrix consists of methacrylate-functionalized polysiloxanes with added silicate oxide. Manufacturers have stated that this asset of composition frees fewer unbound monomers, thus resulting in a higher biocompatibility of composite materials. To learn more about how biocompatible different nanohybrid composite resins are, a cell viability assay was used to test their cytotoxicity on human dermal fibroblast normal (HdFn) cell lines.

Composite resins and denture-base materials are examples of resin-based dental materials that come into close contact with the oral mucosa and have the potential to elicit negative responses. Because they emit substances that can seep through the permeable dentin, restorative materials and dentine bonding agents can also damage the pulp. Consequently, we can evaluate the local unfavorable responses brought on by resin-based products from two perspectives: pulpal toxicity and mucosal toxicity. Assessing and contrasting the cytotoxic effects of six composite resins on human dermal fibroblast normal (HdFn) was the goal of the current investigation.

Materials and Methods

The experiment tested six composites: Activa (bioactive restoration) (Pulpdent) (A2), Beautifil (giomer) (Shofu) (A2), G-aenial anterior (GC Corporation) (A1), Charisma (A2) Diamond, Palfique (Omnichroma) (Tokuyama Dental Corp), and Brilliant (universal submicron hybrid composite) (Everglow®) (A2) (B2). Table (1) lists their components and details.

We first prepare the materials and tools: six different types of resin composite, sample containers, light cure, a mold (Dentsply®), celluloid strips, lubricant (Vaseline), a condensing/placing composite instrument, and disposable dental towels and gloves.

Sample preparation

Composite disc samples with a diameter of 5 mm and a height of 1 mm were prepared according to ISO 10993-12:2012 standards using customized molds, consistent with the manufacturers' instructions (11, 12). The steps are as follows: 1. Lubricate the mold before we put the composite into the mold to prevent any adhesion of the material to the walls of the mold and facilitate removing the sample of composite from the customized mold as shown in Figure (1).

2. Position the mold above the celluloid strip to create a straight and smooth base for the sample and obtain precise dimensions for the composite disks as shown in Figure (2).

3. Place the unpolymerized composite into the mold and condense it using the condenser instrument, or, if the composite is a flowable type, simply inject it into the mold as shown in Figures (3), and (4).
4. Polymerization was accomplished using an LED light source (LED light curing device) at an average of 720 mW/cm² for 30 seconds applied to the bottom and top surfaces to make sure that all surfaces are polymerized with light cure.
5. Next, we remove the composite disk from the mold using the same condenser gently pushing it from the bottom.
6. Mark the number of samples with markers (the code of the composite type) on the composite disk and collect them into the sample container as seen in Figures (5), and (6).
7. To prevent contamination, we UV sterilized the composite disc samples for 2 hours from the top and 22 hours from the bottom before cytotoxicity testing.

Cell culture

Human dermal fibroblast normal (HdFn) cell lines were obtained from the American Type Culture Collection and preserved in cell culture flasks (Falcon®) (Figure 7A). And cultured in Roswell Park Memorial Institute (RPMI 1640 Medium; Sigma-Aldrich, St. Louis, MO, USA) supplemented with 10% fetal bovine serum (FBS) (Sigma Aldrich),11% penicillin, and streptomycin (Sigma Aldrich), cells were incubated at 37℃ in a 5% CO_2 atmosphere in the incubator (The Sanyo MCO-20AIC CO_2 Incubator) as indicated in Figure (7B). All the steps should be done in sterilized conditions in a laminar airflow cabinet as in Figure (8).
Fibroblast Cells are isolated by using trypsin enzyme that breakdown all ligature between the cells in the media. Then the fibroblast cells were added to a 96-well cell culture plate (HiMedia, India) by pulling 200 µl of cells using a micropipette (containing about 1×10^7) and incubated for 24 h at 37℃. Before the MTT assay, the cells are checked under a light microscope to make sure they are in monolayer form. The composites were extracted by eluting them in cell culture medium with a surface area-to-volume ratio of around 1.25 cm²/mL between the sample surface and the medium volume (14). For 48 hours, the extraction vials were incubated at 37°C. After discarding the specimens, the elute extracts were filtered through membranes with pores that were 0.22 µm in size (Millipore; Billerica, MA, USA). The cytotoxicity experiments were conducted using undiluted extracts.

Cytotoxcity test

Methyl Thiazol Tetrazolium (MTT) assay (Figure 9A) was conducted as an indirect screening test to determine the cytotoxic effects of the adhesives byproducts (extracts). According to the following protocol, the MTT assay was used to evaluate the cells viability in response to the adhesive extracts (for the three immersion times at 24h, 72h, and 168h) eluted from the materials according to the International Standard ISO 10993-part 5 in 2009. The cells (1×10^7 cells mL^{-1}) were cultured in a 96-well plate to a final volume of 200 µL of complete culture medium per each well (i.e., for each subgroup of the 6 composite groups, 6 wells cultured with cells were used). The plates were covered with a sterile parafilm, gently stirred, and incubated for 24 hours at 37°C, 5% CO2. 2. After cell incubation, the culture media was removed, and 200 µl of the culture media containing the adhesive eluents (extracts) of each immersion time period were added. A negative control (12 wells; cells + media only) was used to test the responsiveness of the cells. Triplicate (i.e., three times repetitions) was performed for each subgroup. The plates were then incubated for 24 hours at 37°C and 5% CO2. 3. After exposure to the composite extract, 8-10 µL of MTT solution was added to each well. The plates were further incubated for 3 hours at 37 °C, 5% CO2. 4. The media was then carefully removed, and 30-40 µL of dimethyl sulfoxide solubilization solution was added for each well and incubated for 5 minutes. 5. Finally, the absorbance (i.e., optical density) was measured using an ELISA reader (Biochrom, UK) at a wavelength of 620 nm as seen in Figure (9B). Then the statistical analysis was

performed on the optical density readings to calculate the cells viability.

$$\text{Cell viability (\%)} = \frac{\text{OD negative control} - \text{OD sample}}{\text{OD negative control}}$$

Result

The dose-response viability of human dermal fibroblast normal (HdFn) cells treated with culture media containing composite extracts at different immersion times (24 hours, 72 hours, and 168 hours) is summarized in Tables 2–4 and Figure 10. The cytotoxicity of six composite resins was evaluated based on cell viability percentages, expressed as mean values, standard deviations, and the number of duplicates.

At 24 hours (Table 2), the cell viability for all six composite resins ranged between 95.68% and 96.70%, compared to the control group at 98.86%. The standard deviation values were small, indicating consistent results across replicates. No significant differences in cytotoxicity were observed among the resins during this period, suggesting no severe effects on HdFn cells within 24 hours of exposure.

After 72 hours (Table 3), the cell viability ranged between 95.33% and 96.49%, compared to the control group at 98.86%. While resin 1 exhibited a slightly higher variability (SD = 3.65%), overall, the results remained consistent with no significant differences in cytotoxicity across the six composite materials. The viability remained above 80%, indicating no critical effects on cellular health at this time point.

At 168 hours (Table 4), the cytotoxicity levels varied significantly among the six composite resins. Charisma (A2) Diamond (Kulzer) and Briliant EverGlow® (Coltene) showed the lowest cytotoxicity, with cell viability > 80%. In contrast, Activa (bioactive restoration) and Palfique (Omnichroma) exhibited moderate cytotoxicity, with cell viability between 65% and 80%. The resins Beautifil II (Shofu) and G-aenial Anterior (GC Corporation) showed severe cytotoxicity, with cell viability ≤ 65%, indicating a more pronounced effect on HdFn cells after prolonged exposure.

When comparing intergroup cytotoxicity, no significant differences were observed at 24 hours and 72 hours. However, after 168 hours, significant variations in cell viability percentages were detected, leading to the classification of the resins into three groups based on their cytotoxic effects. Group A included Charisma (A2) Diamond and Briliant EverGlow®, which demonstrated mild cytotoxicity (cell viability > 80%). Group B comprised Activa (bioactive restoration) and Palfique (Omnichroma), which showed moderate cytotoxicity (cell viability 65%–80%). Lastly, Group C consisted of Beautifil II and G-aenial Anterior, which exhibited severe cytotoxicity with cell viability ≤ 65%.

In summary, the results revealed that during the first 24 and 72 hours, all six composite resins demonstrated no significant cytotoxic effects, with cell viability consistently above 80%. After 168 hours, distinct differences in cytotoxicity emerged, ranging from mild to severe. These findings emphasize the importance of long-term assessments when evaluating the biocompatibility of dental composite resins. Detailed data are presented in Tables 2–4, with visual summaries in Figures 9 and 10.

Discussion

It has been revealed by many studies that dental composites can release substances that can result in some adverse biological toxic potencies (13). The cytotoxic effects of dental adhesives are usually reduced but not eliminated entirely by the presence of dentin, and it depends on the thickness of available dentin (13, 14). Several in vitro tests were utilized for testing the biological cytotoxic effects of dental adhesive systems. Basically, the in vitro tests, which utilize cell cultures, provide an inexpensive, convenient, repeatable, rapid, sensitive, and reliable method for ranking and screening materials (15). In this study, we conducted a cytotoxicity test on the new and advanced nanohybrid resin composite filling materials. These materials are new and widely used, and

their cytotoxicity is unknown. Therefore, it is crucial to focus on them to understand their potential adverse effects on soft tissue. Because the proportions and composition of the universal adhesives would probably be changed after incorporation of the ascorbic acid-coated magnetite nanoparticles into them, the hypothesis tested by performing the cytotoxic assays was that the nanoparticle incorporation may affect the adhesive materials, which may cause different cytotoxic profiles. Therefore, the purpose of this in vitro cytotoxicity study (MTT) was to evaluate the cytotoxic effects of six distinct types of composite resin: Activa (bioactive restoration) (Pulpdent), (A2), Beautifil II (Shofu), G-aenial anterior (GC Corporation), Charisma Diamond (Kulzer), Palfique (Omnichroma) (Tokuyama Dental Corporation), and Brilliant Everglow® (Coltene). This was done using an indirect MTT assay. The MTT assay is a mitochondrial activity assay in which the elution products from the adhesive samples were used to test the cytotoxic effects of the adhesives by simulating the substances that leach out of the adhesives and into saliva (13). Four different cell viability parameters (i.e., viable cell count, mitochondrial membrane potential, nuclear strength, and cell membrane permeability) of human dermal fibroblast normal (HdFn) cells in direct contact with the resin composite were measured. The International Standards Organization (ISO 7405, 2013; ISO 10993-5) advocates the use of established cell lines, such as HdFn cells, for cytotoxicity tests. These cells were chosen because the fibroblast can differentiate into other connective tissue cells like odontoblasts, cementoblasts, and osteoblasts. They are easy to isolate and culture, and they are commonly used for cell culture-based standardization of cytotoxicity studies (16, 17). In addition, such a cell line is highly sensitive to the lytic action of cytotoxins and exhibits a greater decrease in cell viability than other cell lines. This will provide a greater sensitivity when assessing the degree of cytotoxicity of dental adhesives, and thereby more reliable results can be achieved (16). The present study showed that all the tested adhesives have metabolic effects on the HdFn cells, and there were no statistically significant differences at 24 hours and 72 hours between the six resin composite types and the control groups. In all composite types, the cells viability was never below 65%. At all immersion times, no significant cytotoxicity was found between 24h and 72h adhesive elution times. In this study, it was discovered that the experimentally incorporated composite restorative materials exhibited varying degrees of cytotoxicity and negatively impacted the metabolic activity of the cells at the 168-hour (1-week) exposure elution time in comparison to the control groups. For instance, Beautifil (Shofu Dental Corporation, Japan) exhibited the highest rate of cytotoxicity when compared to the control fibroblast cells. Different resin restorative types' chemical compositions and the monomer released after composite curing may explain this. (18, 19) The amount of TEGDMA leached from composites may affect their cytotoxicity. Indeed, TEGDMA has been reported to be toxic in different cell lines (20-23). In this study, we discovered that Beautifil exhibits severe cytotoxicity due to its released fluoride content. Fluoride was found to be a cytotoxic agent to cultured human pulp cells by inhibiting cell growth, proliferation, mitochondrial activity, and protein synthesis (14,24). They also include Bis-GMA and TEGDMA in their composition, both of which have been reported to be toxic in various cell lines (20-23). Since bis-GMA is reported to exert greater toxicity than TEGDMA, this could be the underlying reason for the greater cytotoxicity observed in Beautifil II compared with Briliant EverGlow (20, 21). While G-aenial anterior (GC corporation) (A1) demonstrated the same cytotoxicity as the Beautifil II composite, and its cytotoxicity was linked to its composition, which includes UDMA, studies revealed that UDMA has a high cytotoxicity; it induced morphological changes in pulp cells and decreased cell viability by 29-49% at concentrations of 0.1-0.35 mM (25, 26). The 45S5 bioglass paste has some cytotoxic effects because it is initially

acidic after mixing (i.e., pH 2.2), even though ACTIVA is the first bioactive composite with an ionic resin matrix and bioactive fillers that mimic the physical and chemical properties of natural teeth (Pulpdent). (27–29). Omnichroma is the first global composite in the world that uses a single shade to aesthetically match all patients, from A1 to D4. Since Omnichroma can match all 16 VITA traditional hues thanks to its evenly sized supra-nano spherical fillers (260 nm spherical SiO_2-ZrO_2), this composite demonstrated < 80% cell survival due to the reduced matrix content (UDMA, TEGDMA). (25) With a smaller range of hues, the Brilliant EverGlow stackable universal submicron hybrid composite enables very appealing restorations. With its easy handling, outstanding blend-in qualities, and long-lasting brightness, this material is a genuine all-arounder that completely satisfies the highest standards for anterior and posterior restorations. Because the Brilliant EverGlow composite contains dental glass with exceptional physical and chemical qualities, including exceptional aesthetics, translucency, low heat conductivity, sufficient strength, biocompatibility, wear resistance, and chemical durability, it demonstrated less cytotoxicity than the other composites in this study (30, 31). Lastly, to ascertain the levels of toxicity at varied doses, the cytotoxicity of each component that was released from the different materials studied in this study should be further examined.

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Competing interests: None.

Figure (1): Lubrication of the mold .

Figure (2): The celluloid strip as a smooth base.

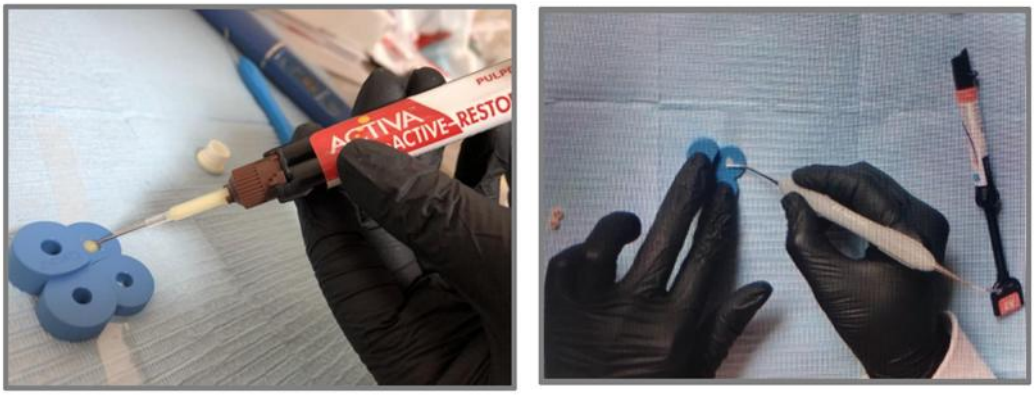

Figure (3, 4): Adding or inject flowable composite into the mold.

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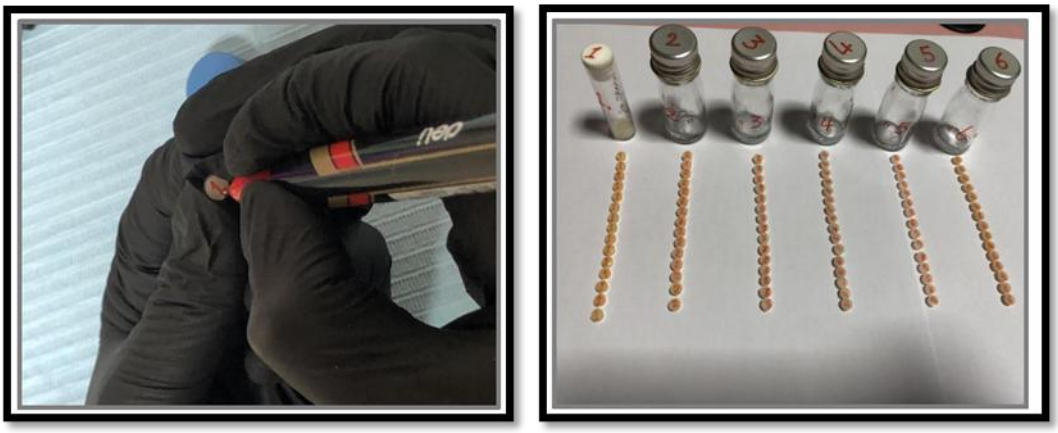

Figure (5, 6): Marking the code number of composite samples, then collect the samples in containers.

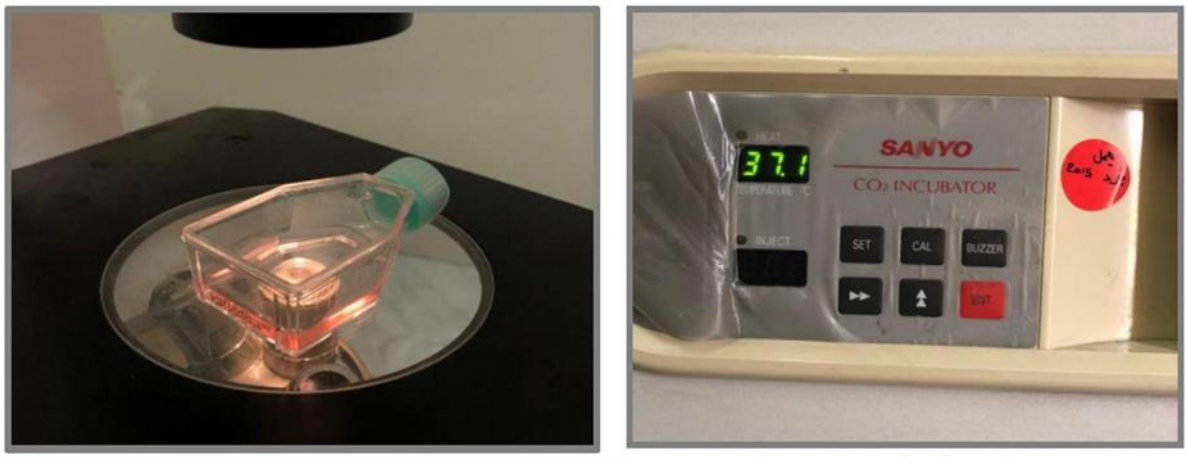

Figure (7): A. Cell Culture Containing Fibroblast cell, B. The incubator

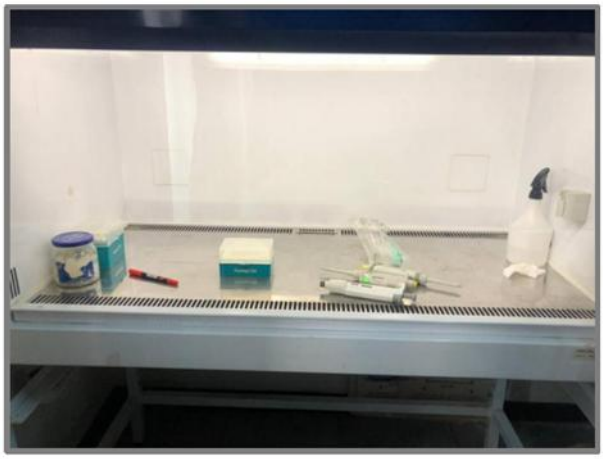

Figure (8): Laminar Air Flow Cabinet

Figure (9): A. The MTT assay kit, B. ELISA reader.

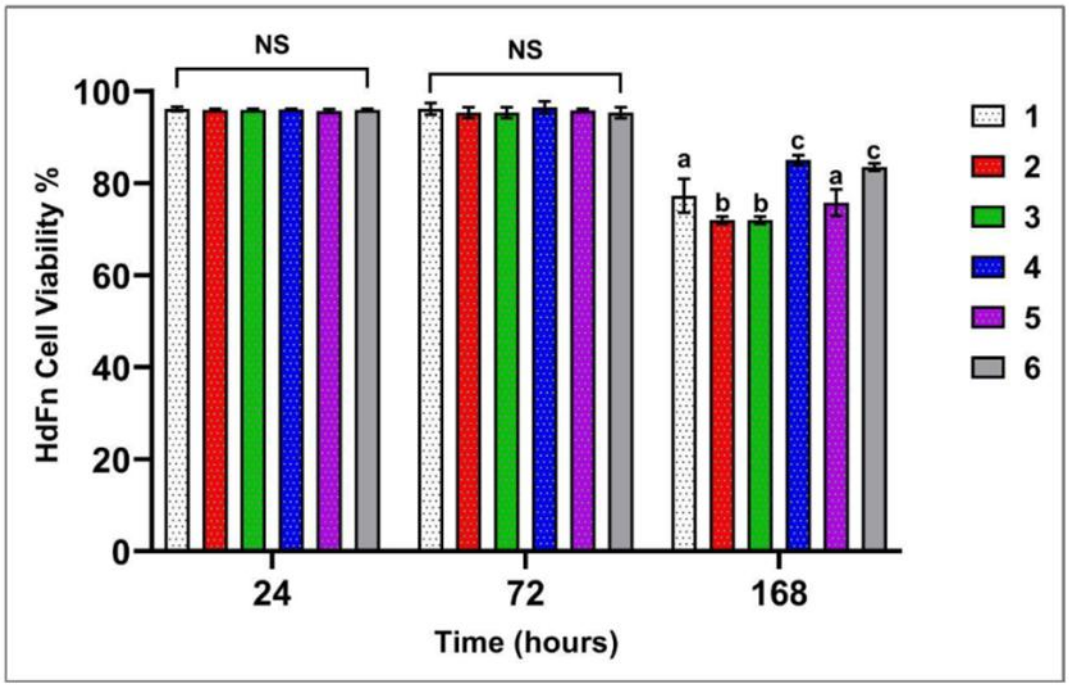

Figure (10): The dose-response viability of human dermal fibroblast normal (HdFn) cells for 24 hours, 72 hours, and 168 hours

Table (1): The specifications of the composite materials**.**

Material	Manufacture	Code	Composition	Filler content	Lot number
Activa Bioactive_restorative	Pulpdent® Corporation ,USA	ABA	Bioglass 45S5	71% (w/w)	190619
Beautifil II	Shofu dental Corporation ,Japan.	B-II	Matrix: Bis-GMA, TEGDMA Filler: S-PRG filler based on fluoroboro-aluminosilicate glass	83%(w/w)	191007
-G-aenial (anterior)	GC Corporation, Tokyo Japan.	GA	Matrix: UDMA, dimethacrylate co-monomers, no bis-GMA Filler:silica, strontium lanthanoid su ondun fluoride	76% (w/w)	191007
Charisma Diamond	Kulzer , Germany.	CA	Matrix Bis-GMA, TEGDMA Filler Ba-Al-B-F-Si glass, Pyrogenic SiO2	64% (w/w)	K010077
Palfique Omnichroma	Tokuyama Dental corporation Tokyo, Japan	POC	Matrix: UDMA, TEGDMA, Mequinol, Dibutyl hydroxyl toluene and UV absorber. Filler: sperical silica-zirconia filler and composite filler.	79% (w/w)	007EYO
Briliant EverGlow	Coltene , Switzerland	BEG	Matrix Methacrylates, Dental glass, Amorphous silica, Zinc oxide. Filler per-polymerised fillers corresponding to the composition of the composite itself.	74% (w/w)	K88524

Table (2): cytotoxicity of six composite resin in 24 h

Time		control	1	2	3	4	5	6	summary
24 h	Mean	98.86	96.10	95.95	95.95	96.70	95.68	95.95	No significant
	SD	0.20	0. 48	0.20	0.20	0.12	0.41	0.20	No significant

Table (3): cytotoxicity of six composite resin in 72 h

Time		control	1	2	3	4	5	6	summary
72 h	Mean	98.86	96.18	95.95	95.33	96.49	95.83	95.33	No significant
	SD	0.20	3.65	1.18	1. 18	1.29	0.31	1.18	No significant

Table (4): cytotoxicity of six composite resin in 186 h `

Time		control	1	2	3	4	5	6	summary
168h	Mean	98.86	77.28	71.95	71.95	85.03	75.77	83.53	significant
	SD	0.20	3.65	0.81	0.81	1.04	2.91	0.81	significant

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