Emergence of Nano-Dentistry as a Reality of Contemporary Dentistry

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Abstract: (1) Background. Nanotechnology offers significant alternative ways to solve scientific, medical, and human health issues. Dental biomaterials were improved by nanotechnology. It manufactures better materials or improves the existing ones and forms the basis of novel methods for disease diagnosis and prevention. Modern nanotechnology makes oral health care services more acceptable for patients. Nanotechnology is now important area of research, covering a broad range of applications in dentistry. (2) Methods. Relevant literature from Scopus published in English was selected using the keywords “nanoparticle” and “dentistry”. To the selected articles we applied the inclusion and exclusion criteria to choose the relevant ones. (3) Results. Based on the relevant articles, a literature review was prepared. This review provides an insight into the applications of nanotechnology in various branches of dentistry. We applied several regression models to fit number of papers versus time and chose the best one. We used it to construct the forecast and its 95%-confidence interval for the number of publications in 2022–2026. (4) Conclusions. It shows that a significant rise in papers is expected. This review familiarizes dentists with properties and benefits of nanomaterials and nanotechnology. Additionally, it can help scientists to consider the direction of their research and to plan prospective research projects.

Keywords: dentistry; nanomedicine; nanoparticle; nanotechnology; regression; forecast

1. Introduction

The formation of the concept of nanomedicine began in the middle of the XX century. In 1959, Richard Feynman published his lecture entitled “There’s Plenty of Room at the Bottom”, in which he substantiated the basic principles of the use of nanotechnology in medicine. Undoubtedly, it was R. Feynman who can be considered a prophet of the development of nanomedicine, because he foresaw the inevitability of the transition of the medical technology from the macro level to the micro-level and further to the atomic level. Nevertheless, establishment of the nano era started far before that date [1,2].

Materials with a size of less than 100 nm in at least one dimension are considered nanomaterials [3]. They may include grains, fibers, clusters, nanoholes, or their combination. The key property is increased surface area per unit mass compared to bulk matter, which significantly modifies the physical and chemical properties of the material [4].
Nanoparticles such as silver, copper, and zinc produce antibacterial properties in bulk form but metals like iron are not antibacterial in macro form but they possess antibacterial activity in nano form. Antibacterial nanoparticles possess multiple mechanisms by releasing metal ions, penetrating into cell walls and producing membrane damage [5].

The nanoparticles possess a good delivery system for the release of micronutrients, protection, and encapsulation. The smaller the size of the nanoparticles the more advantages they show: such as improved bioavailability, high optical clarity, gravitational separation, and stability to aggregate [6].

Nanotechnology is used in various fields of science and technology: physics, biology, microbiology, chemistry, and many others. Medicine and dentistry are no exceptions. To cooperate with the “technology of the future” in this field has become possible and affordable today, including the advent of nanoparticle materials, which have a much larger surface area per unit mass, compared to significantly larger particles (due to its properties, only one gram of a nanomaterial can be more effective than a ton of ordinary substance) [7].

All options for the application of nanotechnology in medicine can be divided into three major groups:

1. Therapeutic approaches based on the use of nanotechnology;
2. Diagnostic nanomedical procedures;
3. The use of nanomaterials in the technology of manufacturing various medical devices.

Nanomedical approaches are being increasingly implemented in specific medical specialties, providing solutions to the problems of treatment of cardiovascular and endocrine disorders, as well as diseases of the nervous, digestive, respiratory and musculoskeletal systems, and cancer. In recent years, separate areas of nanomedicine have been formed, named according to the fields of medical knowledge, such as nanoneurology, nanooncology, nanoendocrinology, etc. Dentistry is no exception to the rule.

Medicine, including dentistry, has become one of the areas of active and promising use of nanomaterials and nanotechnologies. The latter are used in areas such as preventive dentistry, restoration of teeth with nanocomposite materials in a case of caries and tooth wear, abrasion and attrition, treatment of enamel hypersensitivity, local anesthesia, coating of dental implants, nano-restorative bone cements, nano-impression materials, etc. (Figure 1) [8].
Figure 1. Variety of nanodental materials on the market.

Nanotechnology has revolutionized modern diagnostics [9]. Thus, the use of certain types of nanoparticles allows in vivo visualization of individual pathologically altered cells and even molecules that are markers of some common diseases. Nano-diagnostics significantly increases the sensitivity and specificity of methods for recognizing biochemical and molecular markers of disease [10]. With the use of nanotechnology, it is possible to simultaneously diagnose and treat many diseases. Applications of biosensors and nanomaterials in healthcare diagnostics will transform the paradigm of patient diagnosis and care [11,12].

The same as traditional diagnostics, nanodiagnostics aims to detect the disease as early as possible, ideally at the molecular level. This is why the term “molecular imaging” has appeared in nanomedicine. Molecular imaging is possible using the following types of diagnostic tests: optical bioluminescence and fluorescence; computer tomography; magnetic resonance imaging; single-photon emission computer tomography; positron emission tomography.

The aim of this review paper is to focus on application of nanotechnology in dentistry in recent years and forecast trends in this field that may help in planning further scientific research.

2. Materials and Methods

For this review article, a narrative [13] review was performed using a comprehensive literature search using the Scopus database to identify any studies for nanoparticle use in various areas of dentistry. The search considered works published from 2003 until November 2021 by using the keywords ‘nanoparticles’ and ‘dentistry’.

Only relevant literature in English from the electronic search was selected for the present review. The nanoparticles had to be used in broad applications in all aspects of dentistry, and not just a particular specialty. The inclusion criteria are as follows: (i) use of existing commercial materials or their modifications in dental praxis; (ii) use of nanoparticles in various branches of dentistry; (iii) full text journal articles indexed in Scopus written in English; (iv) books and book chapters written in English; (v) scientific works published in 2016 and later (only for the discussion chapter because there we review these relevant papers); (vi) books and book chapters of highly rated publishers (Wiley, Elsevier and Springer) which appear in the references of the materials which meet
our criteria but are not indexed in Scopus. The exclusion criteria are as follows: (i) case reports (clinical trials); (ii) conference papers; (iii) materials published in 2015 and earlier; (iv) randomized controlled studies; (v) editorials.

1. The search was carried out in the Scopus database using the keywords “nanoparticles” and “dentistry”. In total, 222 records were found.

2. Five co-authors analyzed 222 records for compliance with the inclusion and exclusion criteria. In total, 147 records were deleted, i.e., 75 records remained.

3. In the reference lists of these 75 articles, we found 12 books and sections of books by highly rated publishers (Wiley, Elsevier, and Springer or affiliated with them).

4. To the 75 records from Scopus, we added 12 books and chapters of books. That is the total of 87 records. All selected records were distributed among all authors for reading of the full text articles and preparation of the manuscript. The procedure is shown in Figure 2 in the PRISMA flowchart.

Search results were presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 2).

![PRISMA flowchart](image)

**Figure 2.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of inclusion/exclusion criteria.

### 3. Results

The search in Scopus using the keywords “dentistry” and “nanoparticle” indicates 222 papers within the period 2003–2021. The distribution of the papers found in the search using the keywords mentioned above between the branches of science is presented in Figure 3.
Figure 3. Distribution of papers found in the search using the keywords “dentistry” and “nanoparticle” between the branches of science. Taken from Scopus.

We see that only 5% of them belong to dentistry, which shows considerable spread among branches. In our opinion, it shows a great potential of inter-science collaboration of dentistry with other branches to develop dentist materials and technologies.

The list of the top 10 countries, whose representatives published papers on this topic, is given in Figure 4.

From Figure 4 it can be found that 52 papers or 23.4% of the papers were published with the participation of Indian scientists. The total share of the top 10 countries is 189 papers or 85.1%. However, some papers were published by multinational teams so one paper can belong to several countries. Therefore, it is more correct to say that 189 papers or 85.1% papers on this topic were published with participation of scientists from the top 10 countries listed in Figure 4.

Analysis of trends in publications by keywords “dentistry” and “nanoparticle” can be undertaking based on statistics of publications in Scopus by year.
We aimed to find a regression model to describe the trend. In general, the regression model has the form

\[ y = \hat{y} + u, \]  

where \( y \) is the dependent variable, \( \hat{y} \) is a regression that fits the data of the independent variable \( y \), \( u \) is a random variable called the residuals. Residuals \( u \) are not directly observable and depend on the type of model \( \hat{y} \). They are calculated on (1) according to the following formula

\[ u_i = \hat{y}_i - y_i, \]  

where the index \( i \) means that the residuals are calculated for each point of the model. Subtraction order in (2) is unimportant, because the sum of squares of the residuals is used for calculations.

Firstly, we tried to apply linear regression of a type to fit the data

\[ \hat{y} = a_0 + a_1 \times x, \]

where \( a_0 \) and \( a_1 \) are the parameters of the model, which should be determined from the data presented in Figure 5, \( \hat{y} \) the number of publications in a given year is calculated according to the regression model, \( x \) is a year.

![Figure 5. The number of publications among the articles found in Scopus by year.](image-url)

As a result of using the model to fit the data in Figure 5 the following residuals are obtained (see Figure 6).
Figure 6. Residuals of the linear regression (3) that fits the data in Figure 5 to describe the number of articles per year.

The plot shows that at the beginning of the period the residuals have one sign, in the middle of the period the opposite, and at the end again the same. In this case, the sign itself is not important, but its alternation is important. According to [14,15], the distribution of residuals should be random, which is not the case here. In addition, it is clear that over time the scatter of residuals increases, which also should not be the case when a regression fits data well. Therefore, we reject this regression model, despite the rather high coefficient of determination (0.814) and the significance of both the model as a whole and its individual coefficients \( a_0 \) and \( a_1 \). Alternation of residual signs indicates the nonlinear nature of the data. The location of points in Figure 5 gives the reason to consider that either the power or exponential regression can be used. Both describe nonlinear processes, but are linear with respect to coefficients [14,15]. To estimate their coefficients the conventional methods of linearization are used [14,15]. However, before using them, it is reasonable to preprocess the data prior to fitting them.

Linearization of these models involves logarithmization of data [14,15], so the point with the coordinates (2004; 0) should be excluded because the logarithm function is not defined at the point 0 [16]. It is also undesirable to logarithm one, because the logarithm of one is zero. In addition, this requires the regression model to pass through the origin. Such models are specific. Their consideration is beyond conventional statistical courses and is the subject of separate scientific studies [14,17,18]. Therefore, we filtered data for 2003–2005. In total, this includes two publications.

The second stage of preparation of data for modeling is the subtraction from each value of the independent variable (year), the constant equal to 2000. This allows to significantly reduce the rounding error of the model coefficients, because the coefficients of such a model are of the order of unity. Without this subtraction, the order of the coefficients is \( e^{-100} \). Thus, the data after pre-filtering and processing become as presented in Table 1.

Table 1. Data after filtering and preparation for modeling (independent variable \( x \) formed by subtracting from the year the constant of 2000).

| Year (Independent Variable), x | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|-------------------------------|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|
| Number of Papers (Dependent Variable), y | 2 | 4 | 3 | 9 | 6 | 7 | 4 | 6 | 16 | 14 | 26 | 17 | 18 | 22 | 34 | 32 |

However, for a better understanding of the data in the future, the full value of the year in the plots and as an additional column in the tables was used to present the data.

To fit the previously prepared data, we used the power regression

\[ \hat{y} = a_0 \times x^{a_1}, \]
where $a_0$ and $a_1$ are the coefficients of the model to be estimated, $\hat{y}$ is the number of articles calculated according to the model, $x$ is the year in the format of Table 1.

It is reasonable to determine the unknown coefficients [14] by taking natural logarithm of both sides of (4). As a result, we obtained

\[ \ln \hat{y} = \ln a_0 + a_1 \times \ln x. \]  

(5)

We substituted the variables

\[ \ln \hat{y} = \hat{y}^*, \ln a_0 = a_0^*, \ln x = x^*, \ a_1 = a_1^*. \]  

(6)

After substituting the variables, we obtained a linear model with respect to the new variables

\[ \hat{y}^* = a_0^* + a_1^* \times x^*. \]  

(7)

To estimate the coefficients, we used the least squares equations derived in [14,15]. The coefficient of determination of the linearized model is 0.837, which is a good indicator [14,15]. It indicates good fit of the model to data. The whole model is significant, and so are all its coefficients.

Then, we returned to the form of model (4) by inversely substituting the variables

\[ a_0 = e^{a_0^*}, \ a_1 = a_1^*. \]  

(8)

After that, we obtained the regression as follows

\[ \hat{y} = 0.0497 \times x^{2.0892}. \]  

(9)

The complete results of modeling using the power regression (9) are presented in Table 2.

| Year | $x$ (Year) | $y$ (Number of Papers) | $\hat{y}$ (Number of Papers (Model)) | $u$ (Residuals) |
|------|-------------|-------------------------|--------------------------------------|-----------------|
| 2006 | 6           | 2                       | 2.1                                  | 0.1             |
| 2007 | 7           | 4                       | 2.9                                  | −1.1            |
| 2008 | 8           | 3                       | 3.8                                  | 0.8             |
| 2009 | 9           | 9                       | 4.9                                  | −4.1            |
| 2010 | 10          | 6                       | 6.1                                  | 0.1             |
| 2011 | 11          | 7                       | 7.4                                  | 0.4             |
| 2012 | 12          | 4                       | 8.9                                  | 4.9             |
| 2013 | 13          | 6                       | 10.6                                 | 4.6             |
| 2014 | 14          | 16                      | 12.3                                 | −3.7            |
| 2015 | 15          | 14                      | 14.2                                 | 0.2             |
| 2016 | 16          | 26                      | 16.3                                 | −9.7            |
| 2017 | 17          | 17                      | 18.5                                 | 1.5             |
| 2018 | 18          | 18                      | 20.8                                 | 2.8             |
| 2019 | 19          | 22                      | 23.3                                 | 1.3             |
| 2020 | 20          | 34                      | 26                                   | −8              |
| 2021 | 21          | 32                      | 28.7                                 | −3.3            |

The residual plot of power model (9) is given in Figure 7.
As it can be seen from the residual plot in Figure 7, the amplitude of residuals increases with the increase of year. This makes the power model inadequate for use according to the criteria described in [14,15].

Therefore, we tried the exponential regression, whose general appearance is as follows

\[ y = a_0 \times e^{a_1 \cdot x}, \]  (10)

where \( a_0 \) and \( a_1 \) are the coefficients of the model to be estimated, \( y \) is the number of articles calculated according to the regression, \( x \) is year in the format of Table 1.

It is reasonable to determine the unknown coefficients [14] by taking natural logarithm of both sides of (10). As a result, we obtained

\[ \ln y = \ln a_0 + x \times \ln a_1. \]  (11)

We substituted variables

\[ \ln \hat{y} = \hat{y}^*, \ln a_0 = a_0^*, \ln a_1 = a_1^*. \]  (12)

After substituting the variables, we obtained the linear model

\[ \hat{y}^* = a_0^* + a_1^* \times x. \]  (13)

To estimate the coefficients, we used the least squares equations derived in [14,15]. The coefficient of determination of the linearized model is 0.846, which is a good indicator [14,15]. It indicates good fit of the chosen regression to data. The model as a whole is significant, but the coefficient \( a_0 \) is not statistically significant.

Then we returned to the form of model (10) by inversely substituting variables

\[ a_0 = e^{a_0^*}, \quad a_1 = e^{a_1^*}. \]  (14)

We obtained the model as follows

\[ \hat{y} = 0.992 \times 1.1863^x. \]  (15)

Full results of the modeling are presented in Table 3.

**Table 3.** Results of simulation using exponential model (15).

| Year x (Year) | \( y \) (Number of Papers) | \( \hat{y} \) (Number of Papers (Model)) | \( u \) (Residuals) |
|---------------|-----------------------------|----------------------------------------|-------------------|
| 2006          | 6                           | 2.8                                    | 0.8               |
| 2007          | 7                           | 3.3                                    | -0.7              |
| 2008          | 8                           | 3.9                                    | 0.9               |
| 2009          | 9                           | 4.6                                    | -4.4              |
The residual plot of the exponential regression is given in Figure 8.

As it can be seen from Figure 8, the amplitude of the residuals is approximately constant for all points of the model and their distribution is random. However, there is an outlier for 2016. According to \[14,15\] this is a serious drawback of the chosen model. It makes such the model not very good for use.

As it was mentioned above, the coefficient \(a_0\) is insignificant in the linearized model. This is probably due to the fact that the coefficient \(a_0\) is close to one, and the logarithm of one is zero. Due to the statistical feature of the \(t\)-test any coefficient close to zero cannot be considered significant. That is why we had reason to consider both coefficients of model (15) significant.

To check this assumption, we tried a linearized exponential model without an intercept

\[ \hat{y}^* = a_1^* \times x. \]  

(16)

However, such model is not good due to the increase in the amplitude of the residuals with the rise of the independent variable, as shown in Figure 9.
As can be seen from the analysis, simple models have drawbacks in their application to fit the dependence of the number of publications on year. The use of complex models is not reasonable due to the relatively small set of observations (16 observations) and possible overfitting [14,19]. That is, the model will describe this data set well for the cost of losing of generalization properties. Therefore, we decided to focus on model (15) and chose it as the one that has the least shortcomings among the considered models.

Then we estimated the variance of the residuals for regression (15). According to Table 2, this estimate [14] is calculated by the formula

\[ s^2 = \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n-2}, \]  

where \( s^2 \) is an estimate of the variance of the residuals, \( y_i \) and \( \hat{y}_i \) are the number of articles obtained experimentally and calculated according to regression model (15), respectively, \( n \) is the number of observations for model (15). The number \( n-2 \) is also called the number of degrees of freedom [14,15] and for model (15) it equals 14.

For the data in Table 2, the estimation of \( s^2 \) is 17.35. We also found the critical value of the Student’s t-distribution for the level of significance of \( \alpha = 0.05 \) [14,15]. It was found from the table of the Student’s distribution for the corresponding degrees of freedom [14,15].

\[ t_{cr} = t\left(\frac{0.05}{2}; \; 14\right) = 2.145. \]  

We calculated the confidence interval for model (15) according to [9,10]

\[ \text{confidence interval} = \hat{y}_i \pm t\left(\frac{\alpha}{2}; \; df\right) \times s \times \sqrt{\frac{1}{n} + \frac{(x_i - \bar{x})^2}{\sum_{i=1}^{n}(x_i - \bar{x})^2}}, \]  

where \( x_i \) is a particular value of the independent variable, \( \bar{x} \) is the mean value of the independent variable.

As can be seen from (19), the lower and upper limits of the confidence interval of 100% × (1 − \( \alpha \)) at each point of the regression model were calculated. Since we accepted \( \alpha = 0.05 \), the confidence interval was 100 − 5% = 95%. The results of the calculations are presented in Table 4.

Table 4. Lower and upper limits of the 95% confidence interval and model values (15).

| Year | Upper Limit | Lower Limit | Model |
|------|-------------|-------------|-------|
| 2006 | 6.9         | −1.4        | 2.8   |
In Figure 10 the plot of the regression model and 95% confidence interval for (15) are shown.

Based on regression model (15), we forecast the number of publications with the keywords “dentistry” and “nanoparticle” that will be indexed in Scopus in the next 5 years and estimated the 95% confidence interval of the forecast. The predicted values can be obtained by substituting the numbers 22, 23, 24, 25, and 26 in model (15) instead of \( x \). This will correspond to the forecast for the years 2022–2026. For the predicted values we calculated the 95% confidence interval according to the formula [14,15].

\[
\text{confidence interval (forecast)} = \hat{y}_i \pm t \left( \frac{v}{2}, df \right) \times s \times \sqrt{1 + \frac{1}{n} + \frac{(x_i - \bar{x})^2}{\sum_{i=1}^{n}(x_i - \bar{x})^2}}. \tag{20}
\]

The results of the calculations are presented in Table 5 and in Figure 11.

| Year | Upper Limit | Lower Limit | Model Forecast |
|------|-------------|-------------|----------------|
| 2022 | 52.6        | 32.5        | 42.5           |

![Figure 10](image_url). The 95% confidence interval and the regression model for (15).

Table 5. Lower and upper limits of the 95% confidence interval and the value of the forecast of the number of articles in 2022–2026 according to (15).
Therefore, summing up all values from Table 5, we can predict that in the next 5 years with the probability of 95% there will be from 256 to 360 publications indexed in Scopus with the keywords “dentistry” and “nanoparticle”. Currently, there are 222 articles for the period of 2003–2021. The obtained data show us that we should expect a significant increase in the number of publications. Thus, the review of the current state of the field is relevant, as at the moment there is already a significant number of studies carried out in the previous 18 years and we are on the verge of a significant increase in the number of publications in the coming years. Based on this, statistical data processing is a powerful tool for data research and trend research in various fields [14,15,20,21]. Thereby, from the above we can conclude that this topic is urgent, relevant, and promising.

4. Discussion

The use of nanotechnology for the treatment of dental diseases has found great practical interest. The scope of application in clinical dentistry is extremely wide: treatment of dentin hypersensitivity, restoration of teeth, endodontic treatment, surgical, orthopedic interventions, etc. [22,23].

4.1. Conservative Nano-Dentistry

4.1.1. Dentin/Tooth Hypersensitivity

Dentin/tooth hypersensitivity is a common condition that manifests as intense pain of short duration in response to external stimuli. According to the “hydrodynamic theory” proposed by M. Brannstrom and A. Astron in 1964, the presence of damage to the enamel and/or cement in the cervical area with subsequent exposure of dentinal tubules in response to certain stimuli, can cause movement of dentinal fluid inside the tubules, indirectly stimulating the pulpal nerve endings, causing pain [24].
At the macroscopic level, hypersensitive dentin is no different to healthy dentin. Histologically, hypersensitive dentin has dilated dentinal tubules that can be twice as wide as in normal dentin. In addition, there is an increased number of dentinal tubules per unit area compared to normal dentin. As a result of doubling the diameter of the dentinal tubules, the fluid flow increases [25].

The main methods of treatment of dental hyperesthesia are based on the relief of the hydrodynamic mechanism, i.e., on the reduction in fluid movement in the dentinal tubules in response to external stimuli. This can be achieved by blockage of the microspaces with desensitizers; reducing the volume of microspaces with mineralizing agents [26]. Reconstructive dental nanorobots using natural biological materials can selectively and accurately occlude specific tubules within minutes, offering patients rapid and ongoing treatment [27,28].

4.1.2. Tooth Restoration Procedures with Nanomaterials

Nanocomposites

The major problem of resin composites is that more biofilms and plaques can be accumulated on their surface, compared to other restorative materials. Nanotechnology can aid in the development of bioactive dental materials to reduce or modify the influence of caries-related bacteria. Nanomaterials provide superior antimicrobial activity and display better physical properties in comparison to conventional materials. Agents such as silver, zinc oxide, calcium phosphate, calcium fluoride, quaternary ammonium polyethyleneimine, and nanohydroxyapatite and/or nanofluorohydroxyapatite are incorporated into restorative materials such as composite resins, glass ionomer cements, and adhesive systems [29].

The summary information of the nanoparticles listed above is given in Table 6 [29–40].
Table 6. Nanoparticles with antibacterial and remineralizing ability used in dental restorative materials.

| Name of Nanoparticle                  | Advantages/Disadvantages                                               | Mechanism of Co-Interaction                                                                 | Examples of Materials                          | Reason for Introduction into Material                                                                 |
|---------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------------------------------------------------------------|
| NAg (nanoparticles of silver)         | Antibacterial/can alter color of tooth or restoration                 | A bactericidal effect is achieved by interactions with the peptidoglycan cell wall and the plasma membrane; silver ions prevent bacterial DNA replication by interacting with the exposed sulfhydryl groups in bacterial proteins | Composite resin; dental adhesives               | NAg and NZnO have been incorporated in dental materials to kill cariogenic microorganisms in the marginal gaps and on the material surfaces |
| NZnO (nano zinc oxide particle)       | Antibacterial action against several types of microorganisms, including S. Mutans/no evidence about increased mechanical properties | Bactericidal effect is due to modified cell membrane activity and oxidative stress; these generate active oxygen species such as H2O2 that inhibit growth of planktonic microbes | Composite resin                                 | Provide durable and permanent antibacterial capability to the dental material without significantly affecting the biologic balance in the oral cavity |
| Quaternary ammonium poly-ethylenimine nanoparticles | An antibacterial agent is copolymerized with the resin by forming a covalent bond with the polymer network, and therefore is immobilized in the composite and not released or lost over time | Cause bacterial lysis by binding to the cell membrane and causing cytoplasmic leakage | Composite resin; glassionomer cement            | The presence of ACP (amorphous calcium phosphate) nanofillers (NACP) in dental composite resins is an approach to release calcium and phosphate ions continuously into the oral environment |
| Calcium phosphate nanoparticles       | Remineralizing ability: can promote remineralization without loss of the mechanical characteristics of restorative material | Continuous release of calcium (Ca) and phosphate (PO4) ions into oral environment increase the mineral content in the caries lesions | Composite resin; adhesive systems; glassionomer cement |                                                       |
| Calcium fluoride release: caries-inhibiting effect without compromising on mechanical strength | High fluoride release increases with nano CaF2 content, and resin composites containing 20–30% of CaF2 nanoparticles have the same fluoride release rates |                                                                                              | Composite resin                                 | To inhibit cariogenic bacteria and reduce secondary caries rate |


as traditional and resin-modified glass ionomer materials

| Nano hydroxyapatite and nano fluorohydroxyapatite (NHA, NFHA) | An increased resistance to demineralization when incorporated into glassionomer cement (GICs) exceeded the clinically suitable maximum setting time when added into GICs | Has remineralization effect and biological compatibility of synthesized NHA; is used as substitute for the natural mineral constituent of dentin | Resin modified glassionomer | Remineralization rates with NFHA are higher than with micro bioactive glass particles |

One of the mainstreams of nanotechnology, which is widely used in dentistry, is incorporation of nanoparticles in composite materials. Composite resins are the most widely used dental materials for restoring dental cavities, especially because of their biomimetic ability [41]. Nanotechnologies make possible the emergence of materials with completely new characteristics—stronger, lighter, and thinner composite materials, and the quality of many materials can be improved using nanoparticles. Combining these properties in one material has led to the creation of a new class of materials, “nanocomposites”, in which nanomers and nanoclusters are used as fillers [42,43]. The benefits of “nanocomposites” are widely known to dentists. The rationale for use of nanoparticles includes the main indicators that assess the quality of composite materials, namely:

- high strength, which allows them to be used for restoration and filling procedures on anterior and posterior teeth;
- aesthetics, in particular the ability to manipulate the color shade of restorations in a wide range of values, as well as obtaining a stable shine;
- minimal polymerization shrinkage that would help avoid marginal leakage problems as it is the main reason for secondary caries progression.

It is assumed that Indian American chemist Sumita Mitra is responsible for the introduction of nanoparticles in dentistry [44]. A composite material Filtek Supreme XT (3M ESPE) came out from under her microscope, which the American publisher “The Dental Advisor” recognized as a composite of the year for several years in a row together with Vitremer™ triple-cured glass ionomer cement.

The fact is that the traditional material for filling teeth consists of an inorganic filler based on silicon and an organic matrix (resin), and such materials are not universal, they do not combine high strength with aesthetics [45]. This means that if the material is invisible, shines like your own teeth, it can only be used on the anterior teeth. Moreover, if the material is strong, does not wear out, it loses its gloss very quickly and turns yellow.

Nanocomposite Filtek™ Supreme™ XT solved this problem with its appearance. The innovative zirconium-silicon filler sintered in a special furnace. This unique filler adds strength and self-polishing to the material. The material can be used on the anterior and posterior teeth, achieving at the same time durable, completely invisible, aesthetic restorations of extremely high quality. That is why the material has gained popularity among experts.

It is claimed that Premise, Kerr/Sybron, Orange, CA builds on the proven success of Point 4™ Dental Hybrid Composite from Kerr, by using the same 0.4 micron barium glass filler, which provides outstanding blending—making restorations hard to detect. Benefits of this material come from the tri-modal filler system which uses three distinct filler sizes
to increase loading. In addition, the incorporation of PPF (pre-polymerized filler) limits shrinkage and enhances polish ability and wear resistance [46].

The aesthetic properties of nanomaterials are superior to those in traditional composites, primarily due to the optical properties of nanoparticles, as well as better polishing and preservation of the polished surface for a long time. Nanofilled composite materials exhibit better physical properties, including compressive strength, tensile strength, toughness, flexural strength and abrasion resistance, etc., compared to microparticle-filled materials [47]. Therefore, nanocomposite materials are a real breakthrough and revolution in the history of the dental industry. Figure 12 gives a brief idea of the timeline of composite resins/adhesives development.

![Figure 12. Timeline of composite resins and adhesives including the nano era.](image)

**Adhesives**

The development of dental adhesive systems has played a significant role in restorative dentistry, paving the way for minimal invasive dentistry. By using adhesives, dentists can undertake more conservative cavity design, preserving healthy tissue. Bonding of composite materials with tooth tissues is carried out using various systems of adhesive resins [48,49]. The resin–dentin bond depends on the infiltration of the adhesive system into the collagen matrix of the dentin, which is exposed through acid conditioning by creating a hybrid layer. In 2010, VOCO America (a subsidiary of VOCO GmbH, Germany) was the first to introduce nanoreinforced bonding agents. In this scenario, the use of nanosized fillers increases the penetration of resin monomers and the hybrid layer thickness, which in turn improves the mechanical properties of the bonding systems: i.e., Futurabond M VOCO tolerates residual moisture due to its hydrophilic properties that is beneficial in cases of poor moisture control. Integration of nanotechnologies in adhesive systems facilitates the micro shear bond strength as well [50].

Nanoreinforced adhesive Adper™ Single Bond Plus Adhesive give dentists confidence that the adhesive is perfectly mixed every time due to highly dispersed bonded nanofiller which does not allow particles to cluster together. The particles are stable and will not settle out of dispersion. Therefore, unlike some filled adhesives, Adper Single Bond Plus Adhesive does not require shaking prior to use [51].

**Glass Ionomer Cement**
Glass Ionomer Cement (GIC) originated in the middle of the 20th century, as a bio-compatible, cost effective, tooth-colored restorative material and is constantly evolving. Considering its unique ability to bond to the tooth structure without the use of any bonding agent coupled with fluoride releasing potential, GIC has gradually emerged as the material of choice for various applications in the field of dentistry [52].

The glass ionomers with nanoparticles are called nanoionomers. The glass ionomer cement is widely used on the basis of its chemical binding to the tooth surface. Nanomers and nanoclusters are added to fluoroaluminosilicate glass [53]. The nanoionomer produces aesthetic and fluoride releasing properties. The nanoglass ionomer has high translucency and optical properties compared to the conventional GIC [54].

Ketac N-100 is the first resin-modified glass ionomer cement designed based on the nano-filler technology. Ketac N-100 nanoionomer represents a combination of the fluoroaluminosilicate technology and the concept of nanotechnology encountered in Filtek™ Supreme Universal Restorative preparation [55].

Incorporation of nano-sized particles in powder-modified nanoglass ionomers improves their mechanical properties [56]. For the first time, it was assumed by De Caluwé et al. that doping conventional GICs with nano-sized glass particles can decrease the setting time and enhance the compression strength and elastic-modulus [57].

4.1.3. Nanotechnology in Endodontic Sealers

In endodontic practice, the problem of managing bacterial biofilm is extremely important. Persistent in the lumen of numerous dentinal tubules, the microflora is virtually invulnerable to medical and instrumental treatment of root canals. The diameter of the dentinal tubules is only 200–300 nm and this prevents the penetration of even the strongest antiseptics. Incorporation of metallic nanoparticles into antiseptics for root canals can help to manage persistent microflora (Enterococcus faecalis) after one week [58,59].

Research by Leng, D. et al. (2020) showed the potential of using a mixture of calcium hydroxide paste and nanosilver for intracanal drug treatment [60].

The advantages of using nano endodontic sealers are obvious: they seal better in comparison to the conventional sealers and the use of nanoparticles serves as a good antimicrobial agent [61].

The application of nanotechnology in endodontics includes the insertion of bioceramic nanoparticles such as bioglass, zirconium, and glass ceramics in endodontic sealers. A nanomaterial sealer was recently developed on a bioceramic basis EndoSequence BC Sealer—Brasseler USA, consisting of nanosized particles of calcium silicate, calcium hydroxide, CaP. A feature of the material is the formation of complex nanocomposite structural particles of hydroxyapatite and calcium silicate during the hydration reaction in the root canal. The use of nanosized particles helps to easily deliver the material with an ultra-thin capillary needle size of 0.0012 mm. Nanodisperse materials provide excellent tightness and dimensional stability, excellent biocompatibility and bioactivity, excellent antimicrobial properties at high alkaline pH 12.8.

TotalFill BC Sealer (FKG, La Chaux-des-Fonds, Switzerland) and TotalFill BC Sealer HiFlow (FKG, La Chaux-des-Fonds, Switzerland) is a new class of endodontic sealers, with potential further benefits due to their bioactivity.

This study [62] indicates that both TotalFill BC sealer and TotalFill BC HiFlow are biocompatible and exhibit potential bioactivity. TotalFill® BC Sealer™ and BC Sealer HiFlow™ are the “state-of-the-art” in endodontic obturation.

GuttaFlow Bioseal (Coltene/Whaledent AG, Altstatten, Switzerland) is a silicon-based sealer containing polydimethylsiloxane, and a mixture of gutta-percha and calcium silicate particles [63]. It is composed of a unique mixture of finely ground gutta percha, RoekoSeal® root canal sealer and nano-silver. The manufacturing company claims that this sealer has excellent adaptation due to its optimal flowability and can undergo gradual volumetric expansion, thus, it can adapt well to the root canal walls and can be used not only as a sealer but even as a root filling material. The sealer part of GuttaFlow is highly
thixotropic, has a fine grain size (<9 µm), and the material flows well under slight pressure into the lateral canals. [64–68].

Gutta Percha points have been most widely used for years and established themselves as a gold standard in root canal obturation techniques. In addition, it has proved itself successful with different techniques of root canal sealing. Attempts have been made to improve optimum seal and therapeutic effects by addition of various materials including nanoparticles to gutta percha composition [69]. Nanodiamond coated gutta percha embedded with nanodiamond amoxicillin conjugates could reduce the likelihood of root canal reinfection and enhance the treatment outcomes. Antibacterial effects against various intracanal microorganisms are gained by coating standard gutta percha points with silver nanoparticles [70].

4.1.4. Nanotechnology in Periodontology

Chronic generalized periodontitis it is a mainly bacterial dependent disease together with other co-reasons. Due to long lasting inflammation, it can lead to loosening of teeth or tooth loss. The current treatment options include mechanical removal of pathogenic biofilms and providing some drug treatment, both local and systemic. Dental researchers attempted to generate an effective and satisfactory drug delivery system for the treatment of periodontal diseases that will be better than conventional ones. Current trends are the use of microparticles [71] and nano-based delivery systems [72,73].

Microspheres of “Arestin” (minocycline HCl), 1 mg, is a concentrated, locally applied antibiotic that remains active in the pocket for an extended period of time and reduces pocket depth [74]. The microspheres release antibiotic over time, targeting bacteria to reduce pocket depth, so gums can heal better than with scaling and root planing alone. Nano-based delivery systems can find significant application for eliminating bacterial pathogens. The use of charged nanoparticles is extremely useful since many of the microorganisms are themselves charged. The charged nanoparticles could be used to directly affect the bacteria or alter the microenvironment of it [75–77].

4.2. Nanotechnology in the Surgical Field

4.2.1. Nanoanesthesia

In the era of nano-dentistry, a colloidal suspension containing millions of active analgesic micron-size dental robots will be instilled on the patient’s gingiva. After contacting the surface of crown or mucosa, the ambulating nanorobots reach the pulp via the gingival sulcus, lamina propria, and dentinal tubules guided by combination of chemical gradients, temperature differentials, and even positional navigation all under the control of the on-board nanocomputer that is controlled by the dentist [78].

Once installed in the pulp, the analgesic dental robots may be controlled by the dentist to shut down all sensitivity in any particular tooth that requires treatment. After oral procedures are completed, the dentist orders the nanorobots to restore all sensation, to relinquish control of nerve traffic, and to egress from the tooth by similar pathways used for ingress [79].

4.2.2. Nanotechnology in Dental Implants

Structural and functional fusion of the surface of the dental implant with the surrounding bone (osteointegration) is crucial for short-term and long-term results. Titanium dental implants have been used successfully for the past 30 years, but they still have disadvantages due to their full osseointegration and the fact that their mechanical properties do not match the properties of the bones [80].

Advances in the production of nanoparticles for implant surface coating and nano formatting of dental implants lead to better osseointegration and improved physiological functions of implants [81]. The application of nanotechnology on the surfaces of dental implants has many different mechanisms. In particular, the surfaces can potentially take
an organized (isotropic) or unorganized (anisotropic) pattern. Due to the difficulty of applying standardized sequences to complex structures, the template for dental implants is usually anisotropic. Titanium dioxide (TiO₂) nanoparticles have been explored in recent years as antimicrobial agents [82].

A wide variety of methods are used to create nano-features on the surface of dental implants. They can be divided into chemical (anodic oxidation, combinations of acids (bases) and oxidants) and physical (plasma spray, blasting) [83,84].

Antimicrobial peptides (AMPs), such as LL37 peptides, may be immobilized on the surface of medical devices, as dental implants, to render them with antimicrobial and angiogenic properties.

Both soluble and immobilized LL37 peptides have potent antimicrobial activity against Gram-positive and Gram-negative bacteria in the presence of 10% human serum (HS). However, the immobilized LL37 peptides showed less cytotoxicity to endothelial cells (ECs) at a concentration that was able to kill bacteria [85].

4.2.3. Nanotechnologies in the Correction of Deformations and Defects of Bones

Nanophase materials have shown promising results in the treatment of various deformities and bone defects. Nanophase hydroxyapatite and nanophase carbon are the two main promising types of nanophase materials used to treat bone defects.

Nanophase hydroxyapatite shows excellent osteoblastic adhesion compared to traditional materials. Nanoparticles of nanophase hydroxyapatite (HA) are used to treat bone defects—NanOSTM HA (Angstrom Medica, Woburn, USA), Vitosso (Orthovita, Inc, Malvern, USA) HA + tricalcium phosphate (tri CaP), and Ostim HA (Osartis GmbH, Germany) [86,87].

Unlike nanophase hydroxyapatite, carbon nanophase exhibits excellent biomechanical properties due to a combination of not only nanoscale but also similar to natural HA. Thus, making it the material with the greatest potential for the correction of maxillofacial defects and maxillofacial implant material in the future.

4.3. Prosthetic Dentistry

Another area where nanotechnology has been used is the use of submicron grain sized ceramics for the production of all-ceramic restorations. The logic for using nanometer-sized powders for the production of ceramic monoliths is esthetics, wear properties, and for maximizing the strength of the ceramic.

It has been established that nanoglass ceramics cause less abrasion of antagonist enamel than ordinary facing ceramics; in addition, nanoglass ceramics have demonstrated high strength under bending loads [88–90].

The addition of silver nanoparticles to the polymer for the base of the denture has shown positive results in the treatment of stomatitis associated with wearing dentures. In this regard, scientists have concluded that the addition of silver nanoparticles to dentures helps prevent infections of the oral mucosa.

To improve the mechanical properties of methyl methacrylate plastic [91], which is used for the manufacture of bases for removable dentures, it is proposed to add to their composition carbon nanotubes [92].

Nanofillers enhance polish ability and reduce wear. Nanopigments adjust the shade of the restoration to the surrounding teeth (chameleon effect). Nanomodifiers increase the stability (non-slump) of the material and prevent sticking to instruments [93].

4.4. Preventive Nano-Dentistry

The goal of modern dentistry is to prevent rather than treat biofilm-dependent oral diseases, i.e., dental caries, endodontic and periodontal diseases. Nanotechnology offers new approaches for preventive measures in oral diseases, particularly dental caries and periodontal diseases [94].
Prevention of caries is one of the main methods that reduces the prevalence of this disease. Caries prevention methods are constantly improving, but still the most affordable tool is the use of therapeutic and prophylactic toothpastes. With the development of nanotechnology in dentistry, now even daily brushing can ensure hygiene and protection of the oral cavity at the nano level.

Researchers have developed a nano-toothbrush. Including colloidal particles of nanogold or nanosilver between the bristles of a toothbrush [95,96] can lead to a significant reduction in periodontal disease.

Oral hygiene products, such as toothpastes and mouthwashes, have also been nanomodified according to recent reports [97].

For example, nanocalcium fluoride, which is part of mouthwashes, reduces the activity of caries, reduces dentin permeability, and increases the labile concentration of fluoride in oral fluid [98]. Toothpastes containing calcium carbonate nanoparticles and 3% nanosized sodium trimetaphosphate promote remineralization of early carious lesions compared to conventional toothpaste without nano-additives [99]. According to the results of an in vitro study, toothpastes containing nano hydroxyapatite (NHA) crystals significantly increased the value of microhardness in human enamel after erosive influence, compared to the same toothpaste without NHA [100].

The higher reparative capacity of nanomaterials compared to the same material on a micro or macro-level may be due to the fact that inorganic building blocks in enamel have a size of 20–40 nm, which makes it logical to assume a higher affinity for nanosized particles. Remineralizing toothpaste with peptide complex and nano-hydroxyapatite Vivax Dent strengthens tooth enamel, prevents leaching of calcium and phosphorus from bone tissue, fights bacteria and plaque, and prevents caries and odor. It is suitable for the treatment of stomatitis, periodontitis, and other inflammatory processes of the oral cavity, as well as for the prevention of caries.

Unlike traditional oral hygiene products, which act only superficially, the active components of innovative products, due to nanoparticles and effective carriers, penetrate deeply through natural barriers and have a positive effect on all tissues of teeth and gums [101].

4.5. Nanotechnologies in Diagnosis

Nanoparticles are used not only for the treatment and prevention of dental diseases, but also as agents for extra research methods. Thus, more recently, the latest word in dental technology was “laser diagnosis” of caries, based on the optical phenomenon of transillumination. Researchers from the University of Michigan [102] used fluorescent dioxide-labeled cations of 150 nm starch nanoparticles. When irrigating the oral cavity with a solution of such particles, the latter easily penetrated into the micropores of the foci of demineralization, which were then easily detected under the light of a standard light curing halogen lamp. The technology described in 2017 allows detection of actively occurring superficial caries in the early stages of pathogenesis.

Molecular Imaging

Optical coherence tomography (OCT) it is a direct simulation of ultrasound, that is based on low-coherence interferometry, typically employing near-infrared light. OCT shows enormous potential for its application in more effective diagnosis and therapy of caries and erosive tooth wear. This technique is advantageous in qualitative assessment of pit and fissure sealing as well as providing great potential for imaging the outline form of the pulp chamber: pulp horns can be visualized during dental procedures and accidental pulp exposure can be avoided [103].

Nanotechnology is a useful tool for cancer detection and disease monitoring, and also increases the possibility of specific targeted cancer therapy [104].
OCT is used not only in caries diagnostics but also for oral cancer screening and monitoring. The main type of malignant neoplasm of the oral cavity is a squamous cell carcinoma of the oral cavity, which accounts for more than 90% of all cancers of the oral cavity. Squamous cell carcinoma is an aggressive cancer that has a poor prognosis and a high recurrence rate, which can even lead to death.

With the development of nanotechnology, different types of nanoparticles came into use as specific contrast agents for magnetic resonance imaging, optical coherence tomography, etc. Shanavas et al. created a nanoagent that is a combination of folate preconjugated chitosan and poly (magnetic lactide with glycolide) nanoparticles for simultaneous cancer therapy and a contrast agent for magnetic resonance imaging at the same time. Oral cancer cells with positive folic acid receptors showed increased uptake of nanoparticles and caused a significant increase in cytotoxicity [105].

The gold nanoparticles are promising contrast agents for OCT due to biocompatibility; they can provide localized surface plasmon resonances at wavelengths of near-infrared radiation, which avoids the predominant absorption in tissues [106].

Photoacoustic (PA) imaging is a new non-invasive technique of optical diagnostic technology. Near-infrared absorbing organic nanoparticles are used in PA imaging applications. Photoacoustic waves generated by the laser pulse are then converted into photoacoustic images. Photoacoustic images have improved image depth in comparison to conventional optical images. Organic nanoparticles with their exclusive benefits can play an important role in advancing PA molecular imaging in preclinical investigation and clinical use [107].

The nano-based single biomarker method is used to detect oral cancer [108]. Investigation of tumor molecular biomarkers—such as tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor, and interleukin 6 (IL 6)—gives great promise for early cancer detection. The research revealed TNF-α by the method of gold protein chips using fluorescence microscopy of complete internal reflection [109].

Despite of a wide range of benefits of nanoparticle application, there is a disadvantage of cytotoxicity that is seen only in higher concentrations. The cytotoxicity depends on the size—selective difference [110–112]. Therefore, new studies aimed at producing safe and biocompatible materials are needed [113,114].

5. Limitations

The findings of this study must be seen in light of some limitations. There were 349 papers found in Pubmed that fit our search, but we limited our scope to 222 papers indexed in Scopus and books or book chapters published by high-ranking publishers such as Springer, Wiley and sons, and Elsevier with affiliated publishers (Woodhead publishing and William Andrew are part of Elsevier) because they ensure quality peer-review of their scientific publications. We made this decision because our review includes commercial materials. Therefore, we wanted to avoid problems with possible conflicts of interest and hidden advertisements. Web of Science covers fewer journals and books so we decided not to use it for our search and review. We believe there are many good journals among the ones not indexed in Scopus, but we wanted to be sure of the quality of their papers. Therefore, Scopus is a compromise between coverage, quality, and number of indexed materials.

Another limitation imposed on our study is that we focused our attention only on the papers published in English, which can also cut off some important papers from our review.

As it was mentioned above, we limited our scope only to commercial materials, so we might have missed some new materials which are now at the stage of clinical trials as our exclusion criterion cut them off from our review. There are little data concerning the safety of the considered materials that is why we paid no attention to this important problem. We hope the number of studies in this field in the near future will shed some light on this problem.
One more limitation it is our forecast that is based on the rather simple model which has some flaws from a statistical point of view so it can be somewhat unreliable. On the other hand, the chosen model avoids overfitting and ensures a good generalization of data. Therefore, we believe our model and its forecast are reliable enough but the results should be considered with some care.

6. Conclusions

Our review shows that the effectiveness of nanotechnology in dentistry is beyond any doubt. Nanotechnology plays an important and consistent role in the dental industry, as it can bring significant innovations and benefits such as improvement of the quality, appearance, durability, and wear resistance of the dental materials. Each nanoparticle has its specific benefits in some particular areas.

In last 5 years, there were 149 papers published in this field indexed in Scopus. The application of nanotechnology in dentistry is anticipated to grow further. Our forecast shows that we can expect from 256 to 360 papers with the probability of 95% within the next 5 years. There are now 222 papers indexed in Scopus from 2003 to 2021, so within the next 5 years this amount will at least double. We expect interest in this topic and the number of clinical studies of nanoparticle-based bioactive materials and diagnostic techniques with a wide range of applications in restorative dentistry, endodontics, implantology, orthodontics, denture prosthesis manufacturing, and other dental fields will increase. Nevertheless, the main disadvantage of nanoparticles is cytotoxicity.

The general risks of nanomaterials in all healthcare areas remain a concern. Therefore, it will require specific and long-term investigations of safety. The interdisciplinary approach encompassing expertise in nanotechnology-based material science and dentistry is required.

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