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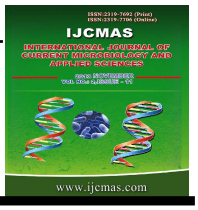

Review Article

Modern Approaches to Use Bioactive Materials and Molecules in Medical and Dental Treatments

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Bioactive materials; molecules; natural source; human disease; treatment.

A B S T R A C T

This review paper focuses on the bioactive material and molecules that has been applied in many of the potential research areas in medical and dental Sciences and highlights their foundation from plants, animals or microbes that can be used to treat human disease. Some ceramics, such as Bioglass, sintered hydroxyapatite, calcium hydroxide, mesoporous silica based ceramics and trioxide aggregate, spontaneously bond to living bone. These materials are called bioactive materials and are already clinically used as important bone substitutes. Bioactive materials and molecules having significant therapeutic benefits in drug delivery, stem cell therapy, cancer therapy, thrombotic diseases and cosmetic surgery in biomedical. Some of dental therapy like Pulp-capping, Root Canal Therapy (RCT) with bioactive molecules provides new prospects. This review paper highlights the properties, natural sources and clinical application of bioactive material and molecules in medical and dental treatment.

Introduction

Research on bioactive material and molecules is one of the thrust areas of development of novel bioactive material and molecules which have wide application in dentistry and biomedical field. Bioactive materials have capacity to interact with living tissues or system. There are several types of bioactive materials like osteogenic, osteoconductive, osteoinductive. Some ceramics such as bioglass, hydroxyapatite, calcium

Sol gel technology has multidisciplinary approach for its various applications. By using this technology ceramics and glass material can be prepared at low temperature that allows the doping of various inorganic, organic and biomolecules (Gupta and Kumar, 2008). Biomaterials are native or synthetic polymers that perform as scaffolds for tissue regeneration and hold wide importance in root canal therapy, tooth repair, pulp therapy and dental surgery in

the field of dentistry (Goldberg, and Smith, 2004; Mauth *et al.,* 2007) and drug delivery (Pavlukhina and Sukhishvili, 2011), cancer treatment (Wei *et al.,* 2013), thrombotic diseases (Yang *et al.,* 2012) and cosmetic surgery (Puppi *et al.,* 2010) in biomedical. The versatility of sol gel technology for making bioactive materials allow manipulating the characteristics of material required for particular application (Gupta and Kumar, 2008).

Bioactive Materials and Molecules

Bioactive materials

A bioactive material and biocompatible material is an artificial or natural material used to change part of living system or to function in internal contact with living tissue. A bioactive material consists of bioactive calcium phosphate ceramics, bioactive glass ceramics and bioactive composite. There are several types of bioactive materials like: -

Osteogenic- materials include living cells that are able to distinguish between bones.
Osteoconductive- scaffold capable to sustain cell attachment and consequent bone matrix apposition and formation.
Osteinductive- scaffold support osteogenic precursor cell to distinguish into matrix bone (Thomas and George, 2002) .

Bioactive glasses- Have property to react in water or in liquid. A quick filtration of sodium ions and congruent suspension of Ca^{2+}, Po_4, and Si_4 takes place at surface, when body fluid interact with bioactive glass. Silica gel polycondensated coating is formed on glass bulk which acts as template for the development of calcium phosphate because of their property and their good biocompatibility. Bioactive glasses have also used in bioregeneration.

Bioaggregate

It is a biocompatible white powder composed of ceramics particles which are used in root canal repair and it promotes cementogenesis and creates ahemetic seal within the root canal. Bioaggregates are novel and inimitable root canal repair material.

Bioceramics

They consist of alumina, zirconium, bioactive glass, glass ceramic and restorable calcium phosphate and radiotherapy glasses. Bioceramics hold enormous application in dentistry and medicine (Grotra and Subbarao, 2012).

Nanoparticles

The utilization of nanomaterial in biotechnology merges the fields of material science and biology. Nanoparticle size ranges from 1 nm to100 nm. It consists of physiochemical property that does not exhibit in bulk form where the materials display constant physical properties apart their size. Nanoparticles hold large surface area to volume ratio which shows high binding capacity. Nanoparticles have potential to easily conjugate with biomolecules and have wide application in drug delivery system (Arruebo *et al.,* 2009).

Nanoparticles show antifungal and antibacterial properties. Silver nanoparticles are used as bactericidal agent since ancient time. Some nanoparticles like silver and copper have also recommended as superior disinfectant for wastewater treatment generated from hospital containing infectious microorganisms (*Varshney et al., 2012).*

Fig.1 Biomaterials/molecules and their role in dentistry and biomedical

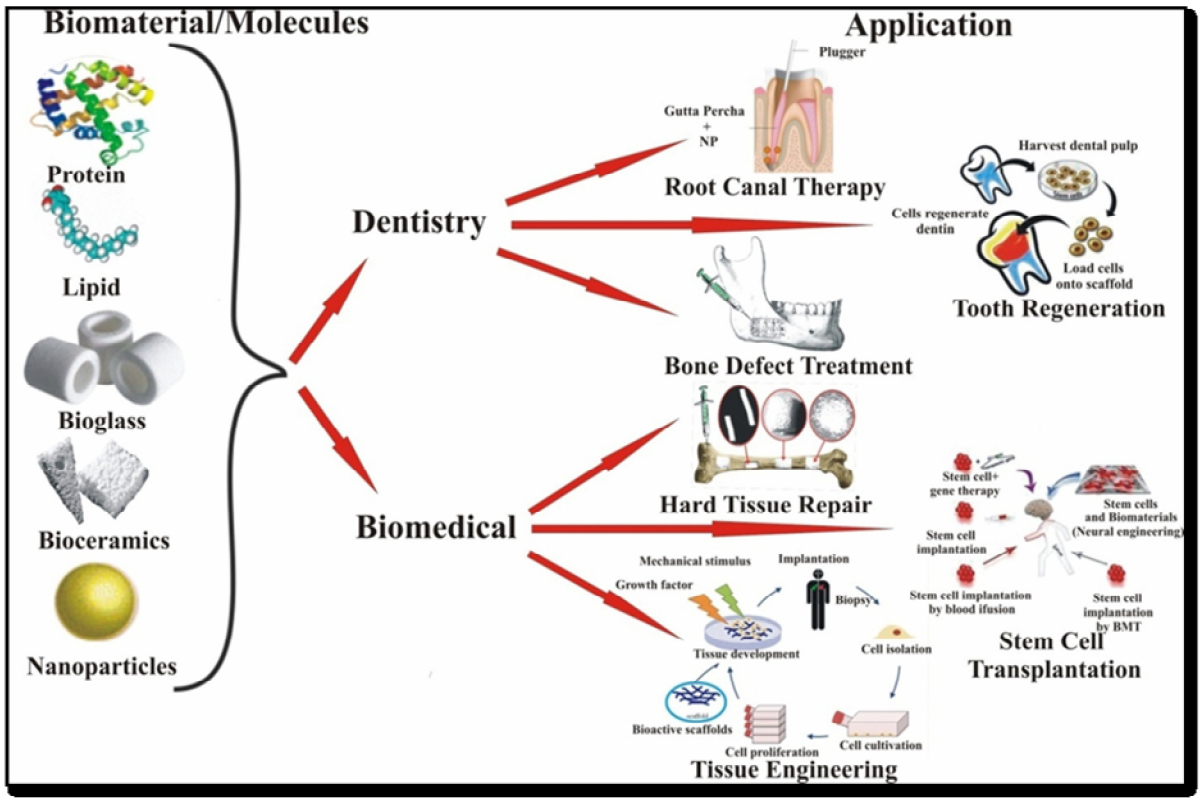
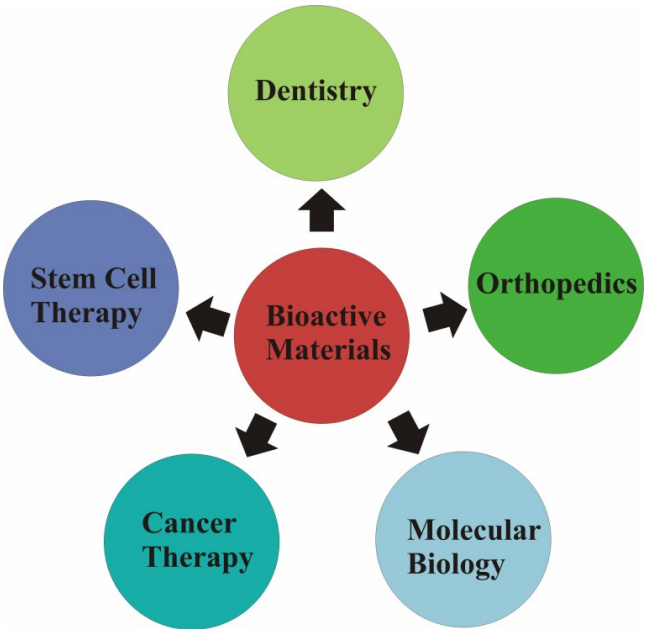


Fig.2 Applications of bioactive materials in different fields



Bioactive molecules

These are the natural molecules that have an effect on the cellular function of an organism or living tissue. The bioactivity of these molecules comprises both beneficial and undesirable effects on living cells. Bioactive molecules are the natural product of biological origin such as palm oil, ginger, bacteria, algae, etc. These bioactive molecules have antioxidative, antiviral and immunodulating effect (Wan-Loy and Ammu Kutty, 2008). Potential applications of lipids, proteins, chitin and minerals in marine bioprocessing as bioactive molecules have increased the value of processing byproduct in recent years (Se-Kwon, Kim, 2006).

Natural sources of bioactive materials and molecules

Natural products or bioactive materials and molecules are organic molecules which is separated from plants, animals or microbes that can be used to treat human disease (Koehn and Carter, 2005). A crude extract from any one of these sources naturally comprise novel, structurally diverse chemical compounds. Plants have rich source of bioactive compounds eg. Morphine, quinine, Alkaloids, cocaine, nicotine, digitalis, tubocurarine and muscarine and Microorganisms such as bacteria and fungi produce a huge range of antimicrobial agents such as cephalosporin's, tetracycline's, amino glycosides, rifamycins and chloramphenicol(Newman and Cragg, 2007). In recent years, there is finding lead compounds from marine sources like coral, sponges and fish. Bioactive materials derived from marine sources include discodermolide, eleutherobin, bryostatins, dolostatins and cephalostatins. Animals can be source of bioactive compounds for example antibiotic peptides were isolated from the skin of African clawed frog and a effective analgesic compound called was extracted from the skin of Ecuadorian poison frog.

Bioactive materials and molecules contain Antitumor, antiviral, antibacterial and antifungal activity (Grabley and Thiericke, 1999). Some important bioactive material with their natural sources and application are given table.1.

Applications of Bioactive Materials and Molecules

Dentistry

Root canal therapy

Portland cement or Mineral trioxide aggregate (MTA) is a bioactive material used for maintaining pulp and periodontal tissue vitality as part of pulp capping and perforation repair procedures (Roberts *et al.*, 2008; Torabinejad and Chivian, 1999). MTA has replaced Calcium hydroxide as the material of choice for repairing injured and broken teeth (Goldberg *et al.*, 2001).

Tooth Repair and Regeneration

Dentin extracellular matrix proteins (ECMPs) contain growth factors which can promote tooth healing and pulp regeneration. ECMPs can stimulate dental pulp stem cell proliferation, differentiation and migration to sites of injury. Dentonin (peptide) can stimulate reparative mineralization of the cornal pulp and occlusion of the lumen of the root canal. The ECMPs and Dentonin biomolecules are among the most potent of all the growth factors available for promoting pulp repair and regeneration (Goldberg *et al.*, 2006).

Table.1 Application of bioactive materials and their natural sources.

Bioactive materials/molecule	**Source**	**Bioactivity/application**
Artemisinin (Se-Kwon, Kim, 2006)	plant *Artemisia annua*	Malaria
Ivermectin (Se-Kwon, Kim, 2006)	Soil a*ctinomycete Streptomyces avermitilis*	Parasitic helminth infections: Lymphatic filariasis and Onchocerciasis
Paclitaxel (Se-Kwon, Kim, 2006)	Pacific yew tree, *Taxus brevifolia*	Cancer
Lovastatin (Se-Kwon, Kim, 2006)	mushroom *Aspergillus terreus*	Atherosclerosis/heart disease
Toxin / proteins (Se-Kwon, Kim, 2006)	*Bacillus Thurigiensis*	Anticancer effect on leukaemic cells
Quercetin (Se-Kwon, Kim, 2006)	Synthetic	Effect on diabetic vascular tissue
Astaxanthin (Se-Kwon, Kim, 2006)	Algae	Anticancer and antioxidative activity
Carrageenan (Se-Kwon, Kim, 2006)	Algae (*Seaweeds*)	Protective effect against UVR-induced toxicity and Mutagenicity
Silk (Grabley, and Thiericke, 1999)	Silkworm	drug delivery system
Streptomycin(Se-Kwon, Kim, 2006)	actinobacterium *Streptomyces griseus*	Antibiotic
Zingerone Gingerol (Se-Kwon, Kim, 2006)	Ginger	Anticancer and apoptotic activity
Coumarins (Se-Kwon, Kim, 2006)	Synthetic	Ant proliferative activity on breast cancer cell lines
Curacin A (Se-Kwon, Kim, 2006)	Marine cyanobacterium	Antitumor activity
Monoclonal antibody (Se-Kwon, Kim, 2006)	Recombinant Proteins	Diagnosis of house mite allergens
Polyclonal and monoclonal antibodies (Se-Kwon, Kim, 2006)	Recombinant Molecules	Filarial antigen detection assay for *Brugia malayi*
Textile dyes (Se-Kwon, Kim, 2006)	Synthetic	genotoxic effects on algae and animal cells
Zorbamycin (Wanq *et al.*, 2007)	*Streptomyces flavovirdis*	Antitumor
Kanamycin (Okami *et al.*, 1959)	*Streptomyces kanamyceticus*	Antibacterial

Kanglemycin C (K-C) (Zhou *et al.*, 2006)	*Nocardia mediterranei var. Kanglensis*	Immunosuppressive
Rapamycin (Lomovskaya *et al.*, 1997)	*Streptomyces hygroscopicus*	Antifungal
Pandavir (nigericin) (Steinrauf *et al.*, 1968)	*Streptomyces hygroscopicus*	Affects ion transport and ATPase activity
Avermectin (Ikeda *et al.*, 1999)	*Streptomyces avermitilis*	Anthelminthic
Oligomycin (Ikeda, and Omura, 1995)	*Streptomyces avermitilis*	Cell growth inhibitor
Resormycin (Iquarashi *et al.*, 1997)	*Streptomyces platensis*	Herbicidal, antifungal
Neihumicin (Wu *et al.*, 1988)	*Micromonospora neihuensis*	Cytotoxic

In dental surgery and cranio-maxillofacial reconstruction

Biomaterials such as Emdogain containing Porcine proteins play an important role in periodontal regeneration following gum disease or injury. Synthetic bone materials and freeze-dried bone are used for maxillofacial and craniofacial reconstruction following trauma or cancer. The ideal biomaterial for dental reconstruction should be biocompatible, able to maintain volume and easily shaped and molded (Chim and Gosain, 2009). N butyl-2-cyanoacrylate also known as histoacryl is widely used as a tissue adhesive. β tricalciumphosphate (βtcp) and histoacryl used as filling material for repairing bone defects. This filling material fixed in a bone defect more quickly due to the adhesive property of histoacryl to hard tissue. Both histoacryl and Btcp improve bioactivity and reduce toxicity ?(Kyeong-Jun *et al.*, 2005).

Coating of implants

Metals are often used in dental and medical devices due to their good physical and mechanical properties such as low density and mechanical resistance (Roessler *et al.*, 2002). Dental implants are made from titanium alloys and have a coating of hydroxyapatite to promote osteogenesis and bone healing.

Tooth Tissue Regeneration

Some scientists have invented a novel biomaterial (Tissue Regenerative Gel) which can promote the regeneration of tooth tissue (Piyush Diwan).

Hypersensitivity

A novel bioactive glass-ceramic (Biosilicate) are applied to the open dentinal tubules of a vital tooth. Bioactive glass-ceramic are capable to induce HCA (hydroxyl carbonate apatite) deposition in open dentinal tubules. Hence, these biosilicate may provide a new opportunity for treating dentine hypersensitivity (Tirapelli *et al.*, 2010).

Biomedical

Stem cell therapy

Recent stem cell study has opened up novel potential within science and medicine. New methods of stem cells with bioactive materials are renovate to

the function of injured tissue by replacing dead or damaged cells with new and healthy cells (Eileen *et al.,* 2008). For example:

Dental tissue regeneration

Material science conjugated with stem cell biology is important in such advances to move regenerative dentistry from the laboratory to the clinic. Combination of nanostructure materials, such as biomimetic matrices and scaffold and stem cells will certainly increase the regenerative impact of dental pathological tissues (Thimios *et al.,* 2012).

Skeletal regeneration

Bone development in the embryo, and adult fracture repair and remodeling, involves a miniature number of cells called mesenchymal stem cells (MSCs). Specific bioactive factors, monoclonal antibody and nutrients are involves in the isolation and *in vitro* mitotic expansion of autologous human MSCs and it is support the treatment of various clinically demanding conditions. For example, bone development, bone repair, and skeletal regeneration therapy (Scott *et al.,* 1994; Arnold, 2005).

Bone graft

bioactive materials such as osteoconductive matrix, which act as scaffold to new bone growth and osteoinductive proteins, which support mitogenesis of undifferentiated cells combined with osteogenic cells (Mesenchymal stem cells), which are capable of forming bone in the appropriate environment in orthopedic field (Nandi *et al.,* 2010).

Stem cell tracking- Nanotechnologies are emerging platforms that could be useful in measuring, tracking, and manipulating stem cells. For example ; nanoparticles, polyplexes and carbon nanotubes for the intracellular delivery of genes/ oligonucleotides and protein/peptides, magnetic nanoparticles and quantum dots for stem cell labeling and in vivo tracking, engineered nanometer-scale scaffolds for stem cell differentiation and transplantation (Ferreira *et al.,* 2008).

Drug delivery

Silica based mesoporous are widely used in drug delivery, bone tissue engineering. The adequate combination of the synthesis techniques, additives and template systems leads to the improvement of materials that combine the bioactive behavior with the drug carrier ability (Maria *et al.,* 2012).

In delivery of growth factors

Bone regeneration is regulated by some hormones, cytokines and growth factors. The bone bonding ability is based on the chemical reactivity of the bioactive glass which contains osteoconductive properties (Samit *et al.,* 2012).

Gene delivery

Silks are eco-friendly and biocompatible proteins that can also be customized via genetic engineering, offering efficacy for drug and gene delivery. This system is used systems for the delivery of tiny molecule drugs, proteins and genes (Numata, and Kaplan, 2010).

Targeted peptides delivery

Bioactive nanotubes like bottom up carbon nanotubes are modified on molecular

Fig.3 Silica based materials used for biomedical applications.

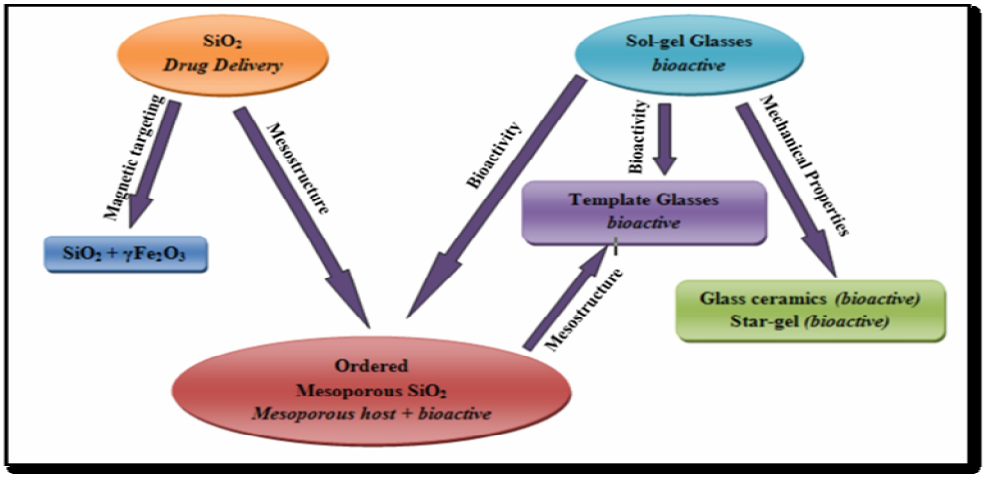
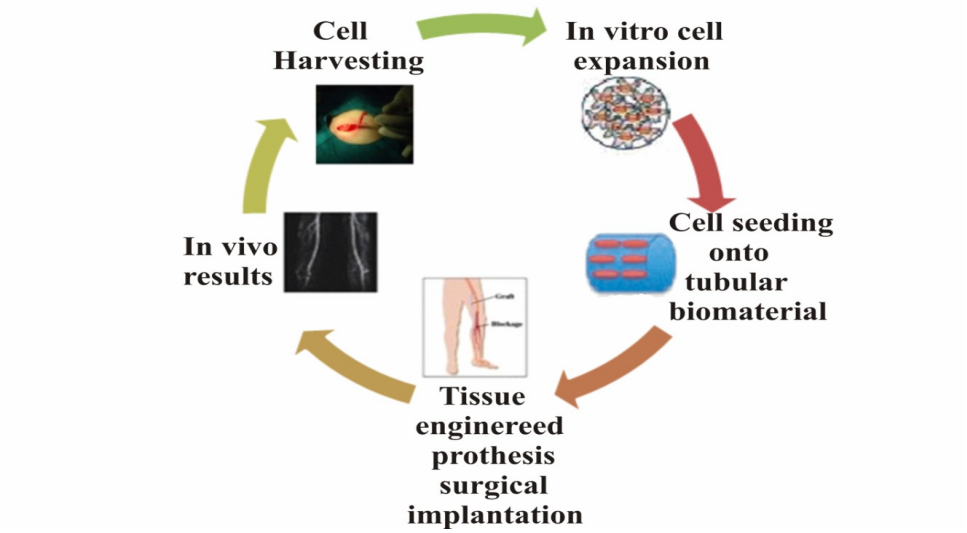


Fig.4 Representation of the different of bioceramics that might be employed t o regenerate hard tissue.

Fig.5 Schematic representation of tissue engineering approach



levels and after this conjugate with biomolecules used as transporter element targeted delivery of peptides and genetic material to cells (Pall *et al.,* 2007).

Thrombotic diseases

Thrombolytic (acute myocardial infarction and ischemic stroke) are the leading cause of death. Magnetic nanoparticles which contain super paramagnetic properties, conjugated with recombinant tissue plasminogen activator are broadly used in thrombolytic therapy (Puppi *et al.,* 2010; Ma *et al.,* 2009).

Control cell cycle

Bioactive materials such as glass-ceramics involves in control over the cell cycle, molecular construction that controls cell differentiation and proliferation (Hench *et al.,* 2000).

Targeted cancer therapy

TAT-PKKKRKV peptides synthesized as a gene carrier and Avidin and biotin transferrin introduced into PAT_1-DNA and PAT_2-DNA complexes. Due to the over-expression of transferrin receptors on cancer cells, PAT_1–p53 complexes showed superior transfection potential in HeLa and HepG2 cells over COS-7 cells. This study specifies that the PAT_1–p53 complex system has enormous potential for targeted cancer therapy (Yang *et al.,* 2012).

Developing cancer vaccines

Tocotrienol used in developing vaccines for cancer. It is obtain from palm oil. Tocotrienol-rich fraction (TRF), a non-toxic natural complex, as an adjuvant to enhance the effectiveness of Dendritic Cells vaccines in treating cancers (Se-Kwon *et al.,* 2006).

Detection of Candida infection

Monoclonal antibody isolate from recombinant protein involves in detection of Candida infection.

Diagnosis of typhoid fever

Proteins used in diagnosis of typhoid fever which is segregate from recombinant proteins (Se-Kwon *et al.,* 2006).

Hard tissue repair (orthopedics)

Hap (hydroxyapatite), bioglass, TCP (tricalcium Phosphate) and bioceramics biomaterials are widely used in hard tissue repair such as bone defect repair, spine/bone graft and joint replacement (Hulbert *et al.,* 1987; Gross *et al.,* 1988).

Cosmetic surgery

Collagen used in soft tissue repair like augmentation as cosmetic surgery (Thomas, and George, 2002).

Tissue engineering

Gelatin used as a natural polymer which is derivative of collagen. Biomolecules released from gelatin controlled-release systems are capable to maintain their biological activity and allow for their use in tissue engineering (Simon *et al.,* 2005). And Scaffolds are also supreme biomaterials for tissue engineering. Several materials have been used to build scaffolds, such as natural proteins, biological materials (allograft, xenografts, and derived products), and both permanent and absorbable synthetic polymers (Vincenzo *et al.,* 2011).

In conclusion, this study has shown that bioactive materials and molecules have antibacterial, antifungal and antitumor

importance with varying spectra of activities. It has a great importance in dentistry as well as biomedical science. Bioactive materials increase in life expectancy and the social obligations to provide a better quality of life. Significant attention has been paid towards the use of synthetic graft materials in bone repair, bone replacement, dental repair and pulp therapy, bioactive glass and ceramics in hard tissue repair and control cell proliferation, nanoparticles in thrombolytic and stem cell therapy. Development new implant technologies have led to the design concept of novel bioactive materials.

Modern approaches implicate the use of biomaterials that can actively interact with tissue and induce there intrinsic repair and regenerative potential. Bioactive material can be isolated from natural sources like plants, animals and microbes have a promising application in various fields such as malaria, cancer, heart disease, drug delivery and diagnosis. The current research is being focused in the development of devices that provide as clinical materials. Although, a huge study has been conceded out on bioactive materials and they are of enormous use for dentistry and biomedical development.

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