Original Article

ASSESSMENT OF BIOCOMPATIBILITY AND BIOINERTNESS OF DENTAL IMPLANTS MADE OF ZIRCONIUM DIOXIDE *IN VIVO*

Vladislav Kokoev[1], Kasum Magomedov[2], Magomedrasul Amirbekov[2], Boris Ferziev[2], Zaira Musaeva[2], Azret Kabardov[1], Madina Kupeeva[2], Alika Kalyanova[3]*

[1]*Department of Dentistry, Faculty of Dentistry, North-Ossetian State Medical Academy, Vladikavkaz, Russia. bucky99@yandex.ru*
[2]*Department of Dentistry, Faculty of Dentistry, Saratov State Medical University named after V.I. Razumovsky, Saratov, Russia.*
[3]*Department of Dentistry, Faculty of Dentistry, Stavropol State Medical University, Stavropol, Russia.*

https://doi.org/10.51847/W6yPLLSwl4

ABSTRACT

This article presents a method of mechanical processing of structural material for the manufacture of individual transcendental implants used to restore the biomechanical characteristics of teeth with a resected root. The technique is reproduced utilizing in-line exposure to zirconium dioxide stabilized with yttrium, aluminum oxide powder of a certain dispersion and particle diameter, under a pressure of 2 atmospheres. Additionally, the influence of structural material and artificially created surface roughness of individual transcendental zirconium dioxide implants on the formation of bone tissue in the jawbones of experimental animals was studied. Samples of individual transcendental implants were fixed in artificially created critical defects of the mandible of laboratory rabbits. Histological preparations were prepared in dynamics, at the time of withdrawal of animals from the experiment 1, 3, 6, and 9 months after surgery. The obtained results indicated the formation of mature bone tissue in the intraoperative defect around analogs of transcendental implants and the absence of inflammatory and macrophage reactions in dynamics. This indicates the biocompatibility, bioinertness, and effectiveness of zirconium dioxide as material for dental implants.

Key words: Transcendental implant, Zirconium dioxide, Osseointegration of dental implants, Biocompatibility.

Introduction

The development and application of new digital technologies in medicine, and in particular in dentistry, has led to the emergence of new structural materials used both for the manufacture of dentures and for the manufacture of artificial supports for these prostheses [1-3]. One of these materials is zirconium dioxide. It has found wide application in medicine due to its mechanical properties, low corrosion potential, low cytotoxicity, and minimal bacterial adhesion [4-6]. Currently, there is evidence of the use of zirconium for the manufacture of intraosseous implants, abutments, and ceramic crowns [7-9]. The advantages of ceramic implants over standard widespread titanium implants are a significantly reduced likelihood of allergic reactions, lower weight, and better aesthetic properties [10-12]. *In vitro* studies have shown that zirconium dioxide does not have a cytotoxic effect on osteoblasts and contributes to the manifestation of moderate proliferation [13-15]. Like a titanium implant, the surface of a zirconium intraosseous implant is important for the process of osseointegration [16-18]. Artificial roughening of the surface and other forms of modification of its topography improve the process of osseointegration and create a stronger connection of the implant with bone tissue [19-21]. At the same time, the development and selection of a technique for creating a special surface of zirconium dioxide implants in order to improve the strength of its connection with bone tissue is an urgent task of dentistry [22-34].

Therefore, this study aimed to evaluate the effectiveness of the proposed surface treatment technique for individual milled transcendental zirconium dioxide implants based on the results of their osseointegration in an experiment on laboratory animals *in vivo*.

Materials and Methods

Analogs of individual milled transcendental implants made of zirconium dioxide with yttrium additives were processed by a sandblasting machine under a pressure of 2 atmospheres with aluminum oxide powder with a grain size of 110 µm [35]. In this case, the treatment was performed in one direction, longitudinally along the axis of the implant. Further, these analogs, after sterilization treatment, were introduced into artificially created critical bone cavities of the jaws of 12 laboratory Chinchilla rabbits **(Figure 1)** [34-42]. Bone defects were created with a diameter of 10 mm and a depth of 3 mm using a drill and a milling cutter, in the projection of 2-3 teeth [43]. Osteoplastic material BioOss (Geistlich, Switzerland) was injected into the defects on both sides [44-48]. The perimeter of the defect was covered with a collagen membrane BioGide (Geistlich, Switzerland). After filling the bone cavities with these implants, the soft tissues above them were sutured tightly in layers [49]. In the postoperative period, clinical observation was carried out, with the use of antibiotics Baitril 0.5 ml intramuscularly for 7 days [50-54]. Animals were removed from the experiment for 1, 3, 6, 9 months: 3 animals for each period in each group by intraperitoneal administration of calypsol at a dose of 750 mg/kg and one at a dose of 200 mg/kg of the experimental animal's weight. Next, the skeletonization of the jaws and the manufacture of preparations for microscopy were carried out [55, 56].

Figure 1. Introduction of an analog of an individual milled transdental implant made of zirconium dioxide into the defect

Results and Discussion

According to the results of the study, 1 month after implantation of an analog of an individual transcendental zirconium implant treated with aluminum oxide powder according to the proposed technology with the BioOss (Geistlich, Switzerland) glass-conductive preparation, numerous fragments of the BioOss material (Geistlich, Switzerland), devoid of cellular elements, were visible in the mandible cavity. Loose connective tissue was formed around these fragments, consisting of numerous cellular elements, such as fibroblasts with a slight admixture of macrophages and lymphocytes [57, 58]. The walls of the cavity of the bone defect were formed from maternal bone tissue [59]. There are practically no inflammatory phenomena and destruction of the defect walls **(Figure 2)**. Phase contrast microscopy showed the disordered fibrillar structure of bone fragments of BioOss (Geistlich, Switzerland) and the fibrous structure of connective tissue (collagen fibers) [60, 61]. Polarization microscopy showed a weaker anisotropy (double refraction) than in normal bone tissue [62]. Notably, there was no obvious and characteristic outline of the implant, since the contents of the defect cavity are loose [22, 63-72].

As a result of the control study at the same time, i.e., a defect formed in the same animal on the opposite side of the rabbit jaw, filled with the BioOss osteoconductive drug (Geistlich, Switzerland) and blocked by the resorbable membrane of BioGuade (Geistlich, Switzerland), but without the introduced analog of an individual transcendental implant, the histological picture of the preparations of the three rabbits was similar. The bone defect was filled with small fragments of BioOss material (Geistlich, Switzerland) with the identification of a fibrillar structure, significantly different from the structures of healthy bone tissue, which were completely devoid of cells and stained with hematoxylin and eosin with varying degrees of intensity with a slight macrophage reaction [73, 74]. During polarization microscopy, bone fragments of the bone replacement drug Bio Oss (Geistlich, Switzerland) were devoid of double refraction, unlike healthy bone tissue, that is, they were anisotropic [75, 76].

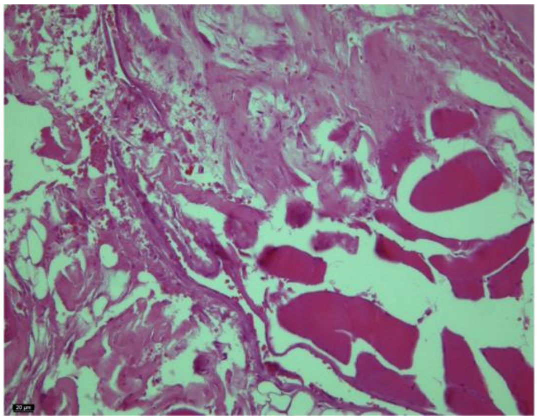

Figure 2. Histological examination. The withdrawal period is 1 month (experiment). There are numerous fragments of Bio-oss bone tissue and connective tissue in the cavity of the defect. Stain: hematoxylin and eosin, ×200

When studying the drugs of the experimental group at the time of withdrawal from the experiment after 3 months, the histological picture is similar in all 3 animals. The wall of the bone cavity formed as a result of the removal of an analog of an individual transcendental implant made of zirconium dioxide is made up of mature fibrous connective tissue represented by intertwined strands of fusiform fibroblasts and collagen fibers **(Figure 3)**.

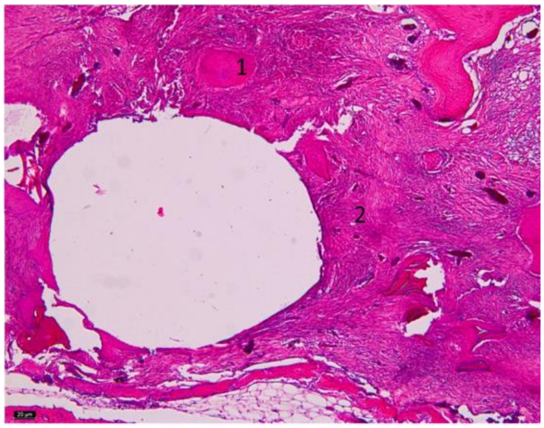

Figure 3. Histological examination. The withdrawal period is 3 months (experiment). The defect is filled with dense connective tissue. A rounded cavity is visible in it, from which the implant has been removed. Small fragments of Bio-Oss material are visible in the tissue (1), as well as elements of newly formed bone tissue (2). Stain: hematoxylin and eosin, ×200

Separate small trabeculae of the newly formed bone are visible in this tissue [77]. The same trabeculae are also visible at a distance from the implant, where the bulk of the osteoconductive drug BioOss (Geistlich, Switzerland) was located. Connective tissue is well vascularized. The macrophage reaction along the boundaries of the location of the analog of the transdental implant is minimal. The inflammatory reaction, characterized by edema, neutrophil infiltration, is completely absent. This indicates the high biocompatibility of the structural material of the analog of the transdental implant. All of the above applies to the wide belt of connective tissue around the cavity from the implant. This fabric fills the entire area of the defect. At the very border between the cavity from the implant and the connective tissue, there is a very thin strip 20-30 µm thick, where the fibers and one or two layers of fibroblasts are located longitudinally. There are also a few macrophages. Hypothetically, it can be assumed that this strip is the implant's connective tissue capsule [78].

In the study of the control group, after 3 months, the cavity of the intraoperative defect was filled with connective tissue of various types. Basically, this connective tissue was represented by a relatively loose connective tissue of the fibroreticular type. However, there was a dense, mature tissue consisting of strands of fibroblasts and collagen fibers with single areas of osteogenesis [79, 80].

After 6 months in the experimental groups after implantation of analogs of individual transcendental implants made of zirconium dioxide and osteoconductive drug BioOss (Geistlich, Switzerland), the defect was filled with connective tissue, mainly this tissue has a dense fibrous character and is represented by coarse fibrous tissue. Minor fragments of Bio Oss material (Geistlich, Switzerland) remain in it and beams of newly formed bone tissue are visible, which grows from the walls of the maternal bone and often surrounds fragments of the glass-conductive material [81]. The wall of the cavity around the extracted implant analog, as well as in the previous period, consists of mature fibrous connective tissue with a high degree of vascularization, represented by intertwined strands of fusiform fibroblasts and, to a greater extent, collagen fibers. In this tissue, individual small trabeculae of the newly formed bone of the experimental animal are visible [82, 83].

Similarly to the preparations of experimental animals withdrawn from the experiment for 3 months, in the preparations after 6 months, there is a very thin strip of one or two layers of fibroblasts located longitudinally, but with a smaller thickness, 15-20 µm, at the boundary between the cavity from the implant and connective tissue. There are also no signs of an inflammatory reaction around the implant analogs **(Figure 4)**.

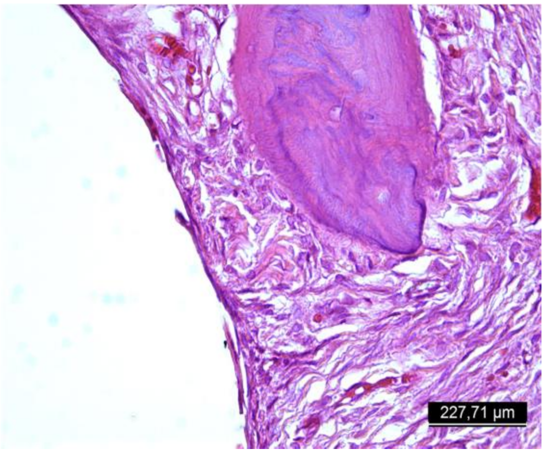

Figure 4. Histological examination. The withdrawal period is 6 months (experiment). Bone defect after removal of a transcendental implant made of zirconium dioxide. The wall of the cavity is made up of mature fibrous connective tissue, represented by intertwined strands of fusiform fibroblasts and collagen fibers. Separate small trabeculae of the newly formed bone are visible in this tissue. Stain: hematoxylin and eosin, ×400

In the control group, after 6 months, the defect cavity, where Bio Oss material was implanted (Geistlich, Switzerland), but without an analog of an individual transdental implant, was filled with fibrous and fibroreticular tissue without inflammatory infiltration. In this tissue, a few fragments of osteoconductive material BioOss (Geistlich, Switzerland) are visible, surrounded by newly formed bone tissue. Phase contrast and dark-field microscopy clearly show the fibrillarity of the connective tissue and the organized microstructure of the newly formed bone [84, 85].

When studying the preparations of the experimental group, after 9 months, a cavity is found in the bone tissue of the rabbit jaw, in which particles of the BioOss glass-conductive material remain reduced compared to the 6 months (Geistlich, Switzerland). The material has an amorphous granular structure. However, at high magnification, osteons with a fuzzy structure appear in places in it: a central vessel from which the rays radiate [86]. With phase contrast microscopy, osteones are more clearly visible, but mostly the material has a granular structure that differs sharply from the bone structure [87, 88]. However, fragments with preserved bone structure are found among this material.

Under dark field microscopy, the Bio-Oss material (Geistlich, Switzerland) differs sharply from the surrounding bone except for the fragments described above. During polarization microscopy, the bone walls of the cavity give anisotropy (double refraction). The destroyed Bio-Oss material (Geistlich, Switzerland), except for the fragments described above, does not give anisotropy [89]. It should be noted that the wall of the cavity consists of healthy mature bone tissue **(Figure 5)**.

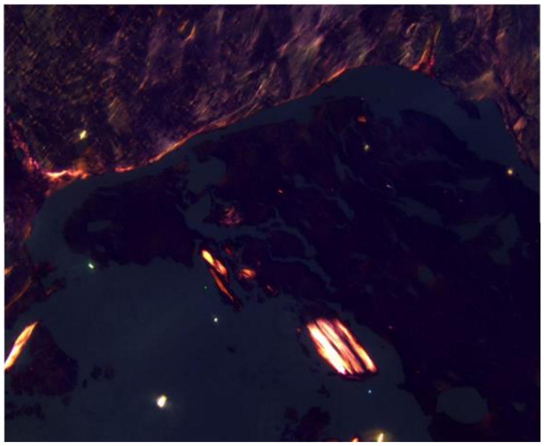

Figure 5. Histological examination. The withdrawal period is 9 months (experiment). During polarization microscopy, the bone walls of the cavity give anisotropy (double refraction). Stain: hematoxylin and eosin, ×400

There are no connective tissue gaps between the cavity wall and the material in it. There are no signs of an inflammatory or dystrophic process in the bone tissue of the cavity walls. This indicates that zirconium dioxide (the structural material from which the transcendental implant is made) does not have any toxic effect on the hard and soft tissues of the animal [63, 90, 91]. Notably, when examining the drugs of the control group after 9 months, the histological picture of all 3 animals was similar. Namely, the defect cavity was filled with mature bone tissue with formed single osteons and a circulatory system. Small granules of Bio-Oss osteoplastic material were observed in places, located in a loose connective tissue capsule.

Conclusion

Thus, by analyzing the results obtained, namely, the formation of mature bone tissue in an intraoperative defect around analogs of transcendental implants and the absence of inflammatory and macrophage reactions in dynamics, it is possible to conclude biocompatibility, bioinertness, as well as confirmation of the effectiveness of the proposed methodology for modeling a special surface of a transcendental implant made by computer modeling and milling from zirconium dioxide.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: The protocol for experiments with laboratory animals complied with the requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Protocol 3 dated by Aug 3, 2024).

References

1. Watanabe H, Fellows C, An H. Digital technologies for restorative dentistry. Dent Clin North Am. 2022;66(4):567-90. doi:10.1016/j.cden.2022.05.006
2. Tian Y, Chen C, Xu X, Wang J, Hou X, Li K, et al. A review of 3D printing in dentistry: Technologies, affecting factors, and applications. Scanning. 2021;2021:9950131. doi:10.1155/2021/9950131
3. Sulaiman TA. Materials in digital dentistry-A review. J Esthet Restor Dent. 2020;32(2):171-81. doi:10.1111/jerd.12566
4. Kongkiatkamon S, Rokaya D, Kengtanyakich S, Peampring C. Current classification of zirconia in dentistry: An updated review. PeerJ. 2023;11:e15669. doi:10.7717/peerj.15669
5. Hanawa T. Zirconia versus titanium in dentistry: A review. Dent Mater J. 2020;39(1):24-36. doi:10.4012/dmj.2019-172
6. Bacchi A, Cesar PF. Advances in ceramics for dental applications. Dent Clin North Am. 2022;66(4):591-602. doi:10.1016/j.cden.2022.05.007
7. Chagas MM, Kobayashi-Velasco S, Gimenez T, Cavalcanti MGP. Diagnostic accuracy of imaging examinations for peri-implant bone defects around titanium and zirconium dioxide implants: A systematic review and meta-analysis. Imaging Sci Dent. 2021;51(4):363-72. doi:10.5624/isd.20210120
8. Blinov AV, Nagdalian AA, Gvozdenko AA, Blinova AA, Maglakelidze DG, Golik AB, et al. A tool for removing metal inclusions from the surface of paint and varnish car coatings. Coatings. 2022;12(6):807. doi:10.3390/coatings12060807
9. Hassan NS, Jalil AA, Khusnun NF, Bahari MB, Hussain I, Firmansyah ML, et al. Extra-modification of zirconium dioxide for potential photocatalytic applications towards environmental remediation: A critical review. J Environ Manage. 2023;327:116869. doi:10.1016/j.jenvman.2022.116869
10. Comisso I, Arias-Herrera S, Gupta S. Zirconium dioxide implants as an alternative to titanium: A systematic review. J Clin Exp Dent. 2021;13(5):e511-9. doi:10.4317/jced.58063
11. Ludovichetti FS, Stellini E, Signoriello AG, DI Fiore A, Gracco A, Mazzoleni S. Zirconia vs. stainless steel pediatric crowns: A literature review. Minerva Dent Oral Sci. 2021;70(3):112-8. doi:10.23736/S2724-6329.20.04432-5
12. Cao R, Chen B, Xu H, Fan Z. Clinical outcomes of titanium-zirconium alloy narrow-diameter implants for single-crown restorations: A systematic review and meta-analysis. Br J Oral Maxillofac Surg. 2023;61(6):403-10. doi:10.1016/j.bjoms.2023.05.005
13. Alammar A, Blatz MB. The resin bond to high-translucent zirconia-A systematic review. J Esthet Restor Dent. 2022;34(1):117-35. doi:10.1111/jerd.12876

14. Saeed F, Muhammad N, Khan AS, Sharif F, Rahim A, Ahmad P, et al. Prosthodontics dental materials: From conventional to unconventional. Mater Sci Eng C Mater Biol Appl. 2020;106:110167. doi:10.1016/j.msec.2019.110167
15. Alrashdi M, Ardoin J, Liu JA. Zirconia crowns for children: A systematic review. Int J Paediatr Dent. 2022;32(1):66-81. doi:10.1111/ipd.12793
16. Alzanbaqi SD, Alogaiel RM, Alasmari MA, Al Essa AM, Khogeer LN, Alanazi BS, et al. Zirconia crowns for primary teeth: A systematic review and meta-analyses. Int J Environ Res Public Health. 2022;19(5):2838. doi:10.3390/ijerph19052838
17. Padhye NM, Calciolari E, Zuercher AN, Tagliaferri S, Donos N. Survival and success of zirconia compared with titanium implants: A systematic review and meta-analysis. Clin Oral Investig. 2023;27(11):6279-90. doi:10.1007/s00784-023-05242-5
18. Fernandes PRE, Otero AIP, Fernandes JCH, Nassani LM, Castilho RM, de Oliveira Fernandes GV. Clinical performance comparing titanium and titanium-zirconium or zirconia dental implants: A systematic review of randomized controlled trials. Dent J (Basel). 2022;10(5):83. doi:10.3390/dj10050083
19. Donohoe E, Kahatab R, Barrak F. A systematic review comparing the macrophage inflammatory response to hydrophobic and hydrophilic sandblasted large grit, acid-etched titanium or titanium-zirconium surfaces during in vitro studies. Clin Exp Dent Res. 2023;9(3):437-48. doi:10.1002/cre2.730
20. Dewan H. Clinical effectiveness of 3D-milled and 3D-printed zirconia prosthesis-A systematic review and meta-analysis. Biomimetics (Basel). 2023;8(5):394. doi:10.3390/biomimetics8050394
21. Raszewski Z, Brząkalski D, Derpeński Ł, Jałbrzykowski M, Przekop RE. Aspects and principles of material connections in restorative dentistry comprehensive review. Materials (Basel). 2022;15(20):7131. doi:10.3390/ma15207131
22. Madhukar CV. Production of potential bio-compost from household and market waste vegetables for the improvement of plant growth. World J Environ Biosci. 2022;11(2):15-9.
23. Dirican S. Wetland of local importance in sivas province (Turkey): Kaz Lake. World J Environ Biosci. 2023;12(1):16-9.
24. Aodh AM, Al-Marshedi AA. Williams-beuren's syndrome: A case report in Prince Sultan Military city, Riyadh, Saudi Arabia 2022. World J Environ Biosci. 2023;12(1):20-3.
25. Mulu E, Jenber AJ, Tesfaye A, Belay B. Integrated management of onion thrips on onion, Mecha district, Ethiopia. World J Environ Biosci. 2023;12(1):32-40.
26. Meena DS, Akash A, Bijalwan K, Bhandari BS, Sharma P. Efficacy of oleoresin obtained from bore-hole method in chir-pine for potential antimicrobial activity. World J Environ Biosci. 2023;12(2):7-12.
27. Tovar NE, Méndez EJ, Cruz WX, Rodríguez DC, Ramos NS, Gómez BJ, et al. Mango peel as a substrate for the production of citric acid. World J Environ Biosci. 2023;12(2):43-7.
28. Cherif BA. The floods in arid areas case of catchment of the Valley Béchar, South-West, Algeria. World J Environ Biosci. 2023;12(3):1-6.
29. Padma KR, Don KR, Dinesh B, Karthikeyan D. Antibiotics are current approaches to improve productivity using soil microbiome. World J Environ Biosci. 2023;12(3):33-9.
30. Bate GB, Adeleye AO, Ijanu EM, Olalere EO, Amoo AO, Asaju CI, et al. Quality assessment of wastewater: physicochemical and bacteriological evidence from dutse abattoir, north-west nigeria. World J Environ Biosci. 2023;12(3):58-66.
31. Tilahun L, Jenber AJ, Degu A, Tizazu TY. Effects of preservative solutions on shelf life and quality of cut gypsophila flowers, Ethiopia. World J Environ Biosci. 2024;13(1):8-14.
32. Karthikeyan V, Muthupriya P, Gopikrishna M, Sivakumar K. Effects of electromagnetic radiation and radio frequency on freshwater calanoid and cyclopoid copepods. World J Environ Biosci. 2024;13(2):1-5.
33. Shaji S, Gowda B, Gurusiddappa LH, Veeresh SJ, Kalikeri S, Bellari K, et al. Navigating the hazards: A review of pesticides and their effects on human well-being. World J Environ Biosci. 2024;13(2-2024):21-30.
34. Obisesan OO, Egbetokun OA. Climate change impacts, food security, Intra-Africa trade and sustainable land governance on food systems in Africa. World J Environ Biosci. 2024;13(3):39-50.
35. Blinov AV, Nagdalian AA, Arefeva LP, Varavka VN, Kudryakov OV, Gvozdenko AA, et al. Nanoscale composite protective preparation for cars paint and varnish coatings. Coatings. 2022;12(9):1267. doi:10.3390/coatings12091267
36. Febrianti Y, Muhajir M, Khoiroh U, Claridho F, Djojodibroto JA, Srihadi N. Prevalence of potentially inappropriate medications in psychogeriatric patients in Indonesia based on the beers 2019 criteria. J Adv Pharm Educ Res. 2023;13(2):144-9.
37. Alamer E. The cross-talk study between immune system and SARS-CoV-2. J Adv Pharm Educ Res. 2023;13(3):56-63.
38. Tsvetkova D, Kostadinova I. Antioxidant activity of medicinal plant compounds and aminoacids for prevention of Alzheimer's disease. J Adv Pharm Educ Res. 2023;13(3):79-87.
39. Solihah I, Herlina H, Munirah E, Haryanti H, Amalia M, Rasyid RS, et al. The hypoglycemic effect of purple sweet potato leaf fractions in diabetic rats. J Adv Pharm Educ Res. 2023;13(3):64-72.
40. Badrieva AB, Bichenov GG, Haluhoeva ZA, Arapieva AA, Baykhanov RM, Khalibekova ZN, et al. Phytopharmacotherapy of neurodegenerative disorders of the rat brain with an aqueous extract of

Chlorophytum comosum. J Adv Pharm Educ Res. 2023;13(3):13-8.
41. Sakhnenkova TI, Abdul-Kadyrova LR, Akhilgova ZA, Brovikova AA, Markov OO, Saribekyan AA, et al. Morphological and biochemical analysis of 3D scaffold based on biocompatible polymer for tissue engineering. J Adv Pharm Educ Res. 2023;13(3):29-33.
42. Yagubova EY, Gusenova GT, Zubiyeva FV, Berezhnaya VV, Pulatova KM, Tomboidi KK, et al. Evaluation of the neuroprotective effect of root and leaf extracts of Chlorophytum comosum. J Adv Pharm Educ Res. 2023;13(3):52-5.
43. Sadyrin E, Swain M, Mitrin B, Rzhepakovsky I, Nikolaev A, Irkha V, et al. Characterization of enamel and dentine about a white spot lesion: Mechanical properties, mineral density, microstructure and molecular composition. Nanomaterials (Basel). 2020;10(9):1889. doi:10.3390/nano10091889
44. Pecherskaya AE, Andreeva DV, Abdulazizova KM, Sampieva FM, Albogachieva MB, Babayan AG, Esenova YR, Lubentseva AG. Evaluation of genotoxicity and cytotoxicity of silver nanoparticles. J Adv Pharm Educ Res. 2023;13(3):23-8.
45. Carpio-Vargas EE, Ibarra-Cabrera EM, Ibarra MJ, Choquejahua-Acero R, Calderon-Vilca HD, Torres-Cruz F. Categorical stress predictors in higher education students amidst remote learning in COVID-19 pandemic. J Adv Pharm Educ Res. 2023;13(2):131-9.
46. Triyono T, Amijaya KA. Regular donor characteristics, inter-donation interval and the presence of subclinical anemia–A 3-year observational single-center study. J Adv Pharm Educ Res. 2023;13(2):118-23.
47. Tatyana Y, Svitlana O, Viktoriia PL, Olga R, Oleksandr K. Treatment of allergic rhinitis: A review of homeopathic therapy. J Adv Pharm Educ Res. 2023;13(2):107-17.
48. Alhmoud HA, HussienAkkam Y, Al Omari D. Naproxen sodium influence, excipients and the dissolution medium on the swelling of the tablets. J Adv Pharm Educ Res. 2023;13(2):1-5.
49. Schendrigin IN, Timchenko LD, Rzhepakovsky IV, Avanesyan SS, Sizonenko MN, Grimm WD, et al. Clinical and pathogenetic significance of amylase level and microtomographic index of synovial fluid in various joint lesions. Mod Technol Med. 2022;14(6(eng)):42-9. doi:10.17691/stm2022.14.6.05
50. Perwitasari DA, Baroroh F, Dania H, Faridah IN, Hidayati A, Nurmaguphita D, et al. Interprofessional education in pharmacogenomics: Perspective of pharmacy and nursing students. J Adv Pharm Educ Res. 2023;13(2):16-23.
51. Kokoeva LM, Kumacheva DD, Dzhalagonia TB, Mikhailova AI, Kamyshova AA, Moiseenko MP, et al. Analysis of the effectiveness of complex pharmacotherapy using antibacterial agents and immunomodulators for bronchial pneumonia. J Adv Pharm Educ Res. 2023;13(2):99-106.
52. Zhou J, Lin Y, Dewey RS, Zhou Y. The distribution of Kolb's learning style in college students from different family backgrounds. J Adv Pharm Educ Res. 2023;13(2):83-91.
53. Khan A, Khan MI, Khan S, Rehman AU, Ullah N, Ur A, et al. Evaluation of HBeAg and HBV viral load among general population of district Bannu, Khyber Pakhtunkhwa, Pakistan. J Adv Pharm Educ Res. 2023;13(2):59-63.
54. Yahyaeva AH, Aslanovna MM, Yariyeva KA, Pogosov AO, Ilyasova NA, Kokova DR. Study of blood-ocular barrier permeability by Fluoroquinolone group drugs. J Adv Pharm Educ Res. 2023;13(2):35-42.
55. Alqifari S, Binswelim M, Alkhiari K, Alshammari R, Alzughaibi M, Alzaaq R, et al. Academic activity aims to early expose medical students to best prescribing practices. J Adv Pharm Educ Res. 2023;13(1):153-7.
56. Nurcahyo H, Febriyanti R, Riyanta AB, Sutanto H, Herdwiani W. The influence of extraction temperature and time on antiradical activity and total phenolic extract of Ceciwis. J Adv Pharm Educ Res. 2023;13(1):31-4.
57. Nikkerdar N, Golshah A, Salmani Mobarakeh M, Fallahnia N, Azizi B, Shoohanizad E, et al. Recent progress in the application of zirconium oxide in dentistry. J Med Pharm Chem Res. 2024;6(8):1042-71. doi:10.48309/jmpcr.2024.432254.1069
58. Dzugutova K, Kozyreva Z, Mekhtieva K, Bertaev B, Agkatsev A, Zaseev R, et al. Experimental in vivo evaluation of the activity of hydroxyapatite modified with selenium nanoparticles against caries in laboratory animals. J Med Pharm Chem Res. 2024;7(1):89-97. doi:10.48309/jmpcr.2025.457522.1243
59. Esiev RK, Samvelyan AA, Kliukina EI, Gazaryants VA, Abdurakhmanova BS, Garibyan VS, et al. Investigation of the effectiveness of nano impregnation of dentine tubules with a molecular complex of copper hydroxyapatite. J Med Pharm Chem Res. 2024;7(1):42-50. doi:10.48309/jmpcr.2025.457568.1244
60. Remizova AA, Sakaeva ZU, Dzgoeva ZG, Rayushkin II, Tingaeva YI, Povetkin SN, et al. The role of oral hygiene in the effectiveness of prosthetics on dental implants. Ann Dent Spec. 2021;9(1):39-46. doi:10.51847/HuTuWdD0mB
61. Ragimov RM, Zakaev CT, Abdullaeva NM, Esiev RK, Pushkin SV, Nauruzova DM, et al. Analysis of the effectiveness of the use of multifunctional biopolymers of chitosan and alginate in dentistry. J Adv Pharm Educ Res. 2022;12(3):21-7. doi:10.51847/yWRLcwYTDC
62. Yusupova MI, Mantikova KA, Kodzokova MA, Mishvelov AE, Paschenko AI, Ashurova ZAK, et al. Study of the possibilities of using augmented reality in

dentistry. Ann Dent Spec. 2021;9(2):17-21. doi:10.51847/BG1ZAzqXRc
63. Feng P, Lin Z, Tan X, Yang J. The physical exercise application in frailty and its underlying mechanisms. Bull Pioneer Res Med Clin Sci. 2024;3(1):37-45. doi:10.51847/AtQjEvBH7v
64. Aldhairyan AH, Alyami SS, Alsaad AM, Al Shuqayfah NI, Alotaibi NA, Mujammami NM, et al. Gastroesophageal reflux disease: Diagnosis and management approach, literature review. World J Environ Biosci. 2022;11(1):1-3.
65. Almuhanna MA, Alanazi MH, Al Ghamdi RN, Alwayli NS, Alghamdi IS, Qari AA, et al. Tachycardia evaluation and its management approach, literature review. World J Environ Biosci. 2022;11(1):4-8.
66. Almohmmadi GT, Bamagos MJ, Al-Rashdi YJ, Alotaibi NS, Alkiyadi AA, Alzahrani AM, et al. Literature review on polycythemia vera diagnostic and management approach. World J Environ Biosci. 2022;11(1):9-12.
67. Alqurashi AM, Jawmin SA, Althobaiti TA, Aladwani MN, Almuebid AM, Alharbi JF, et al. An overview on nasal polyps' diagnosis and management approach. World J Environ Biosci. 2022;11(1):13-6.
68. Alhazmi RA, Khayat SK, Albakri MH, Alruwaili WS, Bayazed HA, Almubarak SA, et al. An overview on the assessment and management of polycystic ovarian syndrome. World J Environ Biosci. 2022;11(1):17-23.
69. Alsayed MA, Alhassan OM, Alzahrany AM, Mutanbak HI, Alamoudi AA, Eid SM, et al. An overview on lumbar disc herniation on surgical management approach. World J Environ Biosci. 2022;11(1):24-9.
70. Dirican S. A look at the change in water occupancy rates of Gölova Dam Lake, Turkey. World J Environ Biosci. 2022;11(1):34-6.
71. Pimple NS. Virtual population analysis and recruitment pattern of osteobrama vigorsii (Sykes, 1839) from Nira River, Bhor Maharashtra. World J Environ Biosci. 2022;11(1):53-9.
72. Baghdadi AM. Isolation and optimization growth parameters for enhanced bioactivity profiles of streptomyces strain isolated from Saudi Arabia. World J Environ Biosci. 2022;11(2):8-14.
73. Sadulaev R, Magomedov T, Khurtueva A, Geteriev A, Turabov N, Koba A, et al. Toxicological assessment of the effect of cadmium chloride on quantitative and qualitative parameters of spermatogenesis in vivo. J Med Pharm Chem Res. 2025;7(2):321-32. doi:10.48309/jmpcr.2025.458716.1257
74. Spitznagel FA, Balmer M, Wiedemeier DB, Jung RE, Gierthmuehlen PC. Clinical outcomes of all-ceramic single crowns and fixed dental prostheses supported by ceramic implants: A systematic review and meta-analyses. Clin Oral Implants Res. 2022;33(1):1-20. doi:10.1111/clr.13871
75. Hossain N, Mobarak MH, Hossain A, Khan F, Mim JJ, Chowdhury MA. Advances of plant and biomass extracted zirconium nanoparticles in dental implant application. Heliyon. 2023;9(5):e15973. doi:10.1016/j.heliyon. 2023.e15973
76. Al-Nawas B, Lambert F, Andersen SWM, Bornstein MM, Gahlert M, Jokstad A, et al. Group 3 ITI consensus report: Materials and antiresorptive drug-associated outcomes in implant dentistry. Clin Oral Implants Res. 2023;34 Suppl 26:169-76. doi:10.1111/clr.14135
77. Ban S. Chemical durability of high translucent dental zirconia. Dent Mater J. 2020;39(1):12-23. doi:10.4012/dmj.2019-109
78. Gali S, Gururaja S, Patel Z. Methodological approaches in graded dental ceramics. Dent Mater. 2024;40(5):e1-e13. doi:10.1016/j.dental.2024.02.016
79. Jauregui-Ulloa J, Marocho SS. Bonding and debonding of zirconia using laser approaches. Int J Prosthodont. 2022;35(4):530-44. doi:10.11607/ijp.7991
80. Bollen C, Hakobayan G, Jörgens M. One-piece versus two-piece ceramic dental implants. Br Dent J. 2024;236(5):383-7. doi:10.1038/s41415-024-7123-3
81. Laleman I, Lambert F, Gahlert M, Bacevic M, Woelfler H, Roehling S. The effect of different abutment materials on peri-implant tissues-A systematic review and meta-analysis. Clin Oral Implants Res. 2023;34 Suppl 26:125-42. doi:10.1111/clr.14159
82. Alqutaibi AY, Ghulam O, Krsoum M, Binmahmoud S, Taher H, Elmalky W, et al. Revolution of current dental zirconia: A comprehensive review. Molecules. 2022;27(5):1699. doi:10.3390/molecules27051699
83. Chopra D, Jayasree A, Guo T, Gulati K, Ivanovski S. Advancing dental implants: Bioactive and therapeutic modifications of zirconia. Bioact Mater. 2021;13:161-78. doi:10.1016/j.bioactmat.2021
84. Afrashtehfar KI, Del Fabbro M. Clinical performance of zirconia implants: A meta-review. J Prosthet Dent. 2020;123(3):419-26. doi:10.1016/j.prosdent.2019.05.017
85. Chopra D, Guo T, Gulati K, Ivanovski S. Load, unload and repeat: Understanding the mechanical characteristics of zirconia in dentistry. Dent Mater. 2024;40(1):e1-e17. doi:10.1016/j.dental.2023.10.007
86. Parrey MUR, Alshammari AO, Bedaiwi AA, Salama B. Digital eye strain: Knowledge, attitude, and practice among university students. Arch Pharm Pract. 2023;14(3):33-7. doi:10.51847/jwUgTazd60
87. Salem MMI, Abdelaal AAM, El-Fiky AA, Ebid AA, Battecha KH, Thabet AAE, et al. High-intensity laser therapy versus shock wave therapy in the management of diabetic frozen shoulder. Pharmacophore. 2024;15(2):113-8. doi:10.51847/twO5acnaXy
88. Kunie K, Kawakami N, Shimazu A, Yonekura Y, Miyamoto Y. Studying the role of managers' communication behaviors in the relationship between nurses' job performance and psychological

empowerment. J Organ Behav Res. 2024;9(1):151-61. doi:10.51847/OXN9xWb1Ub

89. Glamazdin IG, Medvedev IN, Kutuzov DD, Fayzullina II, Nazarova SV, Sysoeva NY, et al. Main parasitic infestations of wild ungulates used for food. J Biochem Technol. 2024;15(2):59-63. doi:10.51847/iKmPtRdbFp
90. Khyade VB, Yamanaka S, Bajolge R. Utilization of BSF-cream for antiaging impact on human skin. Entomol Appl Sci Lett. 2024;11(1):56-66. doi:10.51847/BdrxgiFL1L
91. Patricia A, Hailemeskel B. Turmeric, black pepper, and lemon hot infusion for joint and musculoskeletal pain: A case report. World J Environ Biosci. 2024;13(1):36-8. doi:10.51847/XeYTN4wNsa