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Nanotechnology – A new era in periodontology

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Abstract

The emerging science of nanotechnology, especially within the dental and medical fields, sparked a research interest in their potential applications and benefits in comparison to conventional materials used. Therefore, a better understanding of the science behind nanotechnology is essential to appreciate how these materials can be utilised in our daily practice. The present review will help the reader to understand nanoscience, and the benefits of nanotechnology by addressing its various implications in periodontology. Additionally, nano-applications in dental diagnostics, dental prevention, and in dental treatment will be addressed.

Keywords: Nanotechnology, Nano materials, Nano medicine, Nano robots, Nano dentistry

Introduction

Nanotechnology is a technology on a "nano" scale (billionths of a meter). The vision of nanotechnology was introduced in 1959 by Nobel Physicist Faynman[1]. Drexler published a book named "Engines of Creation" to promote the prospective of molecular nanotechnology.[2] Drexler (engineer, Massachusetts Institute of Technology) invented the term along with his concept of developing machines from an atomic level to molecules to full size.

Nano came from a Greek word which means "dwarf." A widely used definition for nanotechnology is "The creation and utilization of materials, devices, and systems through the control of matter on the nanometer scale (1-100 nm), i.e. at the level of atoms, molecules, and supramolecular structures."[3] However, nanotechnology is much more than the study of small things; it is the exploration and advancement of materials, devices, and systems showing physical, chemical, and biological properties that are divergent from those found on a larger scale.[4] In an effort to create an eco-friendly socially acceptable nanotechnology, the United States National Human Genome Research Institute proposed a new approach to the development process of new technology. This was accomplished by addressing the ethical, legal, and social implications before nano-products reach the market to easily modify and adjust during the early stages of production [5,6].

Atoms are the building blocks in biological tissue, and these atoms are measured using the nanoscale. Introducing nano-sized particles allows for an interaction on a molecular level, by that increasing the overall efficacy and affinity in comparison to biological molecules interacting with micro or macro sized particles [7] The high surface to core ratio, is a unique physical characteristic in nanoparticles, meaning that there are more atoms on the surface of the nanoparticle than deep within its core. This is particularly useful since surface atoms have unbound surfaces in comparison to core atoms, with the potential for creating new and strong bonds, and hens, nanoparticles are more reactive in comparison to micro and macro particles which have more core than surface atoms.[8]

Because of the growing importance of applications of nanotechnology in dentistry, a new field called nanodentistry is evolving. New treatment prospects in dentistry include application of local anesthesia, hypersensitivity cure, complete orthodontic realignment in a single office visit, and continuous oral health care with the help of mechanical dentifrobots that end caries causing bacteria and even renovates blemishes on the teeth where decay has occurred.[9]

History of Nanotechnology

As early as 1867, James Clerk Maxwell proposed a revolutionary concept of nanotechnology. The term nanotechnology was given by Prof. Kerie E. Drexler. In the early 20th century, Richard Zsigmondy brought about the concept of nanomaterials.[10] In 1959, Richard P. Feynman, the Nobel Laureate said that his friend, Albert R. Hibbshad suggested an interesting possibility for extremely small machines.[11]

R.A. Freitas Jr., in the year 2000, coined the term "nanodentistry". He developed visions using nanorobots for orthodontics, dentition regeneration, nanomaterials, and robots in dentifrices–dentifrobots. Although most of his ideas were and remain science fiction, these ideas are gradually being realized into practice. Today many applications of nanoscale technology are known and used in the field of dentistry.[12]

Nano materials

Nanomaterials are classified as zero-dimensional, onedimensional, two-dimensional, and three-dimensional. Different types of nanoparticles are nanopores, nanotubes, quantum dots, nanoshells, dendrimers, liposomes, nanorods, fullerenes (bucky-balls), nanospheres, nanowires, nanobelts, nanorings, nanocap, and many more.[13]

Different approaches for the synthesis of nanoparticles are top-down approach, bottom-up approach and functional approach.[14] In top-down approach, particles are manufactured in the conventional manner and made smaller in size by grinding or milling. Examples of top-down approach are nanocomposites, nanoencapsulation, nanoneedles, nano based bone replacement cement, nano impression materials, nano coatings on implants. While in the bottom-up approach, nanoparticles are synthesized by direct molecular synthesis and bonding, i.e., they are synthesized from molecular level and assembled to form larger units.[15] Examples of bottom- up approach is local anesthesia, tooth regeneration, hypersensitivity cure, nanodiagnostics, oral tissure biomimetics etc.

Properties of Nanomaterials [4]

1. Nanomaterials contain constituents <100 nm in minimum one dimension.

2.They have significant surface effects, size effects, Quantum effects and show better performance properties than traditional materials.

3. They have special chemical, optical, magnetic, and Electro-optical properties.

4. Important property of self-assembly by which they autonomously organize themselves into patterns or Structures without any others intervention.

Generations of Nanotechnology

Table 1:

First generation (from 2000)	Second generation (from 2005)	Third generation (from 2010)	Fourth generation (from 2015/20)
Passive (steady function nanostructures) E.g., Nanostructured coatings invasive, noninvasive diagnostics for rapid patient monitoring	Active(evolving function nanostructures) E.g. Reactive nanostructured materials and sensors; targeted cancer therapies	Integrated nanosystems E.g. Artificial organs built from nanoscales, evolutionary bio systems	Heterogenous nanosystems E.g. Nanoscales genetic therapies; molecules intended to self-assemble themselves

5. Roles of Nanotechnology-Based Approaches

In Nano diagnostics

Nanodiagnostics is a phenomenon that involves the use of nanotechnological advancement for clinical and molecular diagnostic purposes. The increased demands for highly sensitive and early disease detection tools has led to the development of this novel technology, in order to meet the demands of clinical diagnostics. Nanodiagnostics would significantly reduce the waiting time for results after a test is conducted. The technology will help in the use of nanodevices for early disease diagnosis at molecular and cellular level. The possibility of using nanosized Quantum dots technology based on immune fluorescence has provided researchers an opportunity to be able to precisely label specific periodontal pathogenic bacteria, which therefore enable its identification and removal (16)

The various nanodiagnostic tools used are

a) Quantum dots (QDs)

b) Nanoscale cantilevers

c) Gold nanoparticles

d) Nanotubes

e) Nanopores

a) Quantum dots (QDs)

Quantum dots are among the most promising nanostructures for diagnostic applications. These are new material that promise fundamental transformation in medical labeling techniques. Quantum dots are tiny semiconductor nanocrystals that are stable, non-toxic and glow brightly when stimulated by ultraviolet light. Their strong light absorbance property qualifies them to be used as fluorescent labels for biomolecules. [16] Their roles are beyond diagnostic applications, as they have also been found to play the role of photosensitizer and carrier. Quantum dots can attach an antibody to the target cell upon stimulation by UV light, and consequently yield a reactive oxygen species that is capable of destroying the target cells.[17]

b) Nanoscale cantilevers

Nanoscale cantilevers are tiny beams resembling a row of diving boards or those as in atomic force microscopy, and they are fabricated by using semiconductor lithographic techniques. Nanoscale cantilevers exercise its function through nanomechanical deflections and are used for deoxyribonucleic acid (DNA) hybridization to monitor molecular events. [18]Nanoscale cantilevers are developed as an integral division of larger diagnostic tools that can provide sensitive and rapid detection of inflammation and cancer-associated molecules, of which periodontal disease could be an important target. Through the cantilevers, it is possible to detect disease such as periodontitis and to comprehend the mechanism of the disease and its potential cure. [19].

c) Gold nanoparticles

Gold nanoparticles are among the novel diagnostic tools for healthcare investigations. They are developed from thin gold layers or tiny gold spheres and possess good detection sensitivity for various targets. [20]Gold nanoparticles that are coated with silver shells possess strong light-scattering properties with improved detection capacity.[21]The applications of gold nanoparticles stretch from diagnosis to drug delivery for therapy of diseases[22]. Gold nanoparticles can be functionalized to detect specific targets due to their high surface-to-volume ratios which offer higher selectivity as compared to conventional approaches [23].

d) Nanotubes

Nanotubes such as boron nitride or carbon rods are very small and are used as electrodes with single-stranded DNA probes for detection sensitivity in the attomole range, and in hybridization of the target DNA or protein. They can also be adapted for analytes other than DNA, e.g., by attaching enzyme to detect substrate analyte.[24] Nanotubes offer interesting advantages that are relative to or better than spherical nanoparticles in some biotechnological and diagnostic applications.Examples of nanotubes include fullerene carbon nanotubes, organosilicon polymer nanotubes, peptide nanotubes and template-synthesized nanotubes. [25,26].

e) Nanopores

These are tiny (molecular-scale) structures that have great sensitivity and detection capability of the conformation and location of a single molecule that is situated in the pore lumen. (27,28). The nanoholes of nanopores can permit passage of DNA and can also make DNA sequencing even more efficient. The characteristic change in the nanopores conductance enables researchers to be able to electrically elucidate single-molecule kinetic pathways as well as quantify the target easily (28). Significant progress has been made in material science and nanotechnology towards designing intelligently gated nanoporous devices. (29).

In Prevention

For a very long time, conventional dentifrices such as gargles, mouthwashes, toothpaste and throat paints have been the most commonly used traditional products for maintaining oral hygiene and oral preventive measures, until recently when nanotechnology provide novel approaches for preventive measures against oral cavity diseases such as periodontal disease and dental caries (30).Certain agents in nanoscale can be incorporated in these conventional dentifrices to aid in repelling the deposition of bacterial biofilms (plaque and tar) and/or prevent dental caries by remineralization of early carious lesions, and in desensitization of abraded teeth(31). The process of re-deposition of minerals that are lost by tooth enamel is called enamel remineralization (32).

Study conducted by Nakashima et al. (2009)(33) showed that there is 48.8% improvement on the remineralization of artificially produced subsurface enamel lesions when the nanosized calcium carbonate particles were incorporated in dentifrices. . Furthermore, nanocarbonate apatite has proven to be very efficacious desensitizing dentifrice when compared with the conventional agents (34). Mouthwashes containing silver nanoparticles and triclosan-loaded nanoparticles have exhibited plaque control actions which are vital for the prevention of periodontal disease. Silver nanoparticles demonstrated strong antibacterial effects in dental products, because of the antibacterial properties of silver (35; 36).In one investigation, carbonate hydroxyl apatite nanoparticles have been found to be highly effective in repairing some tooth defects (micrometer-sized) in vitro (37), and some of its nanocrystals were incorporated in dentifrices like mouthwash solutions and toothpaste and used as commercial products (38; 39).

Other preventive nanotechhnology-based approach for periodontal disease is fabrication of products for oral health care that are integrated with bioinspired apatite nanoparticles alone or together with proteinaceous substances (like casein phosphopeptides) (40) Casein phosphopeptide demonstrated an important role in biomimetic strategies for overall bacterial biofilm management. In vivo studies showed evidence which indicated that casein phosphopeptide coupled with amorphous calcium phosphate nanocomplexes reduces bacterial adherence on the tooth surface (Figure 1), by adsorbing the bacterial macromolecules, as well as binding to the surfaces of bacterial cells and to the components of the intercellular plaque matrix (41).

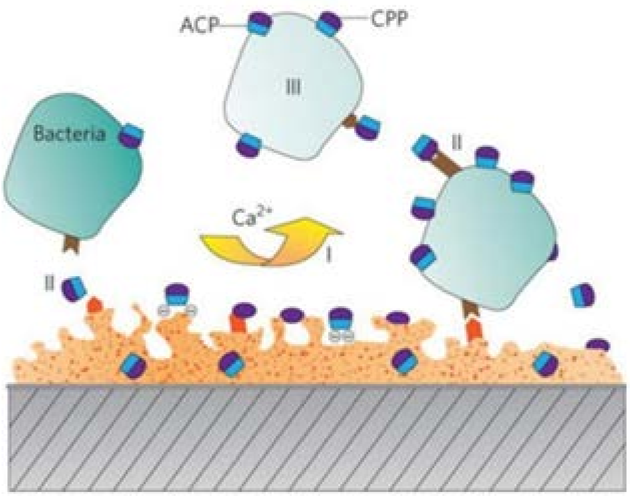

Fig. 1: Diagrammatical demonstration of how ACP–CPP prevent the oral biofilm formation by hindering bacterial adhesion. CPP block the adhesion by binding to the pellicle. It competes with calcium for plaque–calcium binding sites (I) and reduces the quantity of calcium that connects the bacteria with the pellicle, and between the bacterial cells. This will result in blocking specific receptor molecules (red) in the pellicle layer as well as on the bacterial surfaces (brown), which further decreases the adhesion and co-adhesion (II), and will interfere with the viability of the bacteria (III). ACP, amorphous calcium phosphate; CPP, casein phosphopeptide.

Nano robotic Dentifrices (Dentifrobots)

Dentifrobots in the form of mouthwash or toothpaste can clean organic residues by moving throughout the supragingival and subgingival surfaces, metabolizing trapped organic matter into harmless and odourless vapors and performing continuous calculus debridement when left on the occlusal surface of teeth. These nanorobots can move as fast as 1-10 μ/s and are safely self-deactivated when they are swallowed.

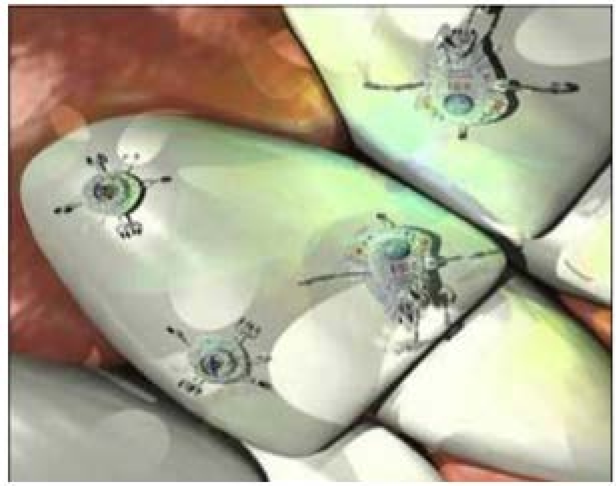

Fig 2: Dentifrobots

In Treatment

a) Nanoneedles and nanoanaesthesia

Nanosized stainless-steel crystals are assimilated into suture needles and in near future cell surgeries may be possible with nanotweezers. The gingiva of the patient is instilled with a colloidal suspension containing active micron-sized dental robots that respond according to the dentist. Nanorobots then can reach the pulp via the gingival sulcus, lamina propria or dentinal tubules. On reaching the dentin, the nanorobots enter the dentinal tubular holes that are 1-4 µm in diameter and advances toward the pulp, guided by various chemical gradients that are all under the control of nanocomputer which is directed by a dentist. Nanorobots can complete its journey into the pulp chamber in approximately 100 s. The presence of various cells like human gingival cells, pulpal fibroblasts, cementoblasts, and odontoblasts suggests that this journey is feasible for cell-sized nanorobots of similar mobility only. As these nanorobots pass through the enamel, dentin, and then reaches into the pulp, the analgesic dental nanorobots may be controlled by the dentist to seal down all sensitivity in selected tooth that requires treatment. . When the dentist permits the icon for the desired tooth on the handheld controlled display monitor, the tooth is immediately anesthetized. Once the oral procedure is completed, the dentist instructs the nanorobots through the same acoustic data links to restore all the sensation and to rescue from the tooth through the same path. This analgesic technique is patient friendly as it reduces anxiety and phobia of needle. Most importantly it is quick and completely reversible procedure. Furthermore, this anesthesia has least side effects or complications in the oral cavity.(42)

b) Drug Delivery

Nanoparticulate drug delivery systems are among the most popular fields of current research for periodontal treatment and regeneration. A significant number of nanoparticulate drug delivery systems have been developed during the last two decades and many of them have yielded promising results (43). Better penetration of the active moiety into the junctional epithelium (site of action) combined with optimal drug release profiles are among the important benefits of this approach. Drug concentration in the periodontal tissue can be improved by incorporating the drug into controlled release delivery systems that can be placed locally in the periodontal pockets (44; 45) The local delivery of antimicrobial agents to the periodontal pockets has the benefit of the drug reaching the target site at low dose thus minimizing exposure of the drug in the entire body (46; 47). Local delivery systems with sustain release effect might also be applicable for areas with accessibility difficulties due to anatomical complexity or depth, as in furcation defects (48).

Table 2

Delivery system	Role(s)	References
Nanoparticles	Triclosan-nanoparticles could help decrease gingival inflammation	Piñón-Segundo et al., 2005
	Potential carrier system for the delivery of active substances to the periodontal pocket	Aminu et al., 2013
	Minocycline-loaded nanoparticles could significantly decrease symptoms of periodontitis	Yao et al., 2014
	Calcium and zinc loaded bioactive and cytocompatible nanoparticles represent a promising tool for therapeutic approach in periodontal regeneration.	Osorio et al., 2016
Nanogels	Nanogels of cholesterol bearing pullulan modified with amino groups (CHPNH2) were utilized as a career to introduce Quantum dots into PDL cells.	Fukui et al., 2007
Nanocomposites	Thin layer of nanocomposites has been used to provide coating on tooth surface, which strongly reduced biofilm formation.	Hannig et al., 2007
	Dental bioactive nanocomposite composed of 2-methacryloyloxyethyl phosphoryl choline and dimethylamino hexadecyl methacrylate is promising for Class V restorations to inhibit periodontal pathogens, combat periodontitis and protect the periodontium	Wang et al., 2016
Nanofibers	Poly-ε-caprolactone (PCL) nanofibers containing metronidazole showed prolonged sustained drug release for at least 19 days and can be used as a retentive, locally controlled delivery system for metronidazole in periodontal diseases treatment	Chaturvedi et al., 2012; Zamani et al., 2010
	Drug loaded hyaluronic acid-polyvinyl alcohol nanofiber patch presented controlled release behavior with good mucoadhesive strength	Joshi et al., 2015
	The in vivo studies confirmed the maintenance of minimum inhibitory concentration over an extended period in addition to a significant anti-inflammatory effect, which suggested the formulation's role as an intra-periodontal pocket drug delivery system.	Joshi et al., 2015

c) Bone Regeneration (49)

Bone regeneration requires three essential elements: Osteoconductive matrix (scaffold), osteoconductive signals, osteogenic cells that can respond to these signals, and an adequate blood supply [Figure 6]. The first step, fabrication of strong and porous scaffolds, holds prime importance in the whole process. Nanotechnology delivers new useful tools to engineer the scaffold's internal surfaces and to create devices used in drug delivery with carefully controlled spatial release patterns. Different techniques have been suggested to successfully seed scaffolds along with cells. They can be roughly divided into two main groups, i.e. either attaching the cells to the internal scaffold surface or distributing them in the scaffold porosity with the help of a gel-like vehicle. Injectable gels comprising of cells could also be used directly in non-load bearing presentations. It has been detected that the presence of calcium within the matrix favors the osteogenic differentiation of the appropriate progenitor cell.

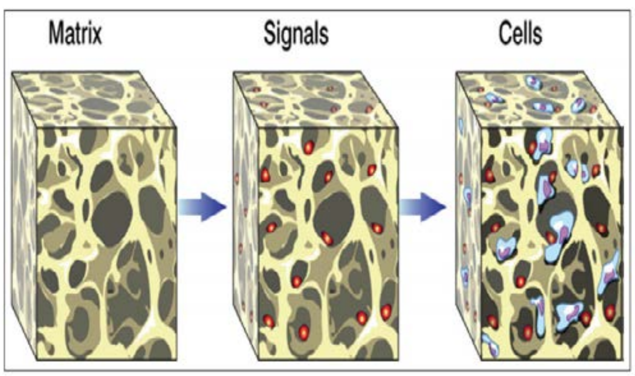

Figure 3: Bone regeneration requires three essential elements: osteoconductive matrix (scaffold), osteoconductive signals, osteogenic cells that can respond to these signals and an adequate blood supply [23] (Adapted from Dental Materials 2013; 29:103-15)

d) Treatment of dentinal hypersensitivity

Changes in pressure transmitted to the pulp hydrodynamically are the main cause of dentinal hypersensitivity. The dentinal tubules of a hypertensive tooth have twice the diameter and eight times the surface density of those in non-sensitive teeth [Figure 4]. Nanorobots selectively and accurately block these dentinal tubules using native materials, thus offering quick and permanent relief to the patient. (50)

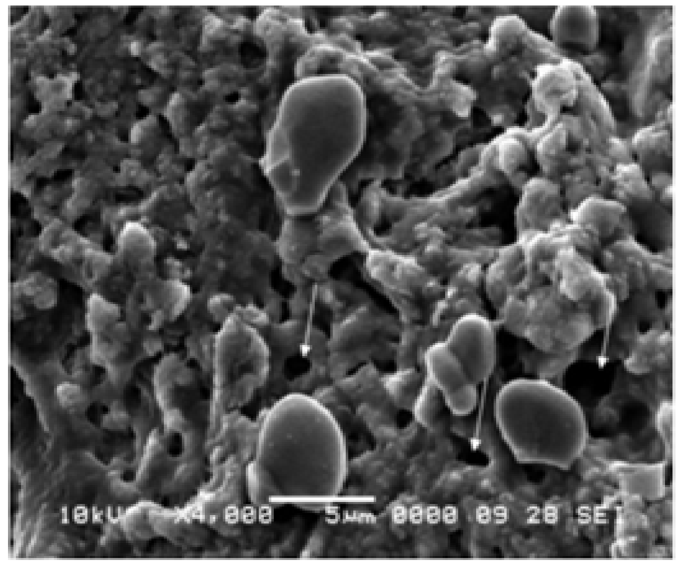

Figure 4: Higher magnification of the image showing significant root surface adhesion of nanoparticles with evident exposed dentinal tubules (arrows)

e) Dental implants

Besides surface contact area and surface topography, bone bonding, and stability play a major role in implant success and osseointegration. Bone growth and implant success can be accelerated by the use of nanotechnology. Osteoblast formation on a more complex implant surface is formed by the addition of nanoscale deposits of hydroxyapatite and calcium phosphate particles. (51,52) Material engineering, and hence implant dentistry, has advanced extensively on the basis of researches conducted on the effects and subsequent optimization of microtopography and surface chemistry. These new implants constructed on the basis of this technology are more acceptable as they enhance the integration of nano coatings resembling biological materials to the periodontal tissues. In addition, implant surfaces coated with titanium oxide nanotubes and laced with silver nanoparticles serve the purpose of fighting infection thus increases the shelf life of the implants.(53)

Recently three nano-structured implant coatings are developed:

•Nanostructured diamond: They have ultrahigh hardness, improved toughness over conventional microcrystalline diamond, low friction, and good adhesion to titanium alloys. (54)

•Nanostructured processing applied to hydroxyapatite coatings: This is used to achieve the desired mechanical characteristics and enhanced surface reactivity and has been found to increase osteoblast adhesion, proliferation, and mineralization. (54)

•Nanostructured metalloceramic coatings: These provide continuous variation from a nanocrystalline metallic bond at the interface to the hard ceramic bond on the surface. (54)

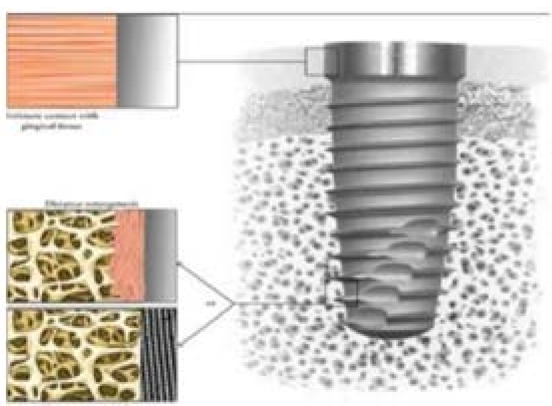

Fig. 5: Nanosurface modification of Implants. Modifying surface roughness has been shown to enhance the bone-to-implant contact and improve their clinical performance.

Conclusion

The advancement of nanotechnology in dental science has brought tremendous progress in periodontal disease therapy. The technology offers significant promise in the disease's early diagnosis even at molecular and cellular level, thereby reduces the waiting time for results. It also play an important roles in the prevention of the disease, through using nanoscale agents to repel bacterial biofilms deposition and accumulation on the tooth surface, and by remineralization and desensitization of abraded teeth. Moreover, there have been significant progress in periodontal drug delivery systems through the recent nanotechnological advancement, whereby therapeutic agents could be loaded in carriers that can facilitate targeted, sustained and controlled release of the loaded drug(s) to the intended location. Certainly, nanotechnology-based drug carrier systems will play a vital role in future drug delivery systems for not only periodontal disease, but for a lot of other oral cavity diseases.

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