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REVIEW

PERSPECTIVES OF ORAL DENTAL CARE

Gertrud-Alexandra PALTINEAN[1], Diana Alexandra FLOREA[1], Gheorghe TOMOAIA[2,3], Sorin RIGA[1,3], Cristina Lavinia ROSOIU[1], Aurora MOCANU[1], Maria TOMOAIA-COTISEL[1,3]

[1]Babes-Bolyai University, Faculty of Chemistry and Chemical Engineering, Research Centre of Physical Chemistry, 11 Arany Janos Str., RO 400028, Cluj-Napoca, Romania
[2]Iuliu Hatieganu University of Medicine and Pharmacy, Department of Orthopedic Surgery, 47 General Traian Mosoiu Str., RO 400132, Cluj-Napoca, Romania
[3]Academy of Romanian Scientists, 3 Ilfov Str., District 5, RO 050044, Bucharest, Romania
*Corresponding author: Maria Tomoaia Cotisel, mcotisel@gmail.com

Abstract. *This research focuses on debating the negative impact on dental enamel produced by unhealthy diet, some alcoholic and non-alcoholic drinks, smoking, drug use, inadequate hygiene conditions due to poor lifestyle and physical-chemical activities. These factors denature the quality of dental enamel, and the demineralization process begins resulting in caries and periodontal diseases. Caries are the most common diseases of the oral cavity that, if not treated in time, lead to dysfunctional mastication, impaired smile, gingival inflammation, abscess, and unbearable pain. The research also addresses the remineralization of dental enamel using materials and composites based on hydroxyapatite that are capable of producing beneficial effects for strong and healthy teeth. Evaluating caries prevention methods is absolutely essential, but the most important of all is educating children from an early age that healthy teeth require proper personal hygiene.*

Keywords: Enamel, caries, hydroxyapatite, remineralization, composites

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1.Introduction

Dental enamel is the hard tissue that covers and protects the crown of a tooth. It is composed of organic components such as (proteins, lipids), inorganic constituents (hydroxyapatite being the main mineral component, octacalcium phosphate, tricalcium phosphate, brusite, struvite, and other components) and water [1, 2]. The teeth are part of the oral cavity that makes the connection between the external and the internal environment. Their role is to allow the chewing of food for good digestion, coherent speech and the smile that is a person's identity card. A healthy and well-maintained dentition leads to adaptation without shame and pain to physiological changes during life [3]. The appearance of teeth occurs from early infancy, classified as the primary dentition, and around the age of six, they change to permanent teeth [4-6].

The oral cavity of a mature person contains 32 teeth in total, contained in two large arches, maxillary and mandibular. The maxillary and mandibular are also divided into 2 hemi arches. A hemi arch contains 1 central incisor, 1 lateral incisor, 1 canine, 2 premolars and 3 molars, being equally distributed on the other hemiarch. Studies highlight that the morphology, nomenclature and shape of teeth is important in identifying each tooth and describing the position of them [7]. The oral system is a complex biological environment that includes interactions and mechanisms present in oral health. These can lead to an improvement of individual quality or the deterioration of health causing the appearance of diseases.

Oral diseases such as caries are the most common dental diseases that, if not treated in time, can penetrate to the root causing their loss. Global Burden Disease (GBD) has estimated, following some studies, that 3.5 billion people are affected by dental caries, the causes of their occurrence being multiple [8, 9]. Currently, most people cannot afford adequate dental care, a periodic check to determine oral condition, or they do not have the time necessary to pay special attention to the care. In this way, dental caries and other acute and chronic diseases that spread in the body and affect other tissues and organs make their presence felt.

From the point of view of current research, dental enamel is the main protective barrier accessible to the flow of ions from consumed food (liquid, solid) that negatively influences the development of ameloblast cells and produces changes in opacity and color [10, 11]. The permeability of the ions increases as cracks in the tooth enamel increase, resulting in dental wear and erosion. These problems are common among the population and not only due to the flow of ions from food, but also due to the poor quality of the dental structure, vicious habits, grinding of the teeth, gastrointestinal disorders, the imbalance of the bacterial flora that increases the excess acid resulting in an unprecedented demineralization of the plaque dental [12-15]. With demineralization of the dental enamel, exposure to pathogenic agents is inevitable, caries intervenes, and the acute and chronic diseases. To this end, it is essential to raise the awareness of the population, to change the living conditions and the infrastructure, but also to support those with low incomes so that they can benefit from the services for the prevention and treatment of dental diseases.

2.Causes of tooth enamel denaturation

The state of oral health has attracted attention in recent years due to the multitude of causes that distort dental quality, starting with dental enamel and continuing until the definitive loss of teeth. Epidemiological studies have highlighted the factors that contribute to the occurrence of oral diseases (caries, dental erosion, periodontitis), so in Figure 1, you can see the representative diagram of a tooth with healthy enamel. Due to an unhealthy diet, poor oral hygiene, smoking, and some alcoholic and non-alcoholic drinks, the first signs of caries and dental erosion appear. In the first phase, they are in the early stage, highlighting a greater roughness, but untreated, they lead to severe diseases [16]. The prevention of dental diseases is largely dependent on the potential of dental applications, which has developed rapidly in the last period as a result of nanotechnology. Thus, correct diagnosis and therapy are fundamental in oral care.

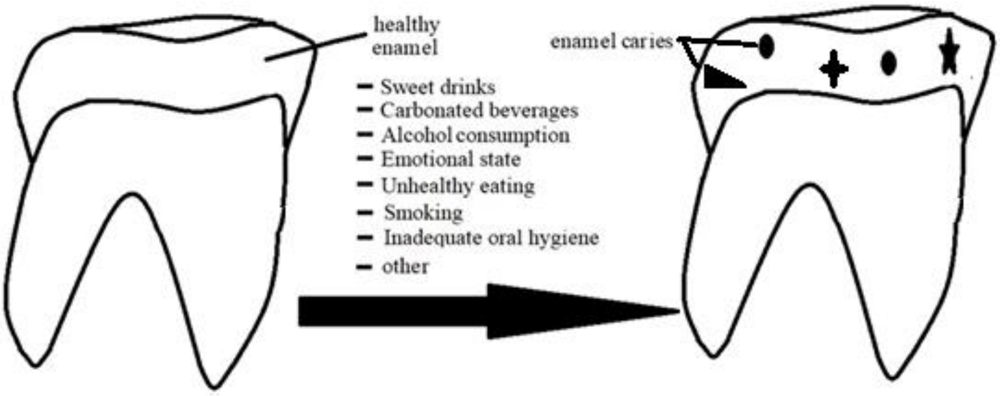

Fig. 1. Cause of enamel caries

2.1. Consumption of alcoholic and non-alcoholic beverages

A main cause of tooth enamel demineralization is the consumption of drinks, whether alcoholic or non-alcoholic, acidic, sweet or carbonated, which are mainly consumed by teenagers. These drinks contain acids (phosphoric, citric, malic) and sugars that, over time, are dangerous for oral health [17, 18]. Acids give drinks an aromatic and artificially sweetened taste and improve shelf life. Young people (children, pupils, students) are the main consumers of liquids, where a significant increase in dental problems such as caries, enamel erosion, and cracks is noticed. Prolonged exposure to acids and sugars involves a series of chemical and biological processes that, associated with abrasion, cause erosive dental wear. Furthermore, daily consumption causes reactions between the bacterial plaque flora and the chemicals that make up drinks to produce lesions in different stages [19]. Very important to mention, the pH, whichis the pH, optimal for the oral cavity, is located between 6.75 and 7.25 [20]. At the same time, it is an indicator of dental erosion and caries (pH 5.5). This study was conducted on the drinks available to the American consumer, where most drinks are potentially erosive to the dentition [18]. They also found that not only does a low pH damage enamel, but also an increased pH also favors the occurrence of erosion. Although specialist research claims that the oldest dental problem remains dental caries, patients should be aware that oral diseases are transmissible and infectious but can be prevented. A 2011 study showed that a nursing mother with active caries can transfer the bacteria to the newborn [20]. In addition to the pH and the composition that influence the appearance of dental anomalies, the acid concentration, retention in the oral cavity, the quality of dental enamel and the properties of calcium to form chelates must also be taken into account.

If young people are the main drinkers, excessive consumption is also due to the summer season, when temperatures are very high and we feel the need to cool off. Unfortunately, these pleasures necessarily lead us at some point to the dental check-up to prevent possible dental problems. Moderate consumption will produce a decrease in oral health, and an adequate care of the teeth will reduce the increase in the level of microorganisms and possible pathologies.

2.2. Oral hygiene

Maintaining oral health depends on how we take care of our teeth [21, 22]. The care procedure involves some well-defined, simple and necessary steps. Brushing and washing the teeth with toothpaste, rinsing with mouthwash, and using dental floss have become the most common daily hygiene measures and are important in maintaining oral health. A single application of brushing the teeth is not enough. Dentists and specialized literature recommend that after every meal, it is good to apply the tooth care procedure; in this way food residues and bacteria are removed. Also, during dental check-ups, doctors should support patients by promoting oral health (correct use of the toothbrush, time allocated to washing and other procedures) [23]. Parents have the duty to educate children about the importance of oral health and the benefits that oral care mechanisms bring to the human body.

Although care procedures are within the reach of any individual, there are still situations where these simple care procedures are not carried out due to the socio-economic status of countries whose development is precarious, lack of interest, or lack of knowledge in this field [24]. However, at some point, due to unbearable pain and other dental infections, the population feels the need for oral care, but, not having the coverage of medical services, individuals choose to treat themselves by changing the diet or using some ancient remedies. Specialized studies have managed to highlight the inequality in terms of low-income people's access to adequate care [25, 26].

2.3. Food and smoking

For proper functioning of the body, it is necessary to supply food, which is closely related to the development of dental caries, demineralization of dental enamel, and diseases specific to the dentition. Food is passed through the chewing mechanism, leading to the onset of dental erosion and the destabilization of oral health [27, 28]. Among the most dangerous foods that damage oral health are carbohydrates [29-31], foods such as those with acid pH (snacks, citrus fruits, vinegar-based sauces), sweets and foods with high hardness (sunflower seeds, peanuts, nuts, popcorn). Smoking is harmful to tooth enamel and is responsible for the appearance of bacterial plaque, yellowing and bad smell of the oral cavity, decreasing the resistance of the teeth. At the same time, smoking favors the appearance of gingivitis and periodontitis and, therefore, the loss of teeth. It should also be mentioned that the temperature during smoking can change the morphology of hydroxyapatite crystals in the dental enamel component [32, 33].

3. Remineralization of dental enamel

Hydroxyapatite is a biomaterial found naturally in bones and teeth. It is a calcium phosphate that the human body to build the bone skeleton. This is one of the reasons why hydroxyapatite has attracted the attention of researchers and because it induces the formation of new bone sites. Synthesizing of hydroxyapatite in the laboratory is done by methods such as dry (solid state and mechanochemical), wet (coprecipitation, hydrolysis, and hydrothermal) and at high temperatures (combustion and pyrolysis). Hydroxyapatite is used in 1) biomedical applications such as bone replacement, HAP-enriched Portland cements applied in endodontics [34, 35], composites for the activation of titanium implant surfaces [36-39], and 2) as a material to protect the environment during the removal of heavy metals from wastewater and soil [40, 41] or in the preservation of marble monuments [42]. The bioactivity of hydroxyapatite can be improved by incorporating elements necessary for the human body into its structure. These elements can be: Mg, Si, Zn, Sr, Na, Cu, Ag, Se and constituents such as (SiO_4) and $(CO_3)^{2-}$ being proven by specialized literature that hydroxyapatite has the ability to very easily accept ions in the network to crystallize [43-55].

The denaturation of the hard components of the body led to intensive research and the preparation of synthetic hydroxyapatite as close as possible in composition and structure to the hard tissues in order to regenerate and replace them. In this review, the specialized literature was debated on the development of optimal models of the composition of toothpastes containing hydroxyapatite and other constituents favorable to remineralization. The importance of composite materials based on hydroxyapatite for biomedical applications was also highlighted. Commercial toothpastes based on hydroxyapatite have been designed by countries such as Germany, Italy, the UK, the USA, Canada, Holland, Portugal, Spain, and Russia. Table 1 shows the commercial name of the toothpaste, the ingredients and the country of manufacture.

Table 1. Commercial toothpastes with hydroxyapatite content

No. Crt.	***Toothpaste with HAP content***	***Ingredients***	***Producing country***	***Refs.***
1	APAGARD® PREMIO	Aqua, dicalcium phosphate, glycerin, xylitol, **hydroxyapatite (nano)**, silica, Peg-8, sodium lauryl sulfate, cellulose gum, aroma, sodium silicate, trimagnesium phosphate, hydrolyzed conchiolin protein, sodium saccharin, glycyrrhetinic acid, cetylpyridinium chloride, lauryl diethylenediaminoglycine HCl	Tokio, Japan and Germany	[56, 57]
2	APADENT TOTAL CARE	Aqua, dicalcium phosphate, glycerin, xylitol, **hydroxyapatite (nano),** silica, Peg-8, sodium lauryl sulfate, cellulose, gum, aroma, trimagnesium phosphate, PVP, Butylene glycol, alcohol, sodium Lauroyl Sarcosinate, Sodium Saccharin, Cetylpyridinium chloride, Glycyrrhetinic Acid, Pyridoxine HCl, Lauryl Diethylenediaminoglycine HCl, *Camellia Sinensis* leaf extract, *Chamomilla Recutilla* (Matricaria) extract, *Salvia Officinalis* (Sage) Leaf Extract	Tokio, Japan and Germany	[57]
3	Boka Ela Mint Toothpaste	Water, vegetable glycerin, hydrated silica, sorbitol powder, silica, **hydroxyapatite (nano)**, sodium benzoate, sodium lauroyl sarcosinate, mentha piperita essential (peppermint) oil, *Mentha viridis* (spearmint) oil, *Illicium verum* (star anise) oil, *Gaultheria procumberis* (wintergreen) oil, xylitol, xanthan gum, *Stevia*	Minneapolis, Minnesota, USA	[58, 59]

		rebaudiana extract powder, methylsulfonylmethane, *Aloe barbadensis* (aloe vera) leaf juice, sodium bicarbonate, *Camellia sinensis* (green tea) leaf extract, *Cucumis sativus* (cucumber) fruit extract, *Persea gratissima* (avocado) fruit extract, *Mangifera indica* (mango) fruit extract, menthol, *Elettaria cardamomum miniscula* seed (cardamom), potassium chloride.		
4	Boka Coco Ginger Toothpaste	Glycerin, water, hydrated silica, erythritol, silica, natural flavors (coconut and ginger), **hydroxyapatite (nano)**, xanthan gum, sodium benzoate, leaf juice of *Aloe barbadensis* (aloe vera), *Chamomilla recutita* (chamomile) flower extract, methylsulfonylmethane (msm), potassium chloride, sodium bicarbonate, Stevia rebaudiana extract powder, sodium lauroyl sarcosinate.	Minneapolis, Minnesota, USA	[58, 59]
5	Boka Kids Orange Cream	Water, Glycerin, Hydrated Silica, Sorbitol, Silica, **Hydroxyapatite (nano),** Sodium Benzoate, Xanthan gum, Xylitol, Sodium Lauroyl Sarcosinate, Potassium chloride, Propylene Glycol, Dimethyl Sulfone, Flavor (Natural Orange), *Aloe Barbadensis* Leaf Juice, *Stevia Rebaudiana* Extract, Sodium Bicarbonate, Flavor (Natural Cream), Menthol, *Mangifera Indica* (Mango) Fruit Extract, *Persea Gratissima* (Avocado) Fruit Extract, *Camellia Sinensis* (Green Tea) Leaf Extract, *Cucumis Sativus* (Cucumber) Fruit	Minneapolis, Minnesota, USA	[58, 59]

		Extract, Phenoxyethanol.		
6	Kinder Karex toothpaste	**10% hydroxyapatite**, aqua, hydrated silica, glycerin, hydrogenated starch hydrolysate, xylitol, silica, cellulose gum, sodium methyl cocoyl taurate, sodium sulfate, 1,2-hexanediol, caprylyl glycol, aroma, sodium cocoyl glycinate	Dr. Kurt Wolff GmbH & Co. KG, Bielefeld, Germany	[60, 61]
7	Biorepair®, Total protection Plus	Aqua, Zinc **Hydroxyapatite***, Glycerin, Hydrated Silica, Sorbitol, Silica, Aroma, Cellulose gum, Sodium Myristoyl Sarcosinate, Sodium Methyl Cocoyl Taurate, Citric Acid, Tetrapotassium Pyrophosphate, Zinc PCA, Sodium Saccharin, Phenoxyethanol, Benzyl Alcohol, Sodium Benzoate.	Coswell S.p.A., Funo, Bologna, Italy	[62]
8	LACALUT white & repair	Aqua, Hydrogenated starch hydrolysate, Hydrated Silica, **Hydroxyapatite**, Silica, Poloxamer 188, PEG-32, Sodium Lauryl Sulfate, Disodium Pyrophosphate, Aroma, Pentasodium Triphosphate, Tetrapotassium Pyrophosphate, Cellulose gum, Sodium Fluoride, Titanium Dioxide, Aluminum Lactate, Sodium Saccharin, Methylparaben, Propylparaben, Eugenol, Limonene	Dr. Theiss Naturwaren GmbH, Germany	[63, 64]

The specialized literature highlights that the inclusion of medical hydroxyapatite in APAGARD and APADENT toothpastes helps prevent tooth decay by removing bacterial plaque, filling surface cracks, and remineralizing the tooth enamel. Medical HAP also helps to restore the specific natural color of the teeth, maintain their health and reduce dental sensitivity. Such actions of medical HAP were clinically proven and officially approved by the Japanese Ministry of Health in 1995 [57]. As for the Boka Ela Mint, Boka Coco Ginger and Boka Kids Orange Cream toothpastes, they are made in America with the exception of hydroxyapatite which is synthesized in European laboratories [58, 59]. The benefits of hydroxyapatite for these toothpastes were studied by E. Pepla and colleagues who claim that nanohydroxyapatite has remineralizing effects on enamel damage and tooth sensitivity. The use of hydroxyapatite in toothpaste as an additive material has improved the already existing material through its chemical bonding properties, does not produce inflammation, stimulates bone growth and improves bone-implant osseointegration [59]. These toothpastes have not been approved by the FDA and the ADA, but their testing has proven to be nontoxic and safe.

Karex toothpaste with a 10% hydroxyapatite has been proven by the study by the authors B. T. Amaechi et al., as an effective toothpaste in the control of root caries, which is an alternative in its management compared to toothpastes containing sodium fluoride [60]. However, E. Paszynska et al. claim that hydroxyapatite has a high biocompatibility and, if it is accidentally swallowed by children, it is safe. They also conclude that hydroxyapatite in toothpaste is a biomimetic alternative to children's fluoride toothpastes [61].

Biorepair toothpaste was studied by M. Bossu et al., in order to evaluate the remineralization and repair properties of dental enamel. The use of this toothpaste with hydroxyapatite content has been shown to have a high potential in the remoineralization of dental enamel and has been shown to prevent caries in children before school age [62]. Lacalut White and Repair toothpaste has the effect of remineralizing tooth enamel and removes and sediment whitens discoloration and deposited on the surface of the tooth. Used regularly, the Lacalut range whitens the enamel, provides protection, and helps to gradually obtain the natural whiteness of the teeth and provides freshness [63, 64]. This is how hydroxyapatite is a main component in toothpastes, helping to remineralize tooth enamel, whiten them, to prevent caries and eliminate unpleasant odors, giving a feeling of freshness. Of course, this component has proven to be effective not only in dentistry, but also in orthopedics, where it has led to exceptional results.

4. Composite materials based on hydroxyapatite

4.1. Hydroxyapatite-Curcumin (HAP-CCM)

Curcumin is a vegetable compound widely exploited for its biological activities. Since its bioavailability, bioactivity, stability and physico-chemical behavior are less effective, strategies have been developed to improve curcumin properties by complexing with whey proteins [65-68], betacyclodextrin [69-74] with natural compounds such as piperine , silymarin, resveratrol [75, 76], lipids and hydroxyapatite. Due to their unique properties, nanoparticles have found various uses in many fields starting from hydrogen production [77-82], synteses of materials with photoluminescence proprieties [83], adsorption capabilities [84, 85], photocatalytic proprieties [86] to bio materials [34-38]. Specialized studies show that curcumin nanoparticles were loaded onto carboxylic acid-functionalized hydroxyapatite, with the effects being evaluated on the MCF7 breast cancer cell line. In this case, the experimental results highlight cell proliferation, cellular absorption of CCM NPs, apoptosis and cell cycle arrest. Such a study could improve the anticancer activity [87]. Nanofibrous composites of hydroxyapatite/gelatin and curcumin were also prepared with the aim of being used as a dental biomaterial. These types of composites were evaluated for their antimicrobial activity against E. Coli, S. Aureus and S. Mutans strains. The antimicrobial effects were significant against them. From this point of view, the use of composites in dental tissue engineering can reduce the resistance of bacteria [88].

The development of composites that improve the biological properties of curcumin is absolutely necessary and another type of composite of zinc curcumin on fluorine-doped hydroxyapatite has been studied to improve dental and orthopedic applications. The study shows that the interaction between zinc and curcumin increases the release of curcumin and the antibacterial efficacy of the complex against S. Aureus was proven due to the presence of zinc fluoride and curcumin [89]. Composites have been developed for the treatment of bone cancer in the MG63 cell line, highlighting the cytotoxic effect by activating apoptosis and increasing the level of AMPK, ARRB1, associated with the G2/M cell cycle [90].

4.2. Hydroxyapatite-icariin (HAP-ICA)

A new composite is that of HAP-ICA. Icarin was encapsulated in PLGA and then incorporated into PCL / HAP scaffolds for bone regeneration. Studies have shown that icariin promotes osteogenic differentiation of MC3T3-E1 and promotes calvarian bone healing [91]. Another study in this direction generated a scaffold prepared from chitosan, hydroxyapatite and icariin. Icarin does not affect the physical structure of the chitosan/HAP scaffold, but decreases its mechanical properties when it is in high dose. From the point of view of cell compatibility and osteogenic differentiation of hBMSC, the results are favorable and the controlled release of icariin from the composite lasted up to 90 days in vitro [92]. A similar study evaluates the effects of icariin on osteogenic differentiation and expression of BMSCs. Micro/nanogranules of HAP were synthesized in order to deliver icariin and tested on a rat femoral plug defect model. In vitro assays have shown that icarin enhances osteogenic differentiation of rat BMSCs through alkaline phosphatase activity, transcription factor 2 (Runx2), ALP, collagen type I (Col I), osteocalcin (OCN) and secretion of OCN proteins [93].

4.3. Hydroxyapatite-piperine (HAP-PIP)

Piperine (PIP is an alkaloid derived from black pepper and has biological activities such as anticancer. Because of poor water solubility, low bioavailability, short half-life, and non-specific targeting, K. AbouAitah and collaborators prepare nanoformulations based on hydroxyapatite nanoparticles (HAPs) functionalized with phosphonate groups (HAP-Ps) and PIP was loaded into HAPs and HAP-Ps at pH 7.2 and 9.3. *In vitro* tests show potential for colon cancer cells HCT116 and strong reduction in MCF-7 cells [94].

Such composite materials based on hydroxyapatite and plant compounds extracted from plants are a new field with wide opening in medicine. Applicability can consist of antimicrobial activities necessary nowadays where pathogens are present at every step and anticancer activities that are expected to produce beneficial effects considering that this merciless disease attacks even the youngest age.

5. Conclusions

This review is focused on dental enamel and the impact produced by unhealthy diet, some alcoholic and non-alcoholic drinks, smoking, drug use, inadequate hygiene conditions, and physical-chemical activities on them.

The research shows the demineralization process produced by the factors mentioned above, caries beginning and disfunctionality that can appears if we do not treat the cause.

Also, enamel remineralization is discussed using toothpastes based on hydroxyapatite. Some examples of toothpaste are shown that their use can prevent caries, eliminate unpleasant odors giving a feeling of freshness, and removes and whitens discoloration and deposited sediment from the surface of the tooth.

The possibility of composite materials based on hydroxyapatite and natural compounds such as curcumin, piperine and icariin that can help bone regeneration in both dentistry and orthopedics has been debated.

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Notations and/or **Abbreviations**

CCM – curcumin, PIP – piperine, ICA – icariin, HAP – hydroxyapatite, GBD - Global Burden Disease

REFERENCES

[1] J. de Dios Teruel, A. Alcolea, A. Hernandez, A. J. Ortiz Ruiz, Comparison of chemical composition of enamel and dentine in human, bovine, porcine and ovine teeth, Arch. Oral. Biol., **60**, 768-775 (2015).

[2] T. Baumann, T. S. Carvalho, A. Lussi, The effect of enamel proteins on erosion, Sci. Rep., **5**, 15194 (2015). https://doi.org/10.1038/srep15194

[3] M. A. Peres, L. M. D. Macpherson, R. J. Weyant, B. Daly, R. Venturelli, M. R. Mathur, S. Listl, R. K. Celeste, C. C. Guarnizo-Herreño, C. Kearns, H. Benzian, P. Allison, R. G. Watt, Oral diseases: a global public health challenge, Lancet, **394**, 249-260 (2019).

[4] M. A. Husain, Dental anatomy and nomenclature for the radiologist, Radiol. Clin. N. Am., **56**(1), 1-11 (2018).

[5] S. J. Nelson, *Introduction to dental anatomy*, in book WHEELER'S Dental Anatomy, Physiology, and Occlusion – Tenth Edition, (Elsevier Saunders, St. Louis, USA, 2015), Chapter 1, pp. 1-19.

[6] M. B. Stephens, J. P. Wiedemer, G. M. Kushner, Dental problems in primary care, Am Fam Physician, **98**(11), 654-660 (2018).

[7] J. C. Turp, K. W. Alt, *Anatomy and morphology of human teeth*, in book Dental Anthropology, Fundamentals, Limits and Prospects, eds. K. W. Alt, F. W. Rosing, M. Teschler-Nicola, (Springer, Vienna, Austria, 1998), chapter 3, pp. 71-94. https://doi.org/10.1007/978-3-7091-7496-8_6

[8] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet, 392(10159), 1789–1858 (2018). doi:10.1016/s0140-6736(18)32279-7

[9] D. A. Florea, C. T. Dobrota, R. Carpa, S. Riga, M. Tomoaia-Cotisel, Current status and trends in oral health care technologies. a perspective review, Int. J. Med. Dent., **26**(1), 38-50 (2022).

[10] R. S. Lacruz, S. Habelitz, J. T. Wright, M. L. Paine, Dental enamel formation and implications for oral health and disease, Physiol. Rev., **97**(3), 939-993 (2017).

[11] L. de Barros Pinto, M. L. Lima Alves Lira, Y. W. Cavalcanti, E. L. De Andrade Dantas, M. L. Oliveira Vieira, G. Garcia de Carvalho, F. Barbosa de Sousa, Natural enamel caries, dentine reactions, dentinal fuid and bioflm, Sci. Rep., **9**, 2841 (2019). https://doi.org/10.1038/s41598-019-38684-7

[12] V. K. Jarvinen, I. I. Rytomaa, O. P. Heinonen, Risk factors in dental erosion, J. Dent. Res., **70**(6), 942-947 (1991).

[13] J. Wu, M. Li, R. Huang, The effect of smoking on caries-related microorganisms, Tob. Induc. Dis., **17**, 32 (2019). https://doi.org/10.18332/tid/105913

[14] R. J. Lamont, H. Koo, G. Hajishengallis, The oral microbiota: dynamic communities and host interactions, Nat. Rev. Microbiol., **16**(12), 745–759 (2018).

[15] A. M. Picoș, I. Petean, A. Picoș, A. Dădârlat-Pop, A.-L. Răchișan, A. M. Tomșa, N. M. Petrăchescu, C. Petri, M. E. Badea, I. D. Măgurean, Atomic force microscopy analysis of the surface alterations of enamel, dentin, composite and ceramic materials exposed to low oral pH in GERD, Exp. Ther. Med., **22**(1), 1-8 (2021).

[16] R. Cheng, H. Yang, M. Y. Shao, T. Hu, X. D. Zhou, Dental erosion and severe tooth decay related to soft drinks: a case report and literature review, J. Zhejiang Univ. Sci. B, **10**(5), 395–399 (2009).

[17] A. Reddy, D. F. Norris, S. S. Momeni, B. Waldo, J. D. Ruby, The pH of beverages available to the American consumer, J. Am. Dent. Assoc., **147**(4), 255–263 (2016).

[18] B. M. de Souza, M. Vertuan, I. V. B. Gonçalves, A. C. Magalhães, Effect of different citrus sweets on the development of enamel erosion in vitro, J. Appl. Oral Sci., **28**, e20200182, (2020). doi: 10.1590/1678-7757-2020-0182

[19] M. B. Mishra, S. Mishra, Sugar-sweetened beverages: general and oral health hazards in children and adolescents, Int. J. Clin. Pediatr. Dent., **4**(2), 119–123 (2011).

[20] S. Sa, M. Zeraatkar, Factors affecting oral hygiene and tooth brushing in preschool Children, Shiraz/Iran, J. Dent. Biomater., **4**(2), 394–402 (2017).

[21] A. Choo, D. M. Delac, L. B. Messer, Oral hygiene measures and promotion: Review and considerations, Aust. Dent.J., **46**(3), 166-173 (2001).

[22] G. Rajeev, A. J. Lewis, N. Srikant, A time based objective evaluation of the erosive effects of various beverages on enamel and cementum of deciduous and permanent teeth, J. Clin. Exp. Dent., **12**(1), e1–e8 (2020). doi: 10.4317/jced.55910

[23] O. Jensen, P. Gabre, U. M. Skold, D. Birkhed, L. Povlsen, 'I take for granted that patients know' – oral health professionals' strategies, considerations and methods when teaching patients how to use fluoride toothpaste, Int. J. Dent. Hygiene, **12**, 81–88 (2014).

[24] A. R. Hosseinpoor, L. Itani, P. E. Petersen, Socio-economic inequality in oral healthcare coverage: results from the world health survey, J. Dent. Res., **91**(3), 275-281 (2012).

[25] R. M. Andersen, H. Yu, R. Wyn, P. L. Davidson, E. R. Brown, S. Teleki, Access to medical care for low-income persons: how do communities make a difference?, Med. Care Res. Rev., **59**(4), 384-411 (2002).
[26] J. Y. Han, J. S. Lee, J. H. Lee, M. H. Jin, S. H. Kim, Associations between dietary habits, emotional state and subjective oral symptoms in 62,276 South Korean adolescents, Int. Dent. J., **70**, 347–359 (2020).
[27] G. A. Scardina, P. Messina, Good oral health and diet, J. Biomed. Biotechnol., 2012, Article ID 720692 (2012). doi:10.1155/2012/720692
[28] I. Casula, L. Bonfanti, A. Ganda, T. Anzaldi, E. Marchesini, M. E. Bianchi, A. Amighetti, Eating and oral hygiene habits in a population of young adults: An observational study, Italian J. Dent. Med., **2**(3), 90-100 (2017).
[29] D. Acatrinei, R. Vinteanu, N. Rosoiu, Biochemical and histological researches regarding the use of new therapeutic methods in some oral and facial pathologies, Academy of Romanian Scientists, Annals Series on Biological Sciences, **8**(2), 35-46 (2019).
[30] D. Acatrinei, N. Forna, B. S. Acatrinei, N. Rosoiu, The action of treatmens with micronutriens and bioactive compounds in stopping the evolution of the periodontal disease, Romanian Journal of Oral Rehabilitation, **13**(1), 68-88 (2021).
[31] D. Acatrinei, N. Forna, I. Diaconu, N. Rosoiu, Interaction of porphyromonas gingivalis bacterium with other bacteria in determining periodontal disease and valid treatments, Romanian Journal of Oral Rehabilitation, **12**(2), 37-51 (2020).
[32] L. N. Ferraz, N. I. Pavesi Pini, G. M. Bovi Ambrosano, F. H. Baggio Aguiar, D. A. Nunes Leite Lima, Influence of cigarette smoke combined with different toothpastes on enamel erosion, Braz. Oral Res., **33**, e114 (2019). doi: 10.1590/1807-3107bor-2019
[33] A. Haiduc, F. Zanetti, X. Zhao, W. K. Schlage, M. Scherer, N. Pluym, P. Schlenger, N. V. Ivanov, S. Majeed, J. Hoeng, M. C. Peitsch, Y. Ren, P. A. Guy, Analysis of chemical deposits on tooth enamel exposed to total particulate matter from cigarette smoke and tobacco heating system 2.2 aerosol by novel GC–MS deconvolution procedures, J. Chromatogr. B, **1152**, 122228 (2019). https://doi.org/10.1016/j.jchromb.2020.122228
[34] A. Avram, M. Gorea, R. Balint, L. Timis, S. Jitaru, A. Mocanu, M. Tomoaia-Cotisel, Portland cement enriched with hydroxyapatite for endodontic applications, Stud. Univ. Babes-Bolyai Chem., **62**(4), Tom I, 81-92 (2017).
[35] I. Hodisan, C. Prejmerean, I. Petean, D. Prodan, T. Buruiana, L. Colceriu, L. Barbu-Tudoran, M. Tomoaia-Cotsel, Synthesis and characterization of novel giomers for dental applications, Stud. Univ. Babes-Bolyai Chem., **62**(4), Tom I, 143-154 (2017).

[36] D. Oltean-Dan, G.-B. Dogaru, E.-M. Jianu, S. Riga, M. Tomoaia-Cotisel, A. Mocanu, L. Barbu-Tudoran, Gh. Tomoaia, Biomimetic composite coatings for activation of titanium implant surfaces: methodological approach and in vivo enhanced osseointegration, Micromachines, **12**(11), 1352 (2021). https://doi.org/10.3390/mi12111352.

[37] D. Oltean-Dan, G. B. Dogaru, M. Tomoaia-Cotisel, D. Apostu, A. Mester, H. R. C. Benea, M. G. Paiusan, E. M. Jianu, A. Mocanu, R. Balint, C. O. Popa, C. Berce, G. I. Bodizs, A. M. Toader, Gh. Tomoaia, Enhancement of bone consolidation using high-frequency pulsed electromagnetic short-waves and titanium implants coated with biomimetic composite embedded into PLA matrix: in vivo evaluation, Int. J. Nanomed., **14**, 5799-5816 (2019).

[38] D. Oltean-Dan, P. T. Frangopol, R. Balint, Gh. Tomoaia, A. Mocanu, M. Tomoaia-Cotisel, Biocompatibility of titanium implants coated with biocomposite in a rat model of femoral fracture, Stud. Univ. Babes-Bolyai Chem., **66**(3), 73-87 (2021).

[39] R. Balint, A. Mocanu, Gh. Tomoaia, S. Riga, M. Tomoaia-Cotisel, Advanced nanomaterials and coated surfaces for orthopedic implants – A review, Annals of the Academy of Romanian Scientists, Series on Physics and Chemistry Sciences, **6**(2), 53-81 (2021).

[40] A. Avram, T. Frentiu, O. Horovitz, A. Mocanu, F. Goga, M. Tomoaia-Cotisel, Hydroxyapatite for removal of heavy metals from wastewater, Studia Universitatis Babes-Bolyai, Chemia, **62**(4), Tom I, 93-104 (2017).

[41] L. Ding, J. Li, W. Liu, Q. Zuo, S.-X. Liang, Influence of Nano-Hydroxyapatite on the Metal Bioavailability, Plant Metal Accumulation and Root Exudates of Ryegrass for Phytoremediation in Lead-Polluted Soil, Int. J. Environ. Res. Public Health, **14**(5), 532 (2017). doi: 10.3390/ijerph14050532.

[42] E. Sassoni, Hydroxyapatite and Other Calcium Phosphates for the Conservation of Cultural Heritage: A Review, Materials, **11**, 557, (2018). DOI: 10.3390/ma11040557.

[43] A. Mocanu, O. Cadar, P. T. Frangopol, I. Petean, Gh. Tomoaia, G. A. Paltinean, Cs. P. Racz, O. Horovitz, M. Tomoaia-Cotisel, Ion release from hydroxyapatite and substituted hydroxyapatites in different immersion liquids: in vitro experiments and theoretical modelling study, R. Soc. Open Sci., **8**(1), 201785, (2021). https://doi.org/10.1098/rsos.201785.

[44] C. Garbo, J. Locs, M. D'Este, G. Demazeau, A. Mocanu, C. Roman, O. Horovitz, M. Tomoaia-Cotisel, Advanced Mg, Zn, Sr, Si multi-substituted hydroxyapatites for bone regeneration, Int. J. Nanomed., **15**, 1037-1058 (2020).

[45] S. Rapuntean, P. T. Frangopol, I. Hodisan, Gh. Tomoaia, D. Oltean-Dan, A. Mocanu, C. Prejmerean, O. Soritau, L. Z. Racz, M. Tomoaia-Cotisel, In vitro response of human osteoblasts cultured on strontium substituted hydroxyapatites, Rev. Chim. (Bucharest), **69**(12), 3537-3544 (2018).
[46] O. Cadar, R. Balint, Gh. Tomoaia, D. Florea, I. Petean, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, Behavior of multisubstituted hydroxyapatites in water and simulated body fluid, Stud. Univ. Babes-Bolyai Chem., **62**(4), Tom I, 269-281 (2017).
[47] E. Forizs, F. Goga, A. Avram, A. Mocanu, I. Petean, O. Horovitz, M. Tomoaia-Cotisel, Thermal analysis of pure and multisubstituted hydroxyapatite pastes, Stud. Univ. Babes-Bolyai Chem., **62**(4), Tom I, 173-180 (2017).
[48] F. Goga, E. Forizs, G. Borodi, Gh. Tomoaia, A. Avram, R. Balint, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, Behavior of doped hydroxyapatites during the heat treatment, Rev. Chim. (Bucharest), **68**(12), 2907-2913 (2017).
[49] A. Avram, Gh. Tomoaia, A. Mocanu, M. Tomoaia-Cotisel, A review on biomimetic hydroxyapatites for biomedical applications, Academy of Romanian Scientists Annals - Series on Biological Sciences, **9**(2), 106-132 (2020).
[50] A. Mocanu, R. Balint, C. Garbo, L. Timis, I. Petean, O. Horovitz, M. Tomoaia-Cotisel, Low crystallinity nanohydroxyapatite prepared at room temperature, Stud. Univ. Babes-Bolyai Chem., **62**(2), 95-103 (2017).
[51] C. Garbo, M. Sindilaru, A. Carlea, Gh. Tomoaia, V. Almasan, I. Petean, A. Mocan, O. Horovitz, M. Tomoaia-Cotisel, Synthesis and structural characterization of novel porous zinc substituted nanohydroxyapatite powders, Particul. Sci. Technol., 35(1), 29-37 (2017).
[52] P. T. Frangopol, A. Mocanu, V. Almasan, C. Garbo, R. Balint, G. Borodi, I. Bratu, O. Horovitz, M. Tomoaia-Cotisel, Synthesis and structural characterization of strontium substituted hydroxyapatites, Rev. Roum. Chim., **61**(4-5), 337-344 (2016).
[53] A. Mocanu, P. T. Frangopol, R. Balint, O. Cadar, I. M. Vancea, R. Mintau, O. Horovitz, M. Tomoaia-Cotisel, Higuchi model applied to ions release from hydroxyapatites, Stud. Univ. Babes-Bolyai Chem., **66**(3), 195-207 (2021).
[54] F. Goga, E. Forizs, A. Avram, A. Rotaru, A. Lucian, I. Petean, A. Mocanu, M. Tomoaia-Cotisel, Synthesis and thermal treatment of hydroxyapatite doped with magnesium, zinc and silicon, Rev. Chim. (Bucharest), **68**(6), 1193-1200 (2017).
[55] O. Cadar, P. T. Frangopol, Gh. Tomoaia, D. Oltean, G. A. Paltinean, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, Silicon release from

hydroxyapatites in water and simulated body fluid, Stud. Univ. Babes-Bolyai Chem., **62**(4), Tom I, 67-80 (2017).

[56] L. Chen, S. Al-Bayatee, Z. Khurshid, A. Shavandi, P. Brunton, J. Ratnayake, Hydroxyapatite in Oral Care Products—A Review, Materials, **14**(17), 4865 (2021). doi: 10.3390/ma14174865

[57] Sangi Central Research Laboratory, Original Product Research, 1928-2018, Apadent Apagard Renamel – remineralizing toothpaste, (Sangi, Co. Ltd., Tokio, Japan, 2018), Parts 2, 3 and 4, pp. 3-8. https://www.sangi-eu.com/en/apagard-premio/xlc2100n

[58] From the Boka website: https://bokabrush.zendesk.com/hc/en-us/articles/6164363646867-Our-Toothpaste
accesat in 27.11.2022

[59] E. Pepla, L. K. Besharat, G. Palaia, G. Tenore, G. Migliau, Nano-hydroxyapatite and its applications in preventive, restorative and regenerative dentistry: a review of literature, Ann. Stomatol. (Roma), **5**(3), 108–114 (2014).

[60] B. T. Amaechi, T. S. Phillips, V. Evans, C. P. Ugwokaegbe, M. N. Luong, L. O. Okoye, F. Meyer, J. Enax, The Potential of Hydroxyapatite Toothpaste to Prevent Root Caries: A pH-Cycling Study, Clin. Cosmet. Investig. Dent., **13**, 315–324 (2021).

[61] E. Paszynska, M. Pawinska, M. Gawriolek, I. Kaminska, J. Otulakowska-Skrzynska, G. Marczuk-Kolada, S. Rzatowski, K. Sokolowska, A. Olszewska, U. Schlagenhauf, T. W. May, B. T. Amaechi, E. Luczaj-Cepowicz, Impact of a toothpaste with microcrystalline hydroxyapatite on the occurrence of early childhood caries: a 1-year randomized clinical trial, Sci. Rep., **11**, 2650 (2021). https://doi.org/10.1038/s41598-021-81112-y

[62] M. Bossù, M. Saccucci, A. Salucci, G. Di Giorgio, E. Bruni, D. Uccelletti, M. S. Sarto, G. Familiari, M. Relucenti, A. Polimeni, Enamel remineralization and repair results of Biomimetic Hydroxyapatite toothpaste on deciduous teeth: an effective option to fluoride toothpaste, J. Nanobiotechnol., **17**, 17 (2019). https://doi.org/10.1186/s12951-019-0454-6

[63] Rapoarte rezultate în urma studiilor clinice efectuate pe Lacalut white & repair (Zentrum für prophylaktische zahnheilkunde Profident, Dr. Med. Sacharowa E.B., Dr. Med. Prokuschewa O.A 2012). https://www.lacalut.ro/white/studii_clinice

[64] A. Muntean, S. Sava, A. G. Delean, A. M. Mihailescu, L. Silaghi Dumitrescu, M. Moldovan, D. G. Festila, Toothpaste Composition Effect on Enamel Chromatic and Morphological Characteristics: In Vitro Analysis, Materials, **12**, 2610 (2019). doi:10.3390/ma12162610

[65] L. Rácz, M. Tomoaia-Cotișel, Cs.-P. Rácz, P. Bulieris, I. Grosu, S. Porav, A. Ciorîță, X. Filip, F. Martin, G. Serban, I. Kacso, Curcumin-Whey

protein solid dispersion system with improved solubility and cancer cell inhibitory effect, Stud. Univ. Babes-Bolyai Chem, **66**(3), 209-224 (2021).

[66] L. Z. Racz, Cs. P. Racz, L.-C. Pop, Gh. Tomoaia, A. Mocanu, I. Barbu, M. Sárközi, I. Roman, A. Avram, M. Tomoaia-Cotisel, V.-A. Toma, Strategies for Improving Bioavailability, Bioactivity, and Physical-Chemical Behavior of Curcumin, Molecules, **27**(20), 6854 (2022).

[67] L. Z. Racz, Cs. P. Racz, O. Horovitz, Gh. Tomoaia, A. Mocanu, I. Kacso, M. Sarkozi, M. Dan, S. Porav, G. Borodi, M. Tomoaia-Cotisel, Complexation of curcumin using whey proteins to enhance aqueous solubility, stability and antioxidant property, Stud. Univ. Babes-Bolyai Chem., **67**(3), 75-99 (2022).

[68] L. Z. Racz, G.-A. Paltinean, I. Petean, Gh. Tomoaia, L.- C. Pop, G. Arghir, E. Levei, A. Mocanu, Cs.-P. Racz, M. Tomoaia-Cotisel, Curcumin and Whey Protein Binding And Structural Characteristics Of Their Complex Evidenced By Atomic Force Microscopy, Stud. Univ. Babes-Bolyai Chem., **67**(3), 61-74 (2022).

[69] P. Arya, N. Raghav, In-vitro studies of Curcumin-β-cyclodextrin inclusion complex as sustained release system, J. Mol. Struct., **1228**, 129774 (2021).

[70] H. Mashaqbeh, R. Obaidat, N. Al-Shar’I, Evaluation and Characterization of Curcumin-β-Cyclodextrin and Cyclodextrin-Based Nanosponge Inclusion Complexation, Polymers, **13**(23), 4073 (2021).

[71] Cs-P. Racz, Sz. Santa, M. Tomoaia-Cotisel, Gh. Borodi, I. Kacso, A. Pirnau, I. Bratu, Inclusion of α-lipoic acid in β-cyclodextrin. Physical-chemical and structural characterization, J. Incl. Phenom. Macrocycl. Chem., **76**(1-2), 193-199 (2013).

[72] Cs. P. Racz, R. D. Pasca, S. Santa, I. Kacso, G. Tomoaia, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, Inclusion complex of beta-cyclodextrin and quercetin. Thermodynamic approach, Rev. Chim. (Bucharest), **62**(10), 992-997 (2011).

[73] Cs. P. Rácz, G. Borodi, M. M. Pop, I. Kacso, S. Santa, M. Tomoaia-Cotisel, Structure of the inclusion complex of-cyclodextrin with lipoic acid from laboratory powder diffraction data, Acta Crystallogr. B, **68**(2), 164-170 (2012).

[74] C. G. Floare, M. Bogdan, M. Tomoaia-Cotişel, A. Mocanu, 1H NMR spectroscopic characterization of inclusion complex of desferrioxamine B chelator and β-cyclodextrin, J. Mol. Struct., **1248**, 131477 (2022). https://doi.org/10.1016/j.molstruc.2021.131477.

[75] A. Paltinean, Gh. Tomoaia, S. Riga, A. Mocanu, M. Tomoaia-Cotisel, Sylimarin based complexes – a mini review, Annals Series on Biological Sciences, **11**(1), 146-166 (2022).

[76] G.-A. Paltinean, S. Riga, Gh. Tomoaia, A. Mocanu, M. Tomoaia-Cotisel, Bioactive Compounds from Plants Used as Therapeutic Agents in Biomedical Applications - A Literature Review, Academy of Romanian Scientists, Annals Series on Biological Sciences, **10**(2), 103-141 (2021).

[77] Zs. Pap, E. Karácsonyi, L. Baia, L.-C. Pop, V. Danciu, K. Hernádi, K. Mogyorósi, A. Dombi, TiO2/WO3/Au/MWCNT composite materials for photocatalytic hydrogen production: Advantages and draw-backs, Phys. Status Solidi B, **12**, 2592-2595 (2012)

[78] L.-C. Pop, L. Sygellou, V. Dracopoulos, K. S. Andrikopoulos, S. Sfaelou, P. Lianos, One-step electrodeposition of CdSe on nanoparticulatetitania films and their use as sensitized photoanodes for photoelectrochemical hydrogen production, Catal. Today, **252**, 157-161 (2015).

[79] L.-C. Pop, V. Dracopoulos, P. Lianos, Photoelectrocatalytic hydrogen production using nanoparticulatetitania and a novel Pt/Carbon electrocatalyst: The concept of the "Photoelectrocatalytic Leaf", Appl. Surf. Sci., **333**, 147–151 (2015).

[80] L.-C. Pop, I. Tantis, P. Lianos, Photoelectrocatalytic hydrogen production using nitrogen containing water soluble wastes, Int. J. Hydrog. Energy, **40**, 8304–8310 (2015).

[81] O. Monfort, L.-C. Pop, S. Sfaelou, T. Plecenik, T. Roch, V. Dracopoulos, E. Stathatos, G. Plesch, P. Lianos, Photoelectrocatalytic hydrogen production by water splitting using BiVO4 photoanode, Chem. Eng. J., **286**, 91–97 (2016).

[82] S. Sfaelou, L.-C. Pop, O. Monfort, V. Dracopoulos, P. Lianos, Mesoporous WO3 photoanodes for hydrogen production by water splitting and PhotoFuelCell operation, Int. J. Hydrog. Energy, **41**, 5902–5907 (2016).

[83] M. Popa, L.C. Pop, G. Schmerber, C. Bouillet, O. Ersen, Impact of the structural properties of holmium doped ZnO thin films grown by sol–gel method on their optical properties, Appl. Surf. Sci., **562**, 150159 (2021).

[84] L.-C. Pop, S. Sfaelou, P. Lianos, Cation adsorption by mesoporoustitaniaphotoanodes and its effect on the current-voltage characteristics of photoelectrochemical cells, Electrochim. Acta, **156**, 223–227 (2015).

[85] A. I. Cadiş, L. E. Mureșan, I. Perhaița, L. C. Pop, K. Saszet, L. Barbu-Tudoran, G. Borodi, Peculiarities on methyl orange adsorption by porous ZnIn2S4 prepared in different conditions, J. Nanoparticle Res., **24**, 74 (2022).

[86] E. Karácsonyi, L. Baia, A. Dombi, V. Danciu, K. Mogyorósi, L.-C. Pop, G. Kovács, V. Coșoveanu, A. Vulpoi, S. Simon, Zs. Pap, The photocatalytic activity of TiO2/WO3/noble metal (Au or Pt) nanoarchitectures obtained by selective photodeposition, Catal. Today, **208**, 19-27 (2013).

[87] W. H. Lee, C. Y. Loo, R. Rohanizadeh, Functionalizing the surface of hydroxyapatite drug carrier with carboxilic acid groups to modulate the loading and release of curcumin nanoparticles, Mater. Sci. Eng. C Mater. Biol. Appl., **99**, 929-939, (2019).

[88] S. Sharifi, A. Z. Khosroshahi, S. M. Dizaj, Y. Rezaei, Preparation, physicochemical assessment and the antimicrobial action of hydroxyapatite -gelatin/curcumin nanofibrous composites as a dental biomaterial, Biomimetics, **7**(1), 4, (2022). doi: 10.3390/biomimetics7010004

[89] A. Bhattacharjee, S. Bose, Zinc curcumin complex on fluoride doped hydroxyapatite with enhanced biological properties for dental and orthopedic applications, J. Mater. Res., **37**, 2009–2020 (2022).

[90] I. A. Neacșu, L. Matei, A. C. Bîrcă, A. I. Nicoară, V. L. Ene, L. D. Dragu, A. Ficai, C. Bleotu, E. Andronescu, Curcumin - Hydroxyapatite Systems Used For Bone Cancer Treatment, Romanian Journal of Materials, **51**(4), 505 – 513 (2021).

[91] L. Zou, L. Hu, P. Pan, S. Tarafder, M. Du, Y. Geng, G. Xu, L. Chen, J. Chen, C. H. Lee, Icariin-releasing 3D printed scaffold for bone regeneration, Composites Part B, **232**, 109625 (2022).

[92] T. Wu, K. H. Nan, J. D. Chen, D. Jin, S. Jiang, P. R. Zhao, J. C. Xu, H. Du, X. Q. Zhang, J. W. Li, G. X. Pei, A new bone repair scaffold combined with chitosan/hydroxyapatite and sustained releasing icariin, Chinese Sci. Bull., **54**, 2953—2961 (2009).

[93] Y. Wu, L. Xia, Y. Zhou, W. Ma, N. Zhang, J. Chang, K. Lin, Y. Xu, X. Jiang, Evaluation of osteogenesis and angiogenesis of icariin loaded on micro/nano hybrid structured hydroxyapatite granules as a local drug delivery system for femoral defect repair, J. Mater. Chem. B, **3**(24), 4871-4883 (2015).

[94] K. AbouAitah, A. Stefanek, I. M. Higazy, M. Janczewska, A. Swiderska-Sroda, A. Chodara, J. Wojnarowicz, U. Szałaj, S. A. Shahein, A. M. Aboul-Enein, F. Abou-Elella, S. Gierlotka, T. Ciach, W. Lojkowski, Effective targeting of colon cancer cells with piperine natural anticancer prodrug using functionalized clusters of hydroxyapatite nanoparticles, Pharmaceutics, **12**, 70, (2020). doi:10.3390/pharmaceutics12010070.