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Review

A Review on the Recent Advancements on Therapeutic Effects of Metallic Ions in the Physiological Environments

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Abstract: This review focuses on the therapeutic effects of metallic ions when released in physiological environments. Recent studies have shown that metallic ions like Ag^{+}, Sr^{2+}, Mg^{2+}, Mn^{2+}, Cu^{2+}, Ca^{2+}, P^{+5}, etc., have shown promising results in drug delivery systems and regenerative medicine. These metallic ions can be loaded in nanoparticles, mesoporous bioactive glass nanoparticles (MBGNs), hydroxyapatite (HA), calcium phosphates, polymeric coatings, and salt solutions. The metallic ions can exhibit different functions in the physiological environment such as antibacterial, antiviral, anticancer, bioactive, biocompatible, and angiogenic effect. Furthermore, the metallic ions can be loaded in scaffolds to improve osteoblast proliferation, differentiation, bone development, fibroblast growth, and improved wound healing efficacy. Moreover, different metallic ions possess different therapeutic limits. Therefore, further mechanisms need to be developed for the highly controlled and sustained release of these ions. This review paper summarizes the recent progress in the use of metallic ions in regenerative medicine and encourages further study of metallic ions as a solution to cure diseases.

Keywords: metallic ions; biomedical; antibacterial; osteoporosis; therapeutic

Statement of Significance

As the human situation has improved, so does the prevalence of chronic diseases, with aging being a potential cause. Metals play an integral role in biological processes. Metals are progressively being recognized as being engaged in cellular and subcellular processes. Metal ions are bound to maintain the human body healthy as several essential biological processes in humans rely on their presence, and their exclusion or scarcity can result in disease. Excessive amounts of essential metal ions can still be harmful, but their involvement is required for survival. Vanadium (V), chromium (Cr), manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn), molybdenum (Mo), and cadmium (Cd) are some of the metals considered today to be essential for safe biological processes in humans, and so are the vanadium (V), chromium (Cr), manganese (Mn), iron (Fe), cobalt (Cd). Metals are important for human survival. Their absence may result in a variety of diseases in the human body. Metals were also used to create pharmacologically active drugs for a range of ailments, including cancer, arthritis, ulcers, and so on. Metals found in enzymes greatly aid in their reaction mechanism.

1. Introduction

With the advancement within clinical advances, the old populace is rising quickly and the world at present is confronting the 'aging era', which accompanies social issues [1]. To cope with such a situation, metal ions gained interest globally owing to their consequential role in a biological system facilitating enzyme function, oxygen transport, and redox chemistry as well as their role as pharmaceuticals and diagnostic agents, in the field of regenerative medicine as well as tissue engineering attributable to the prospect of using

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their novel properties for therapeutic purposes [2]. They are engaged in intercellular and intracellular interactions, maintain osmotic pressure and electrical charges in the body, in photosynthetic and electron transfer reactions, assisting in pairing, stacking, and stability of nucleotide bases, role as cofactors for enzymes, and exciting chain of reactions coupled with cell signaling pathways contrary to tissue equilibrium, and in the regulation of DNA transcription [3]. They play such an important role in the functioning of nerve cells, muscle cells, the brain and heart, oxygen delivery, and other biological processes that we can't envision life without them [4]. The broad range of pathological conditions in which metallic ions are involved reflects these properties, which are far from precise [5]. Metals are effectively used for load-bearing applications in the biomedical system due to their appealing mechanical properties, such as strength, stiffness, and fatigue life [6]. Metals are tightly controlled in the natural environment owing to their reactivity, and abnormal metal ion concentrations are linked to a variety of pathological disorders, as well as cancer [7]. In humans, metal ions are necessary for numerous significant functions [8]. Diseases such as pernicious anemia caused by iron deficiency, growth retardation caused by inadequate dietary zinc, and heart disease in infants caused by copper deficiency extreme malfunction, metabolic disorders such as cancer, central nervous system disorders, infectious diseases, and carcinogenesis or death can all be caused by a scarceness of certain metal ions. Anomaly metallic ion metabolism, on the other hand, may lead to pathological conditions like hemochromatosis, Wilson disease, and Menkes disease [8]. Owing to the Metallic ions' unique properties, such as Lewis acidity, hydrolytic and redox activity, electrophilicity, and valency can modify cellular activities sustaining the cell metabolism or induce lethal effect such as a minimum scarcity of certain metallic ions, are involved in the pathogenesis of different chronic diseases like diabetes mellitus, rheumatoid arthritis, coronary heart disease, epilepsy, nephropathy and a range of bone-related pathologies [9].

Particular "bioinorganic" such as metallic ions like copper, strontium, zinc, cobalt, silicon, and boron have emerged as a promising therapeutic drug with the ability to boost bone formation owing to their stimulating effects on osteogenesis and angiogenesis in the past decades [10]. Moreover, others (such as copper, zinc, and silver) have additional therapeutic properties, such as anti-inflammatory and antibiotic properties [11]. Therefore, it's important to comprehend metal ions at the molecular level to cure ailments due to insufficient metal-ion activity [12]. As a result, monitoring the precise level as well as their role in the body will enhance the effectiveness and selectivity of metallic ions' therapeutic effect [13].

Furthermore, when definite metallic ions are directly absorbed, their ionic states are unstable, causing noxious effects. Immense studies have been undertaken to create matrices to control the local release of metallic ions to cope with that kind of scenario [14]. The design of matrices for the local delivery of relatively high concentrations of metallic-ion-based drugs to target tissues with reduced systemic adverse effects is of high interest because recent metallic ion-based drugs are vulnerable to direct severe systemic toxicity; thus, the design of matrices for the local delivery of relatively high concentrations of metallic-ion-based drugs to target tissues with reduced systemic adverse effects is of high interest (Figure 1) [15]. To optimize metal ion delivery for therapeutic use, the degree of metallic ion loading into matrices for local delivery, as well as the controlled and sustained release of the loaded ions, is undeniably significant [16]. Uncontrolled metal ion release, on the other hand, may have harmful implications, as with the case of metal implant corrosion, which results in the release of large quantities of metal ions into the tissues in intimate interaction with the implant and through the systemic circulation, causing problems such as immune and inflammatory responses [17]. Metals' mechanical and electrical properties have led to their use throughout biomedical engineering, especially in the form of implantable medical devices [18]. Metals are used in almost every orthopedic tool, but metal-on-metal (MoM) bearings are of particular interest due to the possibility of detrimental biochemical functions caused by the inappropriate generation of metallic particles as well as ions[19]. Figure 1A shows a mechanism of action of metal-based drugs and Figure 1B shows different metals used in medicines. Metal ions are effective tools, but further

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research into their interactions with living systems is required to establish the boundaries that restrict their safe and therapeutic use [20,21].

This paper is indeed not conclusive; rather, examples were being chosen to illustrate as well as summarise growth inside the research area. Besides, some work that really details the need for metallic ions to regulate specific metabolic functions is also included, but various approaches may be taken into consideration in the years ahead. This review will cover the scope of metallic ions, their interactions with metabolic processes, as well as their therapeutic potential. The potential physiological significance of metallic ions activation/ inhibition will also be discussed. The recent pharmacological/biomedical applications of all such compounds in various disciplines of life sciences will also be elaborated. A comprehensive list of the results (of metal ions along with their some therapeutic effects) will also be discussed. Consequently, the field's remaining challenges and potential future research are spotlighted.

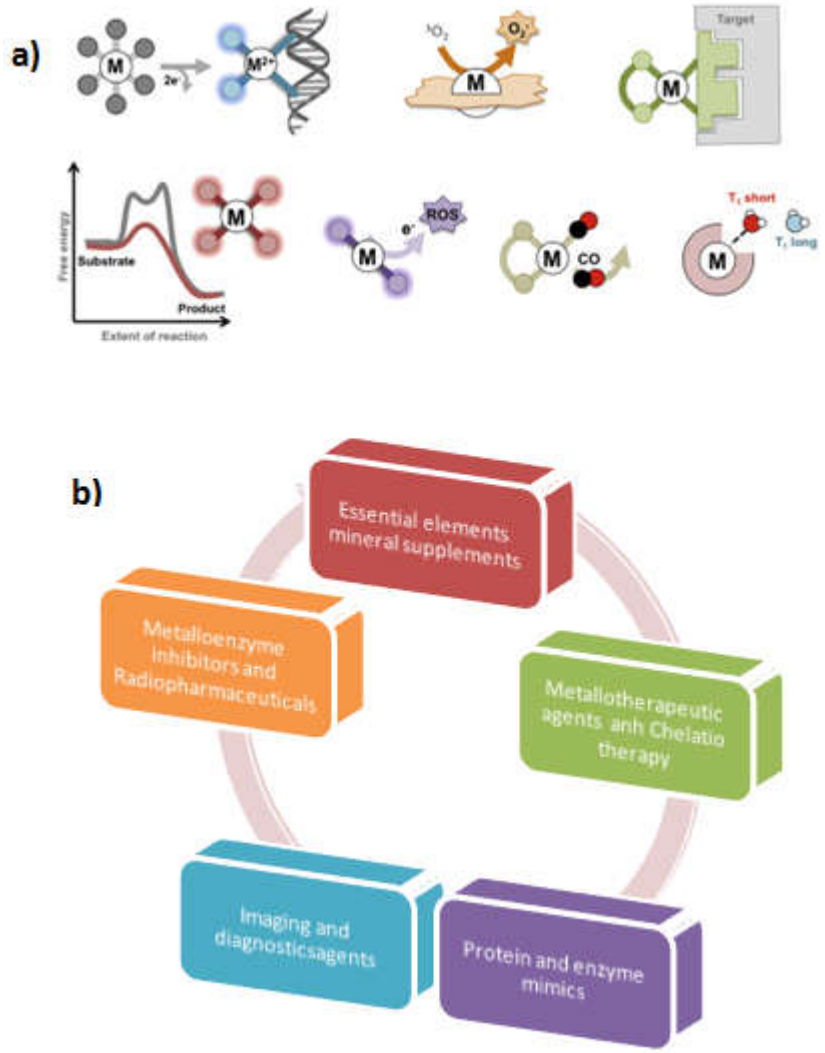

Figure 1. A) Mechanism of Action of Metal-Based Drugs **B)** Schematic representation of different metals used in medicines. Adapted from [21] Reproduced with the permission from Elsevier.

2. Therapeutic Metallic ions

2.1. Gallium

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Gallium (Ga) is a soft, silvery metal member of Group XIII of the periodic table. Though the element itself doesn't have any direct biological function in the human body, it's therapeutically beneficial for many biological processes.

2.1.1. Gallium's Physical, Chemical, and Biological Properties

It was claimed that gallium finds its application due to the close characteristics with the iron (Fe) ion, for instance, the chemistry, ionization potential, radii, etc [1]. Ga does not participate in the redox reactions. Unlike Fe, it does not interfere with oxygen uptake of heme molecules. It also has different stability [1].

Moreover, similarities exist between Ga and Zn as well, thus another therapeutic function involves the substitution of Zn with Ga in metalloproteins to dose-dependently inhibit alkaline phosphate [22]. Due to its compatibility Ga complexes have successfully been doped in several different types of matrices, depending on the application requirements [23]. Recently, Ga doped 45S5 Melt-quench-derived bioglass (BG) was reported to illustrate good biocompatibility [24]. Figure 2A shows the XRD diffraction pattern of the Ga-doped BG, which indicates the amorphous nature of bioactive glass in an unreacted state. Figure 2B, shows a layer of amorphous calcium phosphate upon reacting with SBF (Simulated Body Fluid) [25]. Figure 2C refers to Fourier Transform infrared (FTIR) spectra of Ga doped BG after being immersed in SBF for a week. Carbonate and phosphate bands appeared after immersion in SBF which is a characteristic of Hydroxyapatite (HA) formation. It was evident that Ga doping did not affect the bioactivity of the BG. Furthermore, SEM (Scanning Electron Microscopy) images after immersion in SBF with varying Ga composition are presented in Figure 2D. All the samples showed the formation of fused spherical apatite-like crystals after being immersed in SBF for a week [3].

2.1.2. Characterization techniques

During the research investigations, several different characterization techniques are used, depending on the type of dopant, matrix, required properties, and applications [26]. XRD analysis is usually used to observe the crystal structure of the synthesized materials and to track the changes in the crystal structure such as the formation of HA on the surface of BG upon immersion in SBF. FTIR is used to assess the chemical structure and associated chemical changes i.e. to analyze the dissolution and degradation kinetics of the materials under physiological conditions. XPS analysis is used to study initial elemental compositions and comparative change in body fluid, due to interaction in a physiological environment. Cytotoxicity, cell-viability, ion release profile, and drug release rate are also crucial for biomedical applications [24].

2.1.3. Properties and Applications

- 2.1.3.1. Anticancer effects of Gallium

Ga complexes have been used for the treatment of cancer. The multiplying cells are sensitive to Ga due to their high requirement of Fe in their DNA replication, enzyme activity, respiration, and many other essential cellular processes. Due to chemical and structural similarities [2], Ga is taken into the cells by transferrin (TF) receptors, this changes pH and prevents up-take and utilization of Fe by the cancer cell. This inhibits DNA replication and results in apoptosis [1]. Gallium nitrate is considered the first gallium compound that has exhibited anticancer properties in humans [21].

- 2.1.3.2 Antimicrobial Activity in Gallium Compounds

Gallium nitrate complexes have usually been used for ease of fabrication [27]. Several Ga compounds show antimicrobial activity which is therapeutically promising. Gallium nitrate is extremely effective against *P. aeruginosa* in a dose-dependent manner at concentrations greater than 1μM; at 0.5 μM biofilm growth was prevented [11], and at 100 μM established biofilms were destroyed [28]. Though there is limited research confirming the

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antiviral effect of Ga. Ga was shown to be effective against HIV by targeting the host RNA [29].

- 2.1.3.3 Gallium Compounds as an Anti-Inflammatory and Immunosuppressive Agents

Several studies involving in-vitro and in-vivo systems have shown that gallium compounds have immunosuppressive activity in animal models of autoimmune disease. Gallium nitrate was shown to suppress experimental autoimmune encephalomyelitis and prevent adjuvant inflammatory arthritis through suppression of macrophage function and T-cells in rat models while the anti-cancer effects of Ga were also studied [30]. Pro-inflammatory T-helper type 1 cells become inactive by iron deprivation owing to Ga uptake in place of Fe which is comparatively irreducible [31]. Transferrin-gallium and gallium nitrate were shown to inhibit the mixed lymphocyte culture response and prolong the survival of mice with severe graft-versus-host disease in a murine bone marrow transplant model [12]. Despite these interesting preclinical observations, the immunomodulatory and anti-inflammatory properties of gallium appear to have not been investigated in rigorous clinical studies [9]. Further investigations are required to warrant and establish whether the results of these in-vitro studies are relevant to patients with inflammatory or autoimmune diseases [10]. The potential effects of gallium on inflammation and the immune system should be kept in mind when gallium compounds are being used for the treatment of other conditions [4].

- 2.1.3.4 Effects of Gallium Associated With Hypercalcemia and Bone Metabolism

The anti-bone-resorptive effect of Ga influenced the study on Ga used in the treatment of hypercalcemia and other bone diseases (osteoporosis, Paget's disease, etc.) [5]. Ga dose-dependently inhibits the resorption of bone by osteoclasts, without being toxic to the osteoclasts (It inhibits acid production in osteoclasts) [32]. Osteoporosis affects bone fragility due to its mass reduction, resulting in fractures. Due to its properties such as a bone resorption inhibitor, gallium can influence osteoporosis healing [8]. Researchers have synthesized organic gallium (OG), which is formed through a mixture of gallium and yeast [33]. Results showed that OG may increase bone volume and bone area [34], cortical thickness, trabecular thickness and may decrease the number of osteoclasts in the osteoporotic invoice [35]. Thus, confirming that the obtained data allow the OG to heal osteoporotic fractures [36].

- 2.1.3.5 Antimalarial Agent

Metalloporphyrins are potent heme-polymerization inhibitors and the central ion plays a major role in the inhibitory action of metalloporphyrins. Begum et al. [6] evaluated the in-vitro antimalarial activity of 10 different metalloporphyrins including 4 gallium derivatives: gallium protoporphyrin IX (GaPPIX), gallium salt protoporphyrin IV (GaPPIXNa2), gallium deuteriopropyrin (GaDPIX), and hematoxylin gallium (GaHPIX) [37]. The results showed that all derivatives inhibited heme polymerization, however, GaPPIX and GaDPIX showed more significant results during in-vitro tests, presenting IC_{50} values below 80 μM in the *trophozoite* form of *Plasmodium falciparum* [38].

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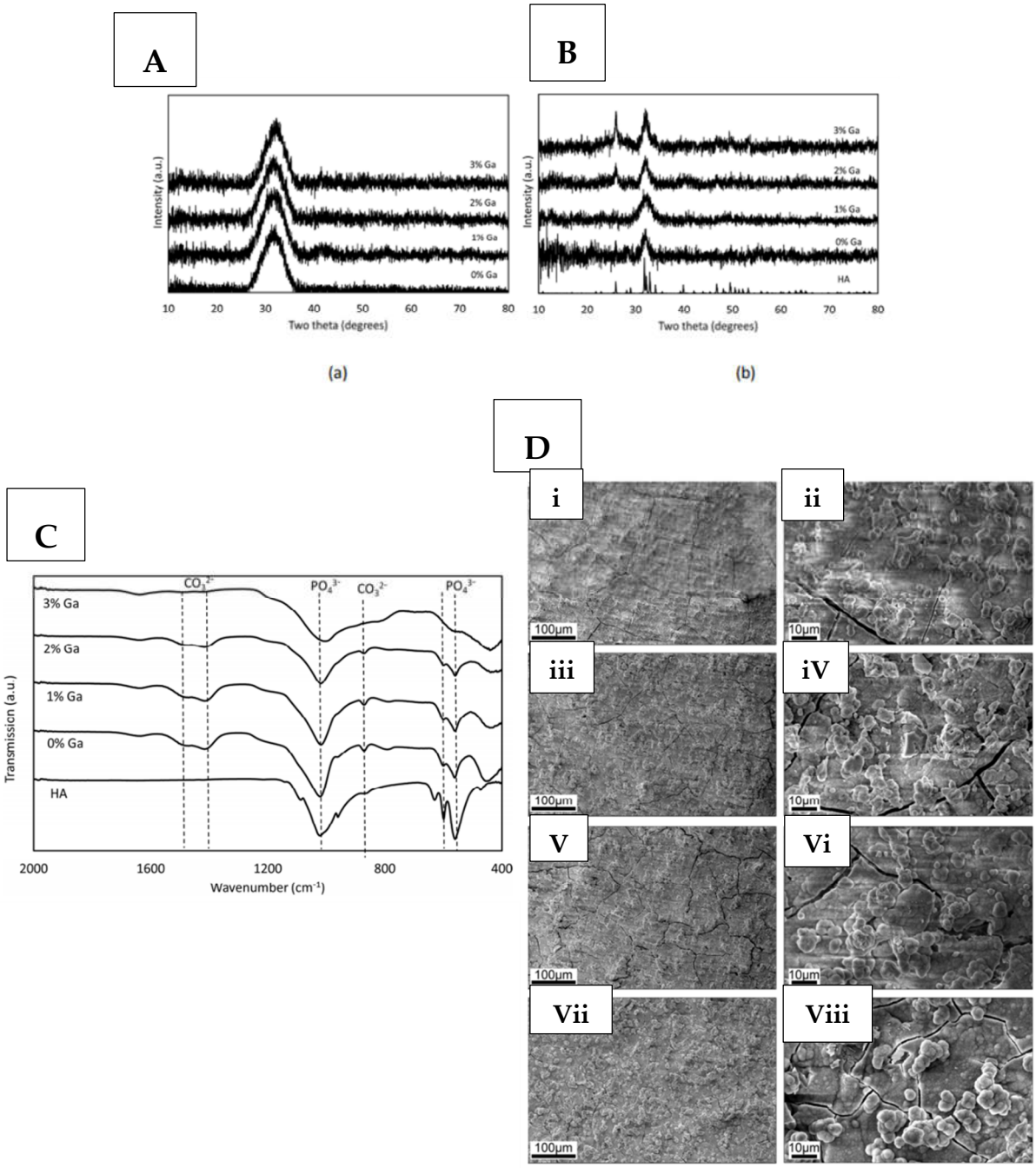

Figure 2. (A) XRD spectrum for unreacted BG (B) XRD spectrum for BG after 7 days in SBF, with Hydroxyapatite shown as a reference. (C) FTIR spectra of BG after 7 days in SBF (D) SEM image of BG after 7 days in SBF, i, iii, V, and Vii represent 0, 1, 2, and 3% Ga- doped in BG at low magnification (500x), ii, iV, Vi, and Viii represent same compositions respectively at higher magnification. Adapted from [39] Reproduced with the permission from ACS .

2.2. Bismuth

Bismuth(Bi) has been used as a therapeutic agent for over two centuries in the form of various complexes. Most of the bismuth salts used nowadays are safe, having fewer side-effects most of which are quantifiable and treatable [40]. They are used within set quantities which have proven to be most effective via research and reported experimentations [41]. Toxicity associated with bismuth compounds is usually a result of their unsupervised use. The clinical efficacy of bismuth compounds was evaluated and the

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possibility of bismuth-induced toxicity is rare when supervised and used according to the specified dose [42].

2.2.1. Properties and Applications of Bismuth

Among the many different biological advantages of bismuth, the most effective and commonly studied is its use in the treatment of gastrointestinal disorders [43]. The earliest recorded use of bismuth is for the protection and healing of skin and ulcers [44]. Other than this, bismuth salts were found to be effective for treatment against syphilis, hypertension, dyspepsia, diarrhea, *H-pylori* infection, etc. [41,42]. Among the various compounds of bismuth, colloidal bismuth subcitrate (CBS), bismuth subnitrate (BS), Bismuth subsalicylate (BSS), and Ranitidine bismuth citrate (RBC) are explored in literature for their effectiveness, mode of action as well as modifications. Figure 3A refers to a list indicating the use of bismuth compounds over the years [42,45].

- 2.2.1.1 Anti-Bacterial action

Bismuth salts exhibit anti-bacterial action against various gastrointestinal tract pathogens including *E-coli, Salmonella, Vibrio cholera,* etc [46]. The mechanism of bactericidal action of bismuth is still unclear, but several proposed mechanisms are summarized in Figure 3B [41]. Complexes of bismuth with bacterial wall and periplasmic membrane have been analyzed via microscopic studies. These structural studies have shown how bismuth complexes bind to the bacterial cell wall disintegrating the H-*pylori*. (Figure 3C) [41,47].

- 2.2.1.2 Anti-Leishmaniasis property

Leishmaniasis is a group of diseases caused by protozoan parasites of the *Trypanosomatidae* family and characteristically caused by the bite of an infected female sandfly [48,49]. The activity of Nonsteroidal anti-inflammatory drugs (NSAIDs) like naproxen, mefenamic acid, ketoprofen, diflunisal, and their corresponding homoleptic tris-carboxylate Bi(III) complexes were investigated against Leishmaniasis major promastigotes and human primary fibroblast cells for 48 h. Studies have shown that the activity remains significant at only the higher highest concentration ~500 μg/mL against L. major parasites, however, that concentration is considered too high for practical use [50].

- 2.2.1.3 Inhibition of enzyme activity

Bi was also used to inhibit enzyme activity, which in turn affects the organism's growth [51]. Adherence of pathogenic organisms to the epithelial cells on the intestinal lining is also prevented by using bismuth compounds [52]. Synthesis of (Adenosine triphosphate) ATP in *E. coli* was shown to be inhibited by bismuth subsalicylate (BSS) [53].

- 2.2.1.4 Peptic ulcer treatment

CBS has been successfully used to treat both gastric as well as duodenal ulcer diseases. CBS especially shows a low relapse after cessation of the treatment, which is attributed to the *H-pylori* eradication [54]. This elimination reduces the possibility of reinfection caused by the organism. It has been practically observed that the effect of CBS is even better when the compound is administered along with antibiotics [55]. CBS and BSS are the most commonly used compounds due to their functional similarities, however; they do have different mechanisms of action referred to in Figure 3D [56]. CBS is mostly used to treat peptic ulcer disease and with the addition of antibiotics is also effective against H-*pylori* [57] while BSS is mostly used for treating and preventing infective diarrhea [58]. CBS, BSS, and RBC when used simultaneously exhibit synergistic effects for eradicating H-*pylori* [59]. Among all the bismuth compounds, RBC is relatively new and brings the added advantage of acid suppression and high compliance. [41,42]

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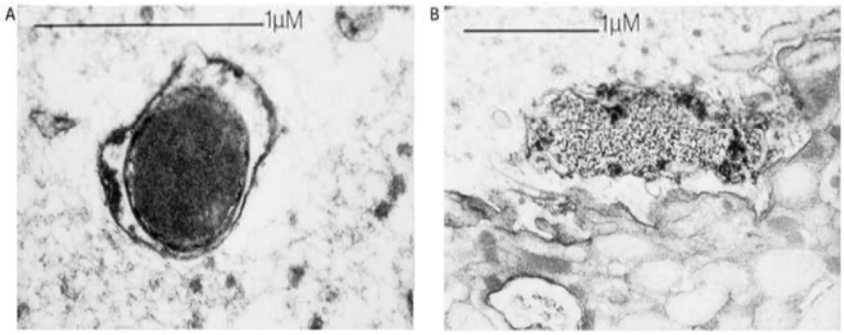
A)

Bismuth compound	Indication
Bismuth subnitrate	Irritable colon, gastric disorders, constipation
Bismuth subgallate	Need to improve stool consistency and odor in colostomy and ileostomy patients
Bismuth phosphate and subcarbonate	Various gastrointestinal disorders
Bismuth subsalicylate	Travelers' diarrhea (prevention), dyspepsia
Colloidal bismuth subcitrate	Gastric and duodenal ulcers, non-ulcer-related dyspepsia

B)

- Complexes in – bacterial wall
  – periplasmic space
- Inhibits – urease
  – catalase
  – lipase/phospholipase
- Inhibits ATP synthesis
- Inhibits *H. pylori* adherence

C)



D)

Action	CBS
Protection of gastric mucosa	+
Antibacterial activity	+†
Binding of ulcer base and mucus	+
Binding of bile acids	+
Reduction of pepsin output and activity	+
Improvement of mucosal ultrastructure	+
Endogenous prostaglandin and alkali secretion	↑
Binding of epidermal growth factor	+

* + = effective; ? = unknown; ↑ = increase; ↓ = decrease.
† Partial effect on *H. pylori*.

Figure 3. (A) use of bismuth salts over the years Adopted from [42] Reproduced with the permission from Oxford university press. (B) bactericidal mechanism of bismuth (C) left side shows H-pylori after 120 min of bismuth action depicting, detachment of bacterial cell wall and with vacuolization, the right image shows structural degradation in and on the surface of H-pylori. Adapted from [56] Reproduced with the permission from Wiley/Blackwell.

2.3. Magnesium

Magnesium is the fourth most abundant cation in the body and the second most intracellular cation. Itis is known to be essential for several enzymatic activities in many biological functions of the human body [60]. The importance of Mg as a therapeutic ion has been explored and it is reported to be vital for several types of cells owing to the interaction with phosphate ions (ATP exists in cells normally as a chelate with Mg^{2+}), it acts as a cofactor for many enzymes, stimulation of growth of new bone tissue and adhesion of osteoblastic cells. Other than this, Mg is an excellent coagulant used especially in cardiac applications[61].

2.3.1. Properties and Applications of Magnesium

- 2.3.1.1 Promotes osteoblast cell proliferation and differentiation

Due to its many biological benefits, Mg has been used as a dopant and in the form of complexes with many different matrices among which glass-ceramic (49.13 wt.% SiO_2-7.68 wt.% CaO-43.19 wt.% MgO) is the most common[62]. The preferred synthesis technique is a sol-gel method. Other than glass ceramics, some quaternary glass systems (64% SiO_2,

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26% CaO, 5% MgO, and 5% P_2O_5 in mol.%) are also used. The synergistic effect of bioactive glasses with Mg ions promotes osteoblast cell proliferation and differentiation[63].

Mg has two main mechanisms of interactions; it can either bind to the enzyme-substrate, forming a complex with which the enzyme interacts or it binds directly to the enzyme altering its structure. All in all, its function is related to ATP utilization, Mg is present in almost all biological cells as Mg-ATP [64]. Therefore, the inability of Mg to perform its function either due to deficiency or uncontrolled release from the scaffolds can result in the hindrance of Mg-activated functions. A possible mechanism for Mg-induced boneloss is presented in Figure 4A Mg plays a crucial role in cellular function, in absence of proper Mg release and activation, cell proliferation can be hindered due to reduced DNA, RNA, and protein synthesis [60]. The addition of Mg ions in scaffolds increases the bioactivity and compatibility of the system by promoting bone cell activity. Mg is mitogenic for osteoblasts in cell culture and its depletion causes cell growth inhibition [65].

Due to its enzymatic activity, Mg is necessary for the proper activity of DNA and RNA polymerases. Mg is an important factor in DNA repair mechanisms within the cell, including nucleotide excision repair (NER), base excision repair (BER), and mismatch repair (MMR). DNA damage occurs constantly because of chemicals, radiation, and other mutagens and to repair it, we need Mg as it is required alongside ATP for proper enzyme activity[66].

- 2.3.1.2 Mg Ions as a Coagulant

An extremely interesting and recently explored use of Mg is as a coagulant. Mg ions play a crucial role in stabilizing the native conformation of coagulation factor IX (Factor IX is a protein produced naturally in the body. It helps the blood form clots to stop bleeding). Mg ions greatly augment the biological activities of factor IX. The cation increases the affinity between factor IXa and factor VIIa, thereby increasing the catalytic efficacy of the enzyme. Approximately 10-folds less concentration of factor XIa was enough to produce the same clotting effect in the same time as in the absence of Mg ion (Figure 4B-i), Similarly reduced clotting time was observed with factor IXa coupled with Mg ions, approximately 3-folds faster clotting (Figure 4B-ii). For factor Xa, Mg ion did not have a reasonable effect on clotting time (Figure 4B-iii) [60,67]

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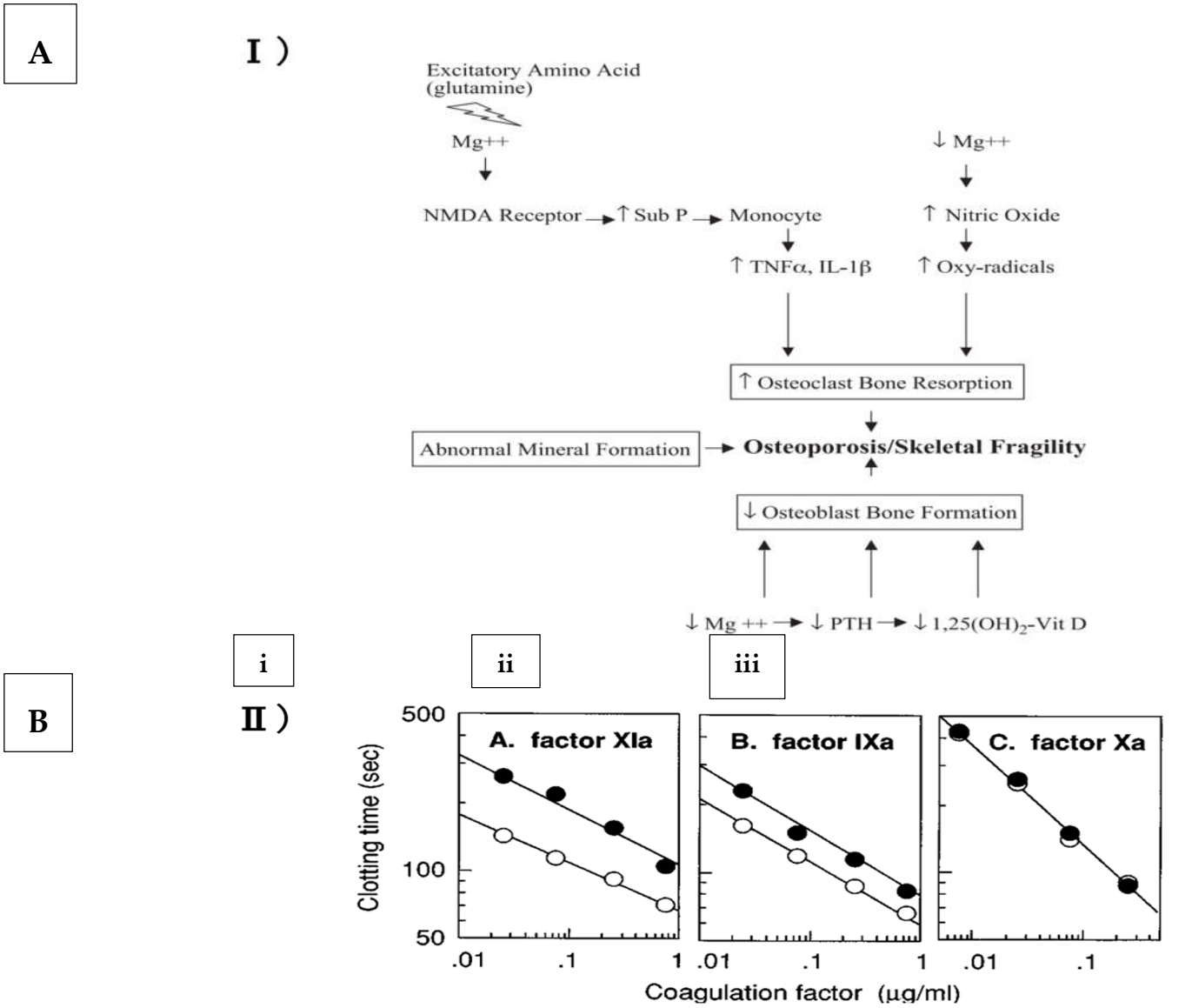

Figure 4. (A) mechanism of Mg-induced bone loss. Adapted from [68] Reproduced with the permission from ASBMB Publications. (B) dialyzed normal plasma was incubated with set concentrations of factor XIa (i), factor IXa (ii) and factor Xa (iii), and 200 mM phospholipids. Adapted from [60] Reproduced with the permission from Elsevier.

2.4. Calcium

Calcium(Ca) is an essential component of the entire skeletal structure and is one of the most abundant metals to exist in the human body. Approximately 99% of body calcium is found in bones. It forms hydroxyapatite in combination with phosphates. The movement of Ca ion in and out of the cytoplasm acts as a signal and activator for several cellular processes [69]. The close association of Ca with bone enables Ca doped scaffolds to promote bone cell differentiation, bone metabolism, mineralization, and osteoclast proliferation [70]. The hydrated calcium ion takes part in many other body functions including muscle contraction, hormonal response, neurotransmitter release, blood clotting, protein stabilization[71].

2.4.1. Properties and Applications

- 2.4.1.1. Cellular proliferation and differentiation

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The biocompatibility of Ca allows it's used in multiple types of scaffold materials, it has been successfully doped in osteochondral composites, using Type-II collagen gel with HA [72]. The compositions of Ca ion can be varied for optimal property profile (2 –4 mmol, 6–8 mmol, less than 10 mmol). It should be noted that low to medium concentrations (2-8 mmol) promotes cell proliferation, differentiation, and mineralization [73], whereas higher concentrations (greater than 10 mmol) are toxic [74]. Moreover, Calcium phosphate treatment of 3D bioactive glasses has also been employed to increase cellular attachment [75]. The latest trend in biomedicine is the use of silica gels, and calcium-doped mesoporous silica xerogels produced using the sol-gel method [76]. Again, low concentrations promote cellular proliferation and differentiation with higher concentrations being toxic [74,77].

The doped mesoporous silica gels resulted in the formation of a smooth xerogel surface as indicated by the TEM analysis (Figure 5A). ICP analysis for Mesoporous silica xerogels with variable calcium compositions (m-SXCs) indicates the change in Ca, P, and Si concentration in SBF after 1, 3, and 7 days (Figure 5B). Ca and P ions lead to the supersaturation of SBF solution around the hybrid membrane and accelerate the formation of a bioactive apatite-like layer [78]. In the present study, the ICP results revealed that Si and Ca ions could be released from them (m-SXC) into SBF, and that m-SXC with Ca resulted in a more rapid increase of Ca and Si ion concentrations, providing a higher basic ion concentration in the SBF solution, which might be helpful to osteoblasts responses [79]. Similarly, the morphology of osteoclasts cultured with m-SXCs for 24 hours was analyzed under the light microscope and the results are shown in Figure 5C. The results indicate that Ca ion in controlled concentrations neither harmed cell morphology nor affected the biocompatibility [74].

The above-mentioned study is an example of Ca's involvement in biomaterial engineering as a therapeutic ion. Moreover, all researches unify the positive function of Ca within a certain composition above which the ion turns toxic [80]. A very common matrix and scaffold for Ca ion, with controlled release of ions is BG [81]. Although the ability of BG to support osteogenesis has been proved, due to its biodegradable properties, it may release ions during the degradation process and the slow degradation helps to provide a controlled release of ions thus, preventing the toxicity [82].

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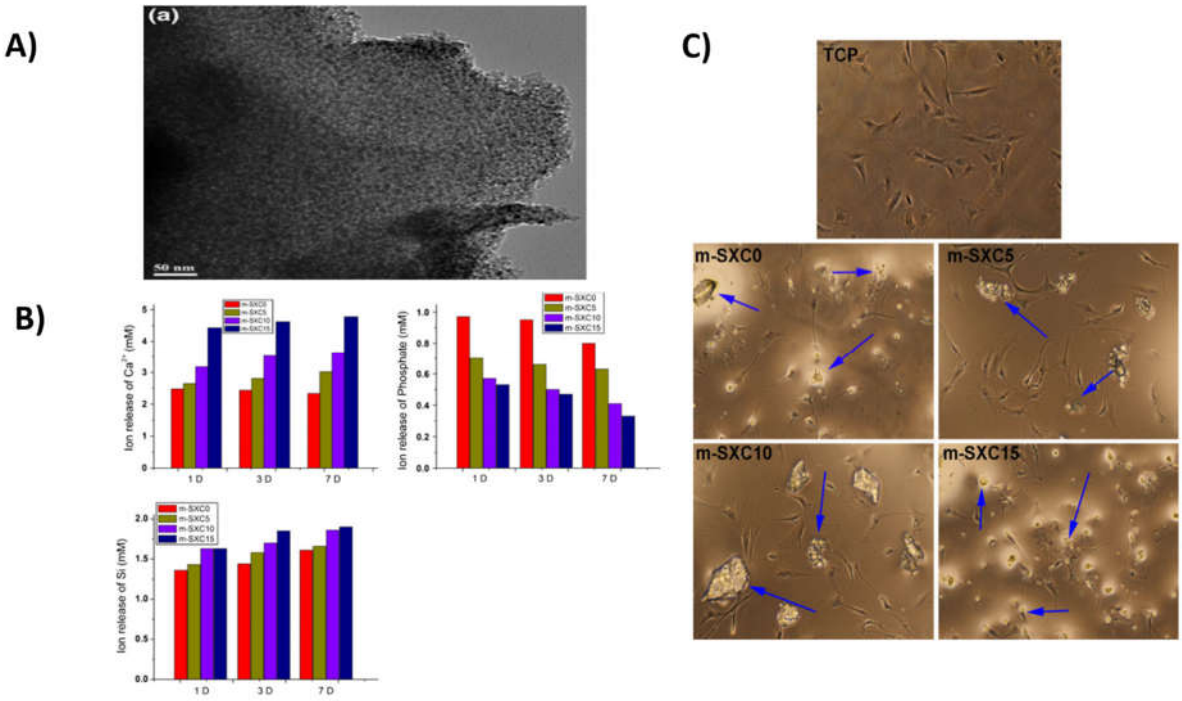

Figure 5. (A) TEM micrograph of Ca doped xerogel surface, (B) change in ion concentration of Ca, Si, and P after m-SXCs immersed in SBF for1,3 and 7 days. Results shown are mean values from three parallel experiments (C) Light micrograph for osteoblast cells cultured with m-SXCs for 24 hours, with (0, 5, 10, and 15%, named m-SXC0, m-SXC5, m-SXC10, and m-SXC15, respectively) and tissue culture plastic. The arrows show silica particles. Adapted from [74] Reproduced with the permission from Springer verlag.

2.5. Germanium

Germanium and its compounds are in use for almost two decades as therapeutic ions. Germanium is found in plants, animals, vegetables, nutrients, dry fish, beans, oysters, and biomaterials documented by Schroeder and Balassa in 1967. Oral administration of Ge-132 results in uniform distribution of germanium with minimal residual concentration. It was observed that 30% of germanium is absorbed after twelve hours [83].

2.5.1. Properties and Applications

- 2.5.1.1 Anti-tumor activity/ Malignant pathology

Ge-132 shows anti-tumor activity through the activation of immune system-based mechanisms involving the role of lymphocytes and macrophages [84]. The augmentation of natural killer (NK) activity and activation of macrophages in mice when orally administrated by Ge132 was mediated by Ge-induced interferon (IFN). The administration of IFN containing sera (blood serum) obtained from Ge-132-treated mice, or the passive transfer of macrophages from Ge-treated mice to mice bearing pathology tumors. Ascites are caused by cancer [85]. It is known as malignant pathology. Malignant pathology is most typical in folks with subsequent cancers such as inhibition of tumor growth in breast cancer patients [86].

The mechanism of Ge-132's anti-tumor activity includes the role of T-cell also known as T lymphocytes, a major component of the immune system. They attack and kill the host cells, resulting in the activation of other immune cells. Thus, cytokines are produced, and other cells of the immune system are influenced due to the production of circulating lymphokines [87]. Activated macrophages were generated from resting macrophages by these lymphokine(s). The transplanted tumors were inhibited by these macrophages. Use of Ge-132 results in inhibition of tumor growth, enhanced anti-metastatic effect (It is related to

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the inhibition of cancer cell motility and invasiveness), prolonged survival time, and recovery of loss of delayed-type hypersensitivity and body weight in tumor-bearing mice [83].

Spirogermanium is an azaspiran-germanium compound that was investigated for anti-tumor effect in phase I/II trials. Spirogermanium was demolished for therapeutic need owing to its significantly negative risk tolerance, neurologic toxicity. Spirogermanium suppresses DNA, RNA, and protein synthesis and reduces cell survival after 24 hours of exposure at 1.0 mg/mL. Quiescent cells appear to be even more resistant [88]. Cytolysis is found at higher concentration levels. Ge-132, Ge sesquioxide, stimulates interferon but also NK cellular activity in spleen cells 24 hours after oral administration as well as induces peritoneal macrophage activity in rats. The general toxicity of Ge is low, aside from the tetrahydride germane, and few observations on the toxicity of Ge in man exist. Ge is not cancer-causing and even seems to inhibit cancer development and, within the type of the organic Ge compound, spirogermanium, to destroy cancer cells [89]. Ge compounds haven't any mutagenic activity and should, below bound conditions, inhibit the mutagenic activity of alternative substances. High doses of Ge could end enhanced embryonic resorption. The mineralization of sponges and limpets occurs as the Ge follows the pathway of silicium at low concentration[90].

- 2.5.1.2 Raynaud's disease

Organic germanium enriches oxygen supply i.e. the oxygen consumption requirement is lowered in the liver and diaphragm. Thus, the survival rate is increased under oxygen stress. Germanium results in increased oxygen supply in the body [91]. The blood viscosity decreases with the increased oxygen supply, resulting in the maximum blood flow to all the organs at a rapid rate. Organic germanium protects against diseases that are associated with oxygen starvation such as carbon monoxide asphyxiation/ poisoning or stroke, and Raynaud's disease conditions. The oxygenated effect of germanium results in a glowing and warm feeling [92].

The patients of Raynaud's disease get relief after taking organic germanium. The lattice structure of germanium contains negative oxygen ions, used as a substitute for oxygen. This results in the elimination and attraction of acidifying hydrogen ions thus detoxify the blood. Water is formed by the transfer of electrons. The deficiency of oxygen results in the acidification of blood due to the accumulation of hydrogen ions. Organic germanium acts as the electron sink increasing the energy without increasing oxygen supply during oxidative metabolism [83].

- 2.5.1.3 Antioxidant effects

Germanium protects against radiations. Lipid peroxidation (LPx) products, DNA hydroxylation, and protein hydroxylation products are the main biomarkers of oxidative damage. Various studies have suggested that germanium compounds show a protective effect against liver injury and have similar oxygen enriching properties and rigorously documented antioxidant effects [93].

The cell membranes are protected against damage by free radicals using antioxidant systems such as superoxide dismutase, glutathione peroxidase, and catalase, etc., and nonenzymatic (glutathione, ceruloplasmin, vitamins) systems [92]. Natural antioxidants such as vitamins C and E exert a protective effect against chromosomal damage by reactive species generated by the irradiation. Glutathione peroxidase is an enzyme system known to have protective effects against cell damage by highly reactive oxidants [89]. GPx activity increases for the elimination of $O^{2-}$and H_2O_2 formed by radiolysis of water [91]. In individuals undergoing radiotherapy, the increase of inflammation results in the production of free radical species, thus inducing an increase in the activity of GPx and other antioxidant defense systems [94].

- 2.5.1.4 As a protective agent

Ge-132 administered to radiotherapy protects cancer patients from the killing of red and white blood cells due to radiation exposure. The germanium atoms attach to the red

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blood cells and protect them from electrons by diverting them [95]. Alpha-tocopherol protects against peroxidation damage via a free–radical–scavenging mechanism [87]. Cysteine is known to increase the endogenous antioxidant levels by enhancing intracellular stores of glutathione . New prepared germanium L-cysteine a-tocopherol is a protective agent against gamma-irradiation-induced free radicals' production and liver toxicity [92].

Liver cells or hepatocytes have access to the liver's blood supply via sinusoids i.e. the small capillaries. Hepatocytes are involved in the production of bile, a metabolic function. Light microscopic examinations of liver sections of control animals exhibited normal constructions (Figure 6A(a), while liver sections of rats exposed to gamma-irradiation showed liver fibrosis and necrosis with mononuclear leucocytic inflammatory cells, infiltrating the dilated portal vein in the portal animals pretreated with germanium L-cysteine a-tocopherol, showed regeneration of the hepatocytes to the normal structure (Figure. 6A (d). Furthermore, the microscopic structure of hepatic cells in the area is associated with the proliferation of diffuse Kupffer cells. The liver section exhibited tissue degeneration and lymphocyte infiltration, and vascular degeneration of the hepatocytes (Figure. 6-A(b). In contrast, the irradiated group of rats treated with germanium L-cysteine a-tocopherol alone showed a normal shape like the control hepatic cells (Figure.6A(c))[93].

2.5.2. Characterization techniques

Figure 6B shows the chemical structure of germanium, dichloro tetrakis (L-cysteinyl-a-tocopherol amide) dichloride [97]. Figure 6C shows the structure of spirogermanium [97]. Figure 6D shows the EDX results of elemental analysis, Nuclear Magnetic Resonance (NMR), and Infrared spectroscopy (IR) for the analysis of the presence of functional groups. The melting point along with the molecular formula of the germanium L-cysteine a-tocopherol complex is presented in Figure 6D [93].

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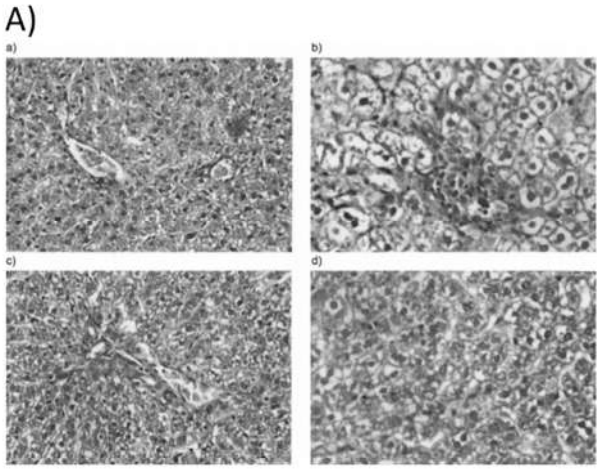

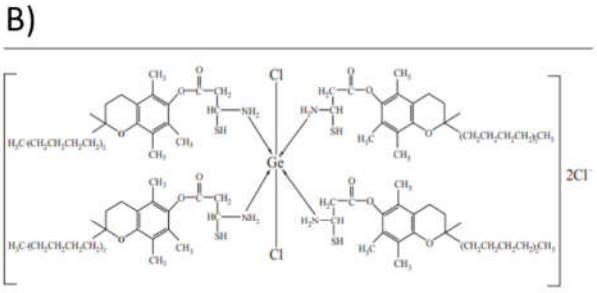

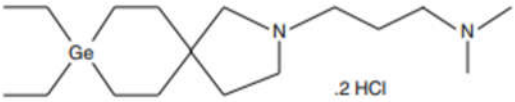

D)

Elemental analysis					
	C	H	N	S	Ge
Calculated (%)	67.09	3.39	2.79	6.37	3.64
Found (%)	67.64	3.97	3.05	6.64	3.31

IR						
Function group	NH	SH	CH_2	CH_3	C=O	CH	Ge-N
ν (cm^{-1})	3328	2358	1489	1413	1724	1332	635

^1H NMR						
Function group	CH_3	CH_3-Ph	CH_2	CH	SH	NH
δ (ppm)	2.35	1.53	1.30	3.77	1.50	2.00

Molecular formula (M_r)	$Ge(C_{32}H_{50}NO_2S)_4Cl_4$ (2329.69)
Melting point (°C)	> 300

Figure 6. (A) a) normal architecture of control liver of rat, b) the necrosis and fibrosis of liver using inflammatory cells, infiltration of lymphocytes and proliferation of Kupffer cells are shown in an irradiated group, c) The normal shape just as stable hepatic cells is observed due to the treatment of rat with germanium L-cysteine a-tocopherol d) The marks of improvement in stable architecture are observed due to the treatment of irradiated group with germanium L-cysteine a-tocopherol,(B) Chemical structure of germanium, dichloro tetrakis (L-cysteinyl-a-tocopherol amide) dichloride, (C) Structure of spirogermanium. Adapted from [97] Reproduced with the permission from Elsevier. (D) shows the EDX results of elemental analysis, NMR and Infrared spectroscopy for the analysis of the presence of functional groups. Adapted from [93] Reproduced with the permission from CPS.

2.6. Chromium

Chromium (Cr) was found in 1797 and given this name due to its color features. In nature, chromium is found as red lead ore i.e. $PbCrO_4$, and chromium iron stone i.e. $FeCr_2O_4$. The commercial use of chromium ironstone is very common nowadays and it is also used in metallurgical processes. It is utilized in lather tanning, paints, wood preservation, production of cement, insulin signaling and chemicals of laboratory, etc. Chromium can cause skin allergies like contact dermatitis [98].

2.6.1. Properties and Applications

- 2.6.1.1 Diabetes mellitus and Insulin signaling

Chromium is widely used in insulin signaling. gene expression, metabolism of various nutrients like proteins, sucrose, and lipids, etc., and mitogenesis are influenced by a hormone called insulin. In the insulin molecule, there are two peptide chains i.e. A and B with 51 amino acids and disulfide bonds [99]. The polypeptide chain is first converted to proinsulin then to insulin. Insulin is released via stimulation i.e. enhanced glucose concentration results in the secretion of insulin, this change in glucose concentration acts as the primary stimulant. Insulin enhances the rate of uptake of glucose thus, maintains and regulates glucose homeostasis. The disturbance in the insulin signaling pathway can cause a disease type 2 diabetes mellitus (T2D). The insulin first binds to insulin membrane receptor (IR) having a and b subunits, this is termed autophosphorylation [100]. The activation of insulin receptor tyrosine kinase (IRTK) is done by the binding of insulin, hence, stimulates autophosphorylation and in the second step, this autophosphorylation of the

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insulin leads to the activation of enzyme towards IRS i.e. intracellular insulin receptor substrate proteins [101].

The trivalent chromium is considered essential for humans for over thirty years. It is involved in the metabolism of lipid and proteins and the insulin signaling system. The intake of chromium in diet i.e. 200– 1,000 mg Cr/day improves blood insulin and glucose level [102].

Insulin sensitivity is increased with the increased phosphorylation of the insulin receptor. The ß subunit undergoes auto-phosphorylation due to the conformational changes caused by the binding of insulin to α subunit in the insulin receptor [103]. The chromium moves to the insulin-dependent cells from the blood when the blood sugar level increases insulin level. After that, the chromium attached to transferrin is transferred to apochromodulin (low molecular weight chromium attaching substance) [104]. Apochromodulin, when binds 4-5 moles of chromium, it becomes activated and thus, insulin receptor kinase activity is increased. Figure 7(A) show a mechanism behind the activation of insulin receptor by chromium with the involvement of insulin. The binding insulin is used to convert inactive insulin to an active form. This activates the binding of Cr to apochromodulin and the movement of Cr from transferrin into the insulin-dependent cells [105].

The chromium in the form of chromium chloride inhibits oxidative stress and (Tumour necrosis factor alpha) TNF-alpha secretion due to the interaction of chromium with cytokines (TNF-alpha, IL-6) and peroxidation of lipid. The antioxidative effect is important in insulin signaling to lower TNF-alpha secretion and to prevent lipid peroxidation [106]. The membrane lipid depots changed due to the chromium insulin signaling action. The decrease in membrane fluidity decreases insulin-stimulated glucose transport. Chromium increases membrane fluidity in the presence of insulin [107].

- 2.6.1,3 Anticarcinogenic Effect

The cellular oxidative damage is caused by hexavalent chromium (Cr (VI)) that is highly reactive [108]. Reactive oxygen species (ROS) are generated, which have high reactivity, a short span of life, and oxygen-containing species i.e. $O_2^{\bullet}$, H_2O_2, and $^{\bullet}OH$. The excessive production of ROS results in oxidative damage mainly in cells and tissues. Cr (VI) is reduced to its lower oxidation state i.e. to Cr(V). The spectrum of ROS is generated by Cr (VI). Antioxidants are used to prevent oxidative damage. However, when more prooxidants exist then the oxidative cell damage by chromium happens. ROS can be generated directly during the reduction of Cr (VI).

In general, there are two pathways in the mechanism of Cr (VI)-mediated ROS generation. Cr (VI) can directly generate ROS during its reduction and subsequent reaction with cellular small molecules such as glutathione (GSH) and H_2O_2 [109].

Glutathione-derived thionyl radical (GS•) is generated by the Reaction of Cr (VI) with GSH. The GS• generation increases with the increase in GSH concentration.

Cr (VI) + GSH = Cr (V) + GS•---------- (Equation-I)

H_2O_2 is formed due to the generation of radicals $O_2^{\bullet-}$ by dismutation reaction. The reduction of Cr (VI) to Cr(V) results in the generation of oxygen radicals. The $^{\bullet}OH$ radicals are produced by the reaction of Cr(V) or Cr (IV) with H_2O_2.

Cr (IV) + H_2O_2 = Cr (V) + $^{\bullet}OH$---------- (Equation-II)

Cr (V) + H_2O_2 = Cr (VI) + $^{\bullet}OH$---------- (Equation-III)

Thus, Cr (VI) can be reduced to Cr(V) [109]. Oxidative DNA damage is caused by the genotoxic activity of carcinogenic Cr (VI) compounds. However, stable Cr-DNA binding is attained by the reduction of Cr (VI). This results in a decrease in electrophoretic mobility of supercoiled DNA as shown in Figure 7B. The unwinding of supercoiled plasmid DNA occurs at a high concentration of Cr (VI) and thus, they comigrate with relaxed DNA molecules. The DNA molecules containing Cr atoms show decreased staining with DNA dye ethidium bromide. Ethidium bromide fluorescence was recorded for the chromium ions involved in Cr-DNA binding. Figure 7C shows that Ethidium bromide is fluorescent due to DNA bases that absorb UV radiations thus, energy is transferred [110]. The amount of intercalated dye is found after direct excitation of ethidium bromide which is the result

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of fluorescence of linear DNA molecules [111]. It was found that at the wide range of dye concentrations, Cr-DNA binding strongly inhibits ethidium bromide intercalation [112].

Figure 7D shows the use of mismatch repair (MMR) to observe the binding of ternary Cr-DNA cross-links that result in toxic DNA- double-stranded breaks [112,113]. This is confirmed by the presence of MMR proteins at the sites of DNA breakage [74].

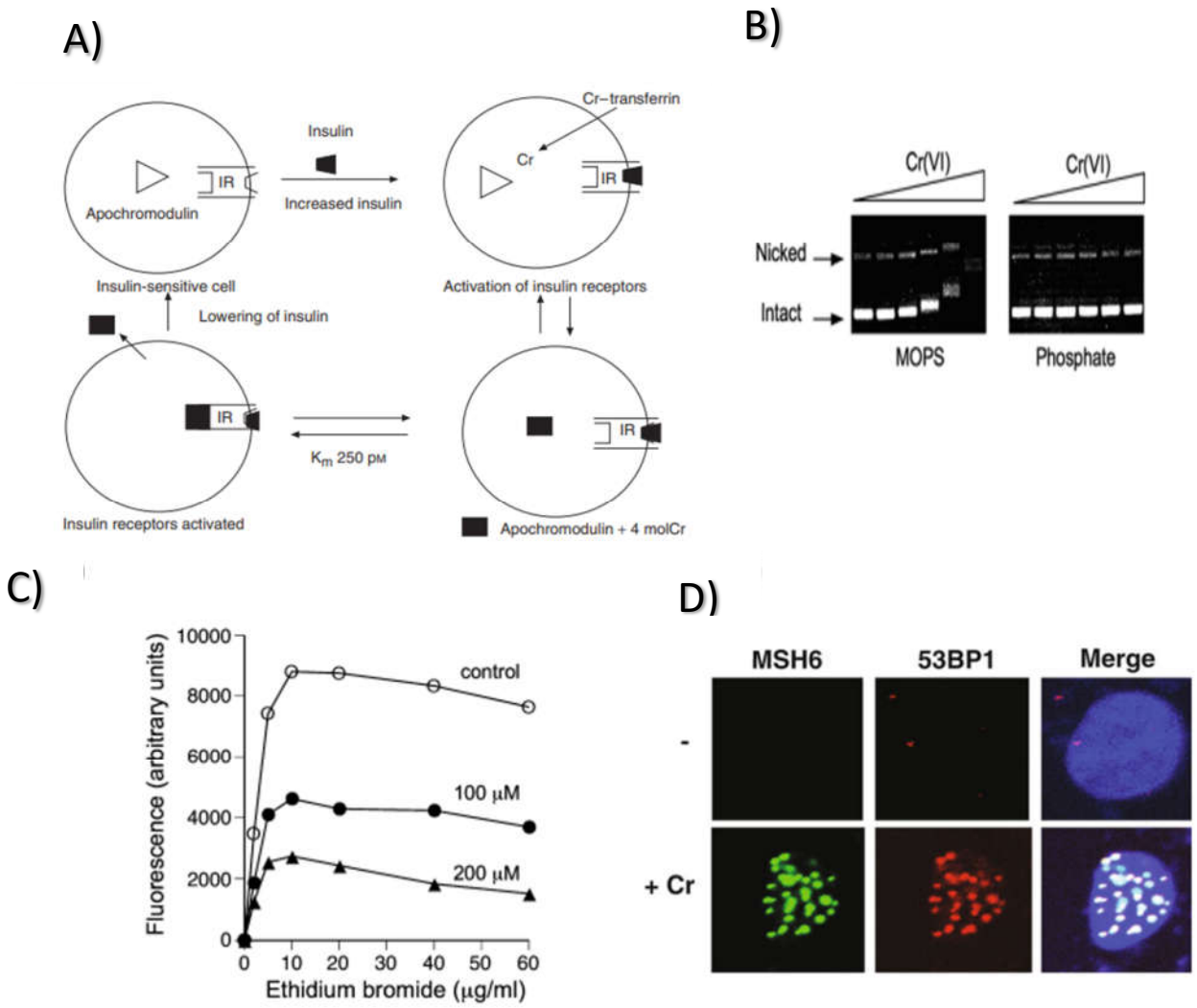

Figure 7. (A) show a mechanism behind the activation of insulin receptor by chromium with the involvement of insulin. The binding insulin is used to convert inactive insulin to an active form. This activates the binding of Cr to apochromodulin and movement of Cr from transferrin into the insulin-dependent cells. Adapted from [105] Reproduced with the permission from Nutrition Society. **(B)** shows electrophoretic mobility of plasmid DNA containing bound Cr; reduction of Cr(VI) does not cause oxidative damage to the DNA sugar-phosphate backbone as confirmed by the lack of conversion of intact (supercoiled) plasmids into nicked (relaxed) conformation, **(C)** shows fluorescence of ethidium bromide and shows that at the wide range of dye concentrations, Cr-DNA binding strongly inhibits ethidium bromide intercalation, **(D)** shows the use of mismatch repair (MMR) to observe the binding of ternary Cr-DNA cross-links that results in toxic DNA- double-stranded breaks. Adapted from [112] Reproduced with the permission from ACS.

2.7. Lithium

Lithium ions provide therapeutic effects in the human body.

2.7.1. Properties and Applications

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- 2.7.1 .1 Manic depression treatment/ Bipolar disorder

The patients having bipolar disorders utilize lithium ions as these ions are effective in overcoming this disorder. Lithium salts are used for the treatment of this disease [115]. The impact of lithium on intracellular neurotransmission results in the normothermic action of Li, the main area of this particular action is the central nervous system. Voltage-dependent sodium channels working on the principle of concentration gradient, are used by lithium for the penetration in the interior of the cell via diffusion mechanism [116]. The permeability of lithium-ion is similar to sodium ions. Thus, they can easily pass through these channels. The ionic radius of anhydrous lithium is the same as anhydrous magnesium but, less than the radius of sodium. The concentration of lithium is more in extracellular fluid than in intracellular fluid due to the use of sodium-lithium counter-transport (SLC) for its displacement from the cell. The therapeutic effect of lithium for the treatment of mental alterations is highly impacted by the regulation of lithium clearance rate. SLC mechanism is not appropriate for the treatment of affective disorders [117]. The action of lithium becomes interdependent with the function of various vitamins, hormones, and enzymes and multi-factorial by incorporating biochemical mechanisms. The action of lithium ions in cells is dependent on its competition with Na^+ and Mg^{2+} ions due to the similarity in their atomic radius [118]. The inhibition of enzymes and dependence on Na^+ and Mg^{2+} ions are responsible for the therapeutic effect of lithium. The therapeutic effect of lithium is utilized in intracellular processes and nerve transmission pathways [119].

Lithium can be incorporated into bioactive glasses (BGs). The most common are silicon-based LiBG, lithium phosphate bioglass (LiPBG), and lithium borate bioglass (LiBBG) [120]. The LiPBG and LiBBG release lithium ions at a faster rate as compared to silicon-based LiBG as it is particle size-dependent [121]. Figure 8(A-D) shows that after four hours, the concentration of lithium in the cell is more than 500ppm and remains stable up to 24h. At the same concentration i.e. 6mg/mL, LiPBG and LiBBG release lithium ions at a faster rate as compared to silicon-based LiBG. Silicon-based LiBG releases 300ppm Li [122].

- 2.7.1.2 Anti-inflammatory agent

Lithium acts as an anti-inflammatory agent. glycogen synthase kinase-3β GSK-3β results in enhanced inflammation in mice by facilitating the activity of transcription factor and nuclear factor (NF)-Kb [123]. The anti-inflammatory effect of lithium associated with GSK-3β inhibition is not only due to the inactivation of NF-κB, STAT (signal transducer and activator of transcription) activation reduction also results in an anti-inflammatory effect. Figure 8E shows the association between lithium and inflammation[124].

SiO_2-Li_2O glass was shown to be synthesized by the sol-gel process. Lithium nitrate (90S10L(N)) or lithium citrate (90S10L(C)) was used as a precursor of Lithium [125]. Figure 8F illustrates the X-ray powder diffraction (XRD) pattern for the SiO_2-Li_2O glass synthesized from lithium citrate and lithium nitrate. Further, the effect of heat treatment at 500°C and 600°C was studies. It was observed that the Li-ion was successfully doped by using both the precursors. The lithium was delivered at a therapeutic level and proved successful for cartilage repair [126]. The response of chondrocyte cells responsible for the cartilage production to the glass was observed. The stabilization parameters are set for the doping of lithium ions in the silica network. Figure 8G is showing the results of Thermogravimetric analysis (TGA) and X-ray powder diffraction (XRD) with the increment of 50°C from 400°C to 650°C [127].

90S10L(C) and 90S10L(N) are immersed in Dulbecco's Modified Eagle Medium (DMEM) without cells, the successful release of lithium and silicon ions is observed. The results of changes in concentration are tabulated and analyzed after three days of immersion. Figure 8H shows the concentration profiles of lithium and silicon immersed in the DMEM[127].

- 2.7.1.3 Wound healing/ Anti-coagulating agent

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Lithium plays a significant role in preventing blood clotting thus, promote wound healing. The pathway factors are prothrombin and fibrin stabilizing factors. The carboxylation of the clotting factor is caused by the reduced form of Vitamin K [128]. The clotting factor gets a negative charge by the addition of carbon dioxide i.e. carboxylation. The positively charged lithium ions attract the negatively charged clotting factors and platelets. In this manner, the process of coagulation is completed [129,130].

- 2.7.1.4 Schizophrenic disorders

Lithium should only be used to treat schizophrenic disorders as some antipsychotics have failed; it has limited efficacy when it's used solely. The observations of various research trials on the efficiency of merging lithium to antipsychotic therapy in the treatment of schizophrenic disorders also differed [131].

- 2.7.1.5 Major depressive disorder

Whenever antidepressant therapy doesn't really wholly relieve the symptoms of major depressive disorder (MDD), a second augmentation entity might be incorporated to the therapy. Due to the fact that the FDA has also not endorsed lithium to be used as an augmentation agent for any antidepressant for treatment of MDD, it's been recommended for such a purpose since 1980s and is among the few antidepressant augmentation agents to exemplify efficacy in treating MDD in multiple controlled studies [121]. The disorder is defined by both a pervasive and persistent depressed mood, as well as low self-esteem and a feelings of worthlessness in normally pleasurable activities. In contrast to certain other minor symptoms, the disease causes somatic symptoms such as decreased appetite (and therefore also weight fluctuations), fatigue, sleep disturbance, decreased libido, motor retardation, and bowel disturbance (Schacht et al., 2014; Sharpe and Lawrie, 2010). Patients suffering from major depressive disorder are at likelihood of developing suicidal thoughts [132,133].

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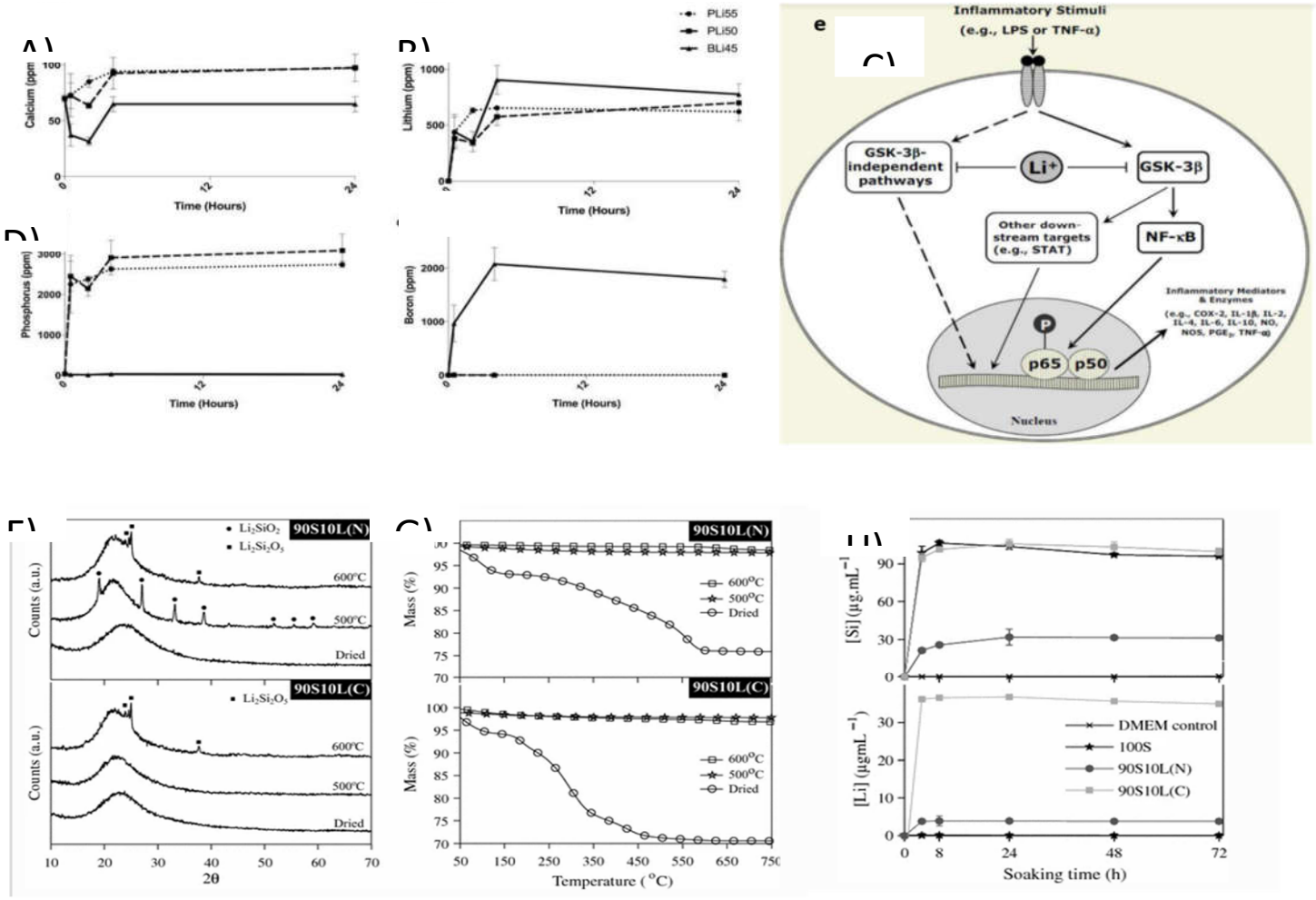

Figure 8. (A-D) shows that in four hours, the concentration of lithium in the cell is more than 500ppm and remain stable up to 24h, elemental analysis results are shown **A)** Ca, **B)** Li, **C)** P and **D)** B after the soaking of 6mg/mL LiPBG and LiBBG for 24 hours . Adapted from [122] Reproduced with the permission from Dental Materials, **E)** shows the association between lithium and inflammation. Adaapted from [124] Reproduced with the permission from Springer. **F)** shows XRD patterns, **G)** shows the TGA results for thermal stabilization of sol-gel glasses at 500 and 600°C, **h)** shows the concentration profiles of lithium and silicon immersed in the DMEM. Adapted from [127] .Reproduced with the permission from Spinger.

2.8. Potassium

Potassium is utilized for the regulation of cellular electrolyte metabolism, nutrients transportation, cell signaling, and analysis of enzymes.

2.8.1. Properties and Applications

- 2.8.1.1 Cellular electrolyte metabolism

It can maintain the electrolyte balance of living organisms like sodium and chloride ions.

- 2.8.1.2 Cell signaling

It is involved in cell functioning. Na^+-K^+-ATPase is present in almost all cells which pumps potassium ions into the cell and sodium ions out of the cell and hence, potassium ion gradient is formed around the cell membrane. The potential difference is generated that is crucial for the functioning of the cell mainly for muscles and nerves. The overall

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potassium ion content is maintained in the body. Moreover, the potassium ions are properly distributed in the body[134]. Figure 9A shows sodium-potassium pump [135].

- 2.8.1.3 Diuretic agent

Potassium is used to control blood pressure. Potassium ions in the body trigger the heart to squeeze the blood. Potassium acts as a diuretic agent, hence, decreases blood pressure by reducing extracellular fluid volume. Figure 9B shows the lowering of systolic and diastolic blood pressure by 5.9 and 3.4mmHg, respectively due to the potassium intake [136].

- 2.8.1.4 Nerve functioning

Potassium plays an important role in nerve functioning. Potassium finds a sodium-potassium exchange across the cell membrane. This results in the conduction of nerve cells. Extra potassium is pumped by the cell into the interior. The creation of active impulses in neurons occurs when these ions pass through the channels in nerve cells and return to their original position.

There are wire-like extensions in the nerve cells named axons, the pulses are carried from one cell to the other by axons. Figure 9C shows that the nerve axons having channels of potassium. Nerve axons have two key regions i.e. initial segment from where the impulse starts and nodes where the impulse is received. The nerve impulse starts with the movement of sodium ions into the cell. Then, in response to this potassium channels open and permit the potassium ions movement [137-*139*].

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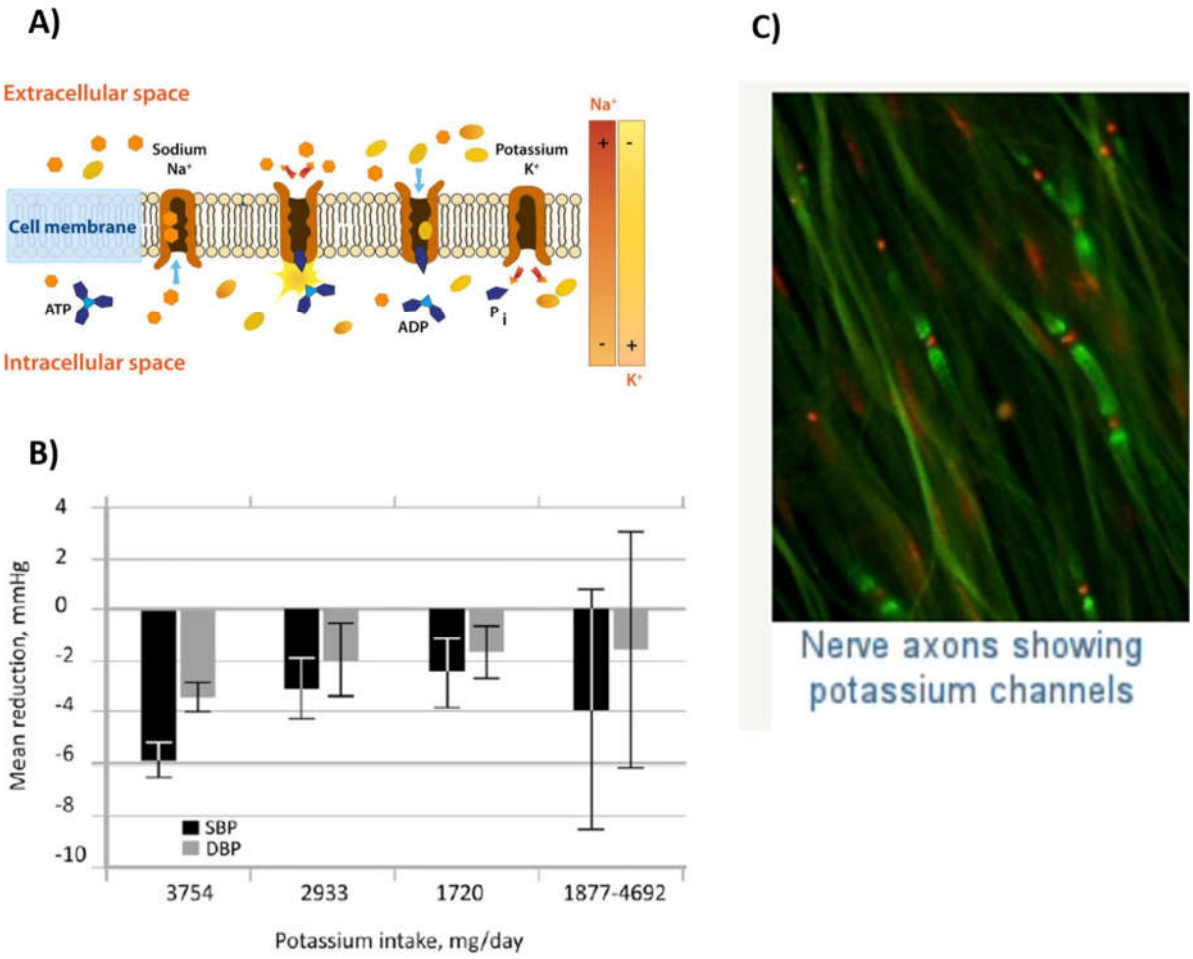

Figure 9. (**A)** Shows sodium-potassium pump, **(B)** shows the lowering of systolic and diastolic blood pressure by 5.9 and 3,4mmHg respectively due to the potassium intake. Adapted from [138]Reproduced with the permission from American society for nutrition , (**C)** shows nerve axons having channels of potassium. Adapted from [139] Reproduced with the permission from from American society for nutrition.

2.9. Strontium

Strontium Sr^{2+} belongs to the alkaline earth family and contains non-radioactive properties. In the late '70s, it was discovered and isolated in 1808. Due to the rapid oxidation of Sr to form $Sr^{2+,}$ it is rare to find Sr in nascent form. It is a soft silvery metal, highly reactive in water, and can bind with different proteins [140]. Due to these properties, it is involved in different processes to form chelates and complexes. Sr^{2+} and Ca^{2+} have similar properties in the physiological environment as they both belong to alkaline earth series and strontium is involved in various mechanisms of bone binding as an alternative to Ca^{2+}. Due to similar properties between Sr^{2+} and Ca^{2+}, strontium participates in ion exchange with calcium [140]. Various anionic compounds bind with strontium depending on the preference, some prefer to bind with calcium while others prefer to bind with strontium. For example, alginates prefer to bind 1.5-4.3-fold times with Sr^{2+} than Ca^{2+}. Similarly, Ca^{2+} prefers to bind with collagen and is involved in manipulating anions [140].

2.9.1. Properties and Applications

- 2.9.1.1 Treatment of cancer

It is also utilized for the treatment of prostate cancer and bone cancer. At low concentration, Sr^{2+} is beneficial, assist in bone binding, and enhance the osteoblast cell

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proliferation [141]. But at a high dose, bone resorption and bone density decrease [142] which leads to osteomalacia, a disease generated due to the collection of the unmineralized matrix in the skeleton [143]. Thus, Sr^{2+} is not equivalent to strontium due to these drawbacks.

- 2.9.1.2 Osteoporosis treatment

Furthermore, scientists are employing strontium ranelate to analyze the treatment of osteoporosis [144]. Drugs incorporated with sodium ranelate assist in bone growth, bone density, and inhibit osteoclast cells. Strontium ranelate consists of ranelic acid which contains dual action bone agent (DABA) and provides favorable bone resorption and harmless effects [145]. Sr shows the beneficial response in various parts of the human body. Mesoporous bioactive glass (MBG) doped Sr^{2+} nanoparticles were synthesized using a sol-gel process. MBG provided a bioactive response and excellent biocompatibility when it was utilized with doped Sr nanobiocements than Sr-free. Due to the fast degradation and intriguing role of Sr^{2+}, it assists in achieving bioactivity. Large radii of Sr^{2+} than Ca^{2+} expand the glass network and high odontogenic potential can be acquired [146].

- 2.9.1.3 Osteogenic response

The modified Stöber method is solely used to synthesize Mesoporous Bioactive Glass Nanoparticles (MBGNs). As Sr provides bioactive and osteogenic response so it is incorporated in different materials to acquire properties. Figure 10A (a-d) shows TEM images of 0%, 6% and 14% Sr-BGNP's. Similarly, Naruphontjirakul et al [147] studied Sr-doped MBGNs with two different compositions of 6 mol. % and 14 mol.% Sr as shown in Figure 10B. It was shown in Figure 10D that the Osteoblast Cells were not affected up to the concentration of 250 μg/ml. An in-vitro investigation was carried out in preosteoblast cell line MC3T3-E1 to study osteogenic response. Dissolution studies in Figure 10C provide evidence of complete dissolution of Sr^{2+} at pH 4.5. Total cation content arises, in addition to Ca by incorporating Sr in MBGNs which ultimately increase dissolution rate without affecting the shape and size of particles. It was observed that Sr can enhance Alkaline Phosphate (ALP) activity and osteogenesis without incorporating osteogenic supplements. Thus, Sr-MBGNs assist in bone regeneration application promoting cell proliferation [147,148]. Furthermore, the incorporation of Sr in Hydroxyapatite (HA) was shown to improve the bioactivity of HA [149,150].

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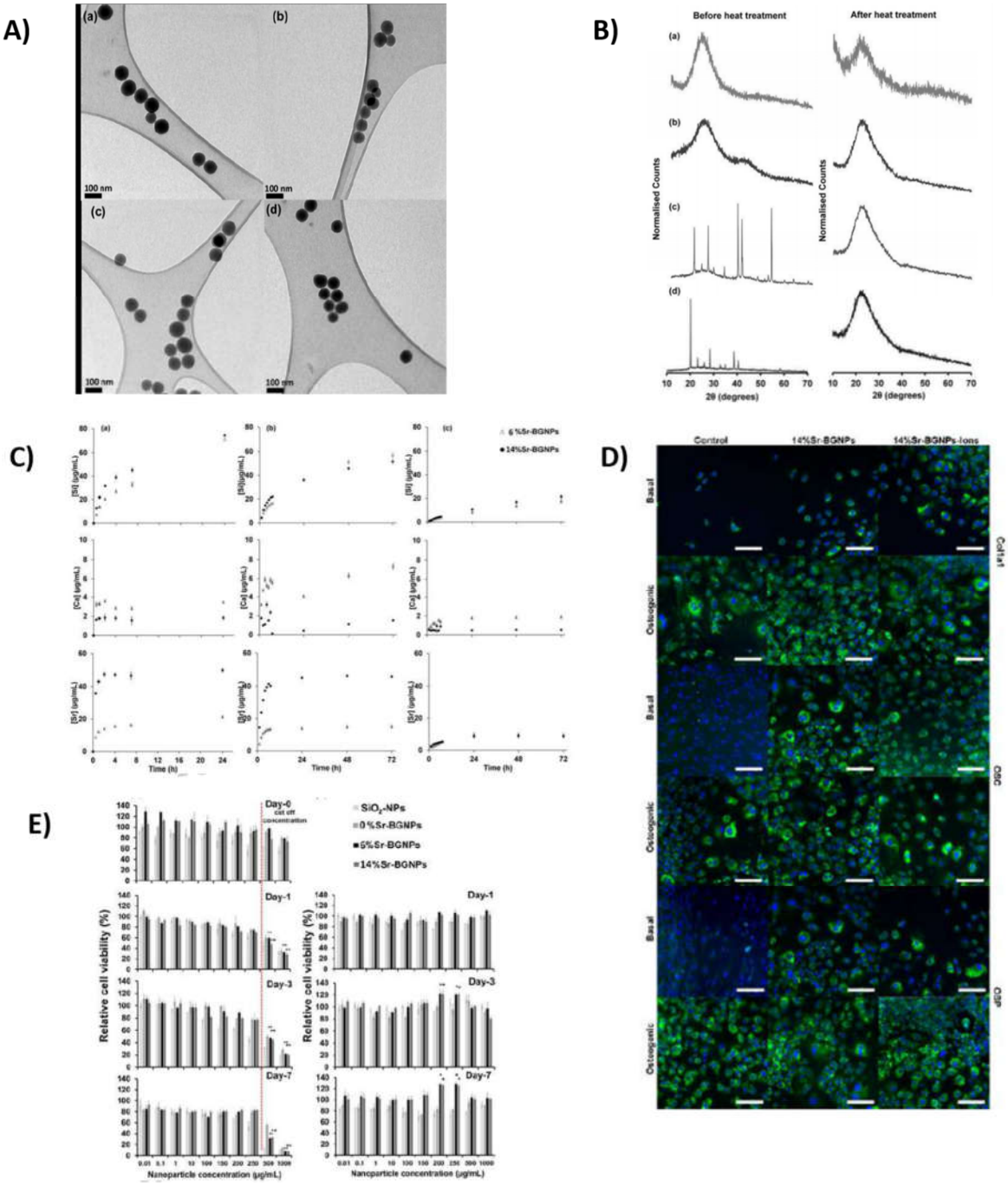

Figure 10. depicts (A) TEM images of Sr-BGNPs (a) Silica NPs reference sample (b) 0%Sr-BGNPs (c) 6% Sr-BGNPs (d) 14% Sr-BGNPs (B) XRD patterns before and after heat treatment (a) reference sample $Si0_2$ (b) 0% Sr (c) 6% Sr (d) 14% Sr. (C) Dissolution profiles at 6% Sr and 14% Sr in (a) a-MEM media (b) ALF media (c) PBS media. Adapted from.[147] Reproduced with the permission from Elsevier. (D) This shows fluorescence images of 14% Sr exposed to MC3T3-E1 cells and their ionic release at 250 μg/mL in basal and osteogenic conditions for 3 weeks. (E) shows effect of Sr-BGNPs on left side and analyzed ionic release at different concentrations of 0%,6% and 14% for day 1,3 and 7 with $p<0.05$. Adapted from [150] Reproduced with the permission from Elsevier.

2.10. Boron

Boron (atomic no.5) is a vital mineral that plays a very crucial part in many biological procedures. It is essential for plants, animals, and human growth. The expanding proof of this supplement showing a spread in effects of pleiotropy, starting from

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medication and inhibitor effects to modulating various processes of the body. A few years back in history, the experiments showed illness connecting polymorphisms of boron in numerous breeds, that has drawn scientists mind to the importance of boron to the healthiness of species. Low boron profile has related to weak immune operate, augmented risk of fatality, pathology, and psychological feature disintegration [151]. Boron's High concentration unconcealed damage to the cell and proved toxic for numerous humans and animals. A few studies have shown some advantages of a high concentration of boron; however, findings are usually mixed, which may accentuate the very fact that dietary intake can profit as long as the supplemental quantity is suitable. The health advantages measure varied in humans and animals; as an example, it alters the expansion at a safe intake. With the consumption of boron, there is Improvement of the nervous system and immunity of immune organs also increases [151].

2.10.1. Properties and Applications

- 2.10.1.1 Bone mineralization and proliferation

The element's physiologic quantities will affect the chemical reactions occurring in the body and intake of assorted substances concerned in growth and advancement [152]. Moreover, it is useful for various organs, due to its connection with metallic elements Ca, Calciferol, and Mg [3,4]. Due to this reason borates square measure being employed industrially in numerous medicines and supplements. Boron is a good treatment selection for inflammatory disease and is responsible for improving bone development observed in 95% of cases by increasing metallic element level effectively into the skeletal system. Furthermore, it alters many hormones, including androgen and steroid hormones [155]. The treatment of cancer may be assured by element nucleon catching agents. The H_3BO_3 is incredibly helpful to beat carcinoma cells in vitro [156]. It is presumed that elements will influence several curdling factors within the body. The element plays a very important role in the improvement of bones [157] because it is useful in chemical reactions occurring inside the body [158] and rebirth [157] of bones. Boron plays an important character in Bone mineralization and proliferation [159]. It is acknowledged that element alters several chemical activities in bones. It encounters Mg, calciferol, and metallic element, all that serves a very crucial role in the metabolic activities of bone [155].

- 2.10.1.2 Anticancer activity

Bortezomib (PS-341), trade name Velcade, is a boron compound from Millennium Pharmaceuticals (now Takeda Pharmaceutical) and is the first proteasome inhibitor approved for the treatment of newly diagnosed MM, relapsed/refractory MM, and mantle cell lymphoma [160]. It is a dipeptide boronic acid derivative that contains pyrazines acid, phenylalanine, and leucine with boronic acid. Besides MM and mantle cell lymphoma, this compound alone, or in combination, has been investigated for the treatment of solid tumors such as carcinomas of the breast, lung, colon, prostate, and pancreas [161]. Bortezomib exhibits its anticancer activity by reversibly and specifically inhibiting the threonine residue of the 26S proteasome, which has a key role in regulating protein degradation in a controlled manner. Inhibition of this enzyme causes an imbalance between the inhibitory and stimulatory proteins involved in the cell cycle, thereby causing cell death [162]. Bortezomib has been reported to inhibit nuclear factor-κB, and to induce cell cycle blockade and apoptosis *in vitro*, as well as tumor growth inhibition *in vivo*. Moreover, intracellular calcium metabolism dysregulation, which causes caspase activation and apoptosis, is also responsible for the anticancer activity of bortezomib [163].

- 2.10.1.3 Antiviral activity

Various boron-based compounds for the development of antiviral agents against hepatitis C virus (HCV). This is a disease that affects more than 170 million people worldwide and is the major cause of chronic liver disease, which can lead to cirrhosis, carcinoma, and liver failure. As HCV NS3/4A protease is vital for replication of the HCV virus, it has emerged as a good therapeutic target for the development of anti-HCV agents. A

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novel series of P2–P4 macrocyclic HCV NS3/4A protease inhibitors with α-amino cyclic boronates at the P1 site were designed and synthesized [164].

- 2.10.1.4 Antifungal activity

Boron is also an unusual element for organic chemists, but it interacts strongly with organic biochemicals and it has significant bioactivity, particularly as both an antifungal as well as insecticide. The most well-known bioactive boron compounds are boric acid, its salt borax, as well as the closely related boronic acids. Tavaborole (trade name Kerydin) is a newbie that was developed as well as approved in 2014 for the topical treatment of onychomycosis, a fungal infection of the nails and also the nail bed. A few dihydrobenzoxaborole derivatives with aryl, heteroaryl, or vinyl substituents are developed. The antifungal activity of these dihydrobenzoxaboroles against *Candida albicans* was discovered during a library screening. Further screening against yeast, filamentous fungi, as well as dermatophytes revealed that certain compounds seemed to have broad-spectrum activity against such fungal pathogens, along with the *major onychomycosis dermatophytes*, *Trichophyton rubrum* and *Trichophyton mentagrophytes[165]*. An investigation for effective therapy for onychomycosis, a fungal infection of the toes and fingernails, confirmed the presence of 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxazole (AN2690 or tavaborole), which would be generally in Phase III clinical trials for onychomycosis topical treatment. The compound was shown to form a covalent adduct with 3′ adenosine of tRNAleu and suppress leucyl-tRNA synthetase. One other candidate, (AN2718), recently finished a Phase I clinical trial for the treatment of fungal infections of the skin and nails [164].

- 2.10.1.5 Antibacterial activity

β-lactam antibiotics are one of the most common drug for the treatment of bacterial infections [166]. The most prevalent mechanism of resistance for such a class of antibacterial agents in clinically significant Gram-negative bacteria is β-lactamase hydrolysis of β-lactam antibiotics [164]. The relationship between the three classical β-lactamase inhibitors (clavulanic acid, tazobactam, and sulbactam) to β-lactam antibacterial is arguably the most popular strategy for combating β-lactamase-mediated resistance. The amino acid sequence is used to classify β-lactamases, which are divided into class A, C, and D enzymes that use serine for β-lactam hydrolysis as well as class B metalloenzymes that use divalent zinc ions for substrate hydrolysis [167]. Even though clinically significant inhibitors do seem to be particularly active on class A enzymes, broad-spectrum inhibitors are required [168].

- 2.10.1.6 Boron in drug delivery

BNNTs, structural analogs of carbon nanotubes in nature, because of their unique 1D hollow nanostructure, are being investigated for the possibility of developing a new class of nanodevices for cell therapy or other medical applications [169]. It has been demonstrated that BNNTs can deliver DNA oligomers to the interior of cells with no cytotoxicity, supporting the idea that BNNTs can be used as biological probes and in biomaterials [163].

- 2.10.1.7 Wound healer

Boron is a wound healer if 3wt% of the boric acid solution is incorporated which improves fibroblast cells in less than expected time [170]. Borates in extremely low proportions are used in the medication of various injuries nowadays. The mechanism of B in the healing of injuries is uncertain, however, few experiments have unconcealed that it is used in the synthesis of proteoglycan [11,12], supermolecule, and collagen. Researchers have observed that it controls the extracellular matrix assembly, which shows a vital character within the course of healing injuries by increasing the discharge of proteoglycans, proteins, and collagen. Neoplasm death issue synthesis and discharge are also encouraged by Boron [10,11].

- 2.10.1.8 Angiogenic effect or stimulate angiogenesis

Boron has various properties in biomedical applications. Researchers have found recently that it archly increases the angiogenic effect or stimulates angiogenesis rapidly, a

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reaction that assists in the fast transportation of oxygen and nutrients, cells, and cultivation factors that are involved in regeneration processes. Durand *et al.* [173] doped 2 wt.% B_2O_3 in 45S5 bioactive glass system and analyze the dissolution product for angiogenic effect. It was observed that doped product increases the angiogenic effect positively. The chorioallantoic membrane (CAM) was utilized to analyze angiogenesis and anti-angiogenesis effects. Figure 11A-B shows the increase in expression of integrin $\alpha v\beta_3$ and vascular density when treated with HBSS+45S5.2B or HBSS + 45S5.2B/bFgF which provide evidence of the rise in angiogenesis. Moreover, the important aspect to consider in biomaterial study is the release of therapeutic ions. Different concentration of borate ions provides a different effect like HBSS+45S5.2B has 160 ±10 µM which gives positive effect and above this value it shows cytotoxic effect such as (15,50 µM) [173].

However, these cytotoxic values show proangiogenic ability so it can be deduced that borate is responsible for the angiogenic effect. The concentration of 5,10,150 µM are incorporated in the system and a rise in effect can be seen after 2- and 5-days posttreatment with an increase in borate ions as depicted in Figure (11C-E) [173,174].

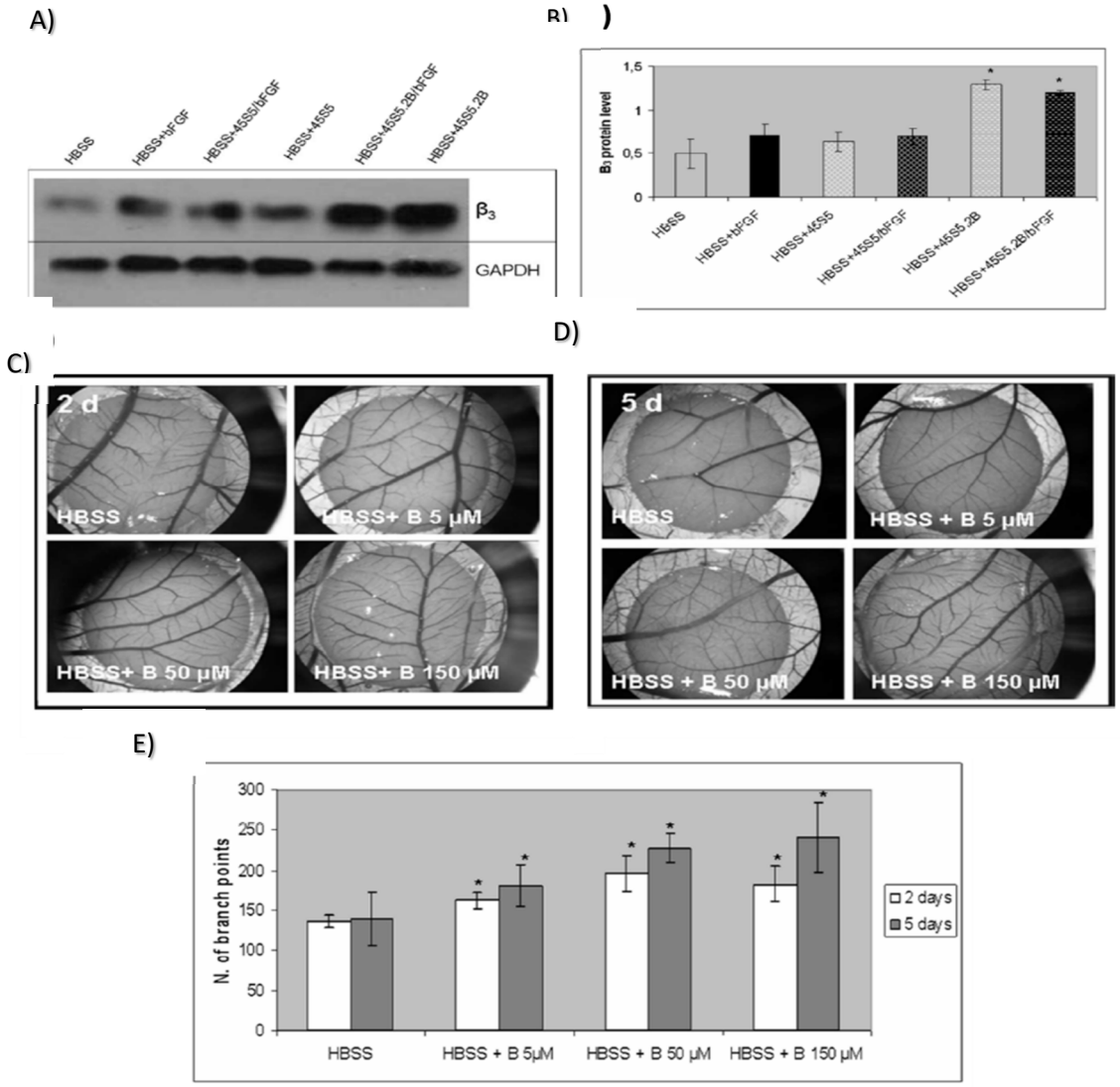

Figure 11. depicts (A) Western blot and subunit of integrin $\alpha v\beta 3$ relative expression (B) concerning HBSS.2B and HBSS/bFgF (C) shows various borate concentration angiogenesis effect of CAM at (2d) (D) shows various borate concentration angiogenesis effect of CAM at two days and (5d) five days post-treatment. (E) Number of branch points with different concentrations of borate at 2 and 5 days. Adapted from [174] Reproduced with the permission from RSC.

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2.11. Silver

Silver is commonly employed in the structure of NO_3^- to produce the impact of antimicrobe.

2.11.1. Properties and Applications

- 2.11.1.1 Antimicrobial agent

Various salts of Silver are utilized commercially as an antimicrobial agent [175]. These nanoparticles are used for antibacterial properties [176–180]. Researchers have carried out commendable efforts on this ion to explore its various property using electron microscopy as shown in Figure 12A(a) which depicts TEM (Transmission Electron Microscopy) images of silver nanoparticles (AgNP's) in accumulated and monodispersed form and Figure 12A(b-c) shows the diffraction pattern and magnification morphology of silver nanoparticles which revealed that size and concentration will provide different results with bacteria [179]. However, when nanoparticles of Ag are utilized, there is a gigantic expansion in the upper territory which is present for the microorganism to be revealed. It has been observed that Ag nanoparticles can cause the breakdown of cell or repress cell signaling. Silver nanoparticles can secure the bacterial cell divider and hence enter it, accordingly, causing underlying changes in the cell film like the eradication of the cell layer and demise of the cell as shown in Figure 12B-D. There is the development of 'pits' and gathering of the nanoparticles on the cell surface [180-*183*].

Ag^+ particle is important for its valuable antimicrobial advantages in tissue culture functions [183]. Also, research has shown that the expansion of Ag tissue societies of in vitro bone does not meddle with markers of ontogenesis, for example, the creation of Hydroxyapatite (HA) [183]. So, the joining of silver into tissues of bone recovery inserts could turn out to be useful by assisting to inhibit diseases with insignificant injurious impacts. Moreover, late discoveries have indicated that the openness of MC3T3-E1 cells to Ag-based nanoparticles brought about upregulation of bone development and guideline markers and quickened the separation and expansion of the cells [184].

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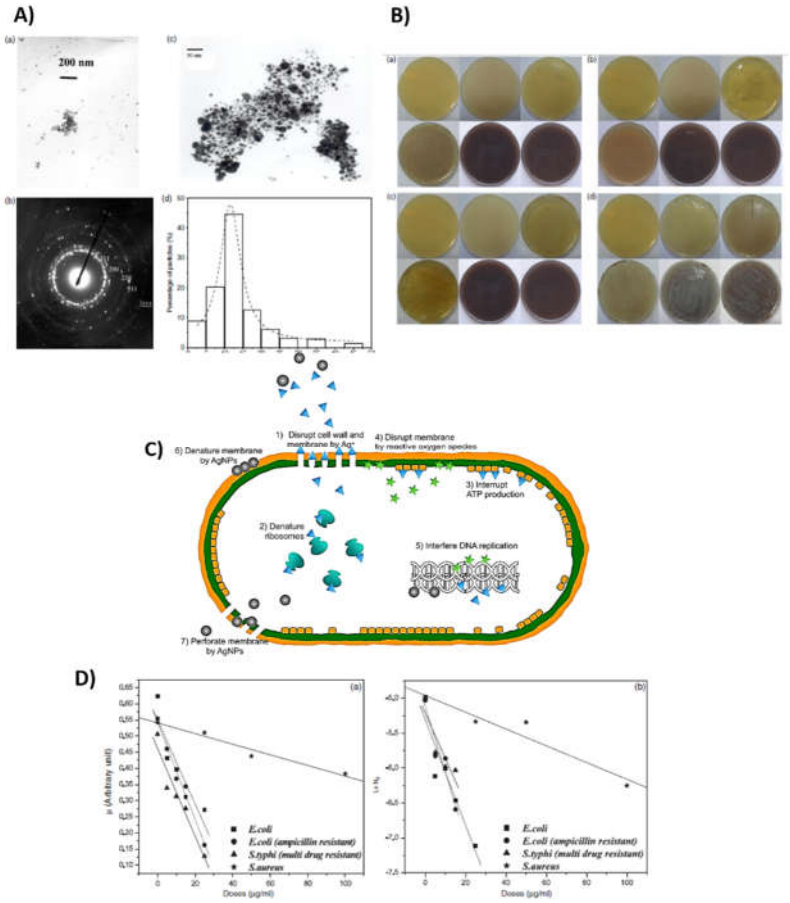

Figure 12. shows (A) silver nanoparticles with TEM microscope of different sizes (a) accumulated and monodispersed form (b) diffraction pattern (c) Higher magnification morphology of silver nanoparticles (d) size range from 10-15nm of Ag-NPs are depicted utilizing particle size distribution. (B) Preparation of various bacteria on Agar plates (C) Mechanism Action of Ag Nanoparticle (D) Effect of AgNPs at (a) bacterial growth rate constant and (b) initial cell count. Adapted from [182] Reproduced with permission from Elsevier.

- 2.11.1.2 Antibacterial properties

Silver is widely considered an antibacterial owe to its ability to generate reactive oxygen species (ROS). For example, Figure 12A(d) showed that the Ag-particles in the range 10-15nm presented a strong antibacterial effect against gram-negative bacteria than gram-positive [182,185]. In another study [176] *E. coli*, *S. aureus*, *ampicillin-resistant E. coli,* and multiple drug-resistant were exploited to the silver ions. In another this study, it was observed that the growth of gram-negative bacteria was strongly inhibited with the rise in silver concentration [176,186]. It is suggested that the release of silver in particulate form is toxic to the human body. However, the controlled release of silver in an ionic form can provide antibacterial with good biocompatibility. For example, Ur Rehman *et al* [186] and Nawaz *et al.* [187] deposited silver-silica nanoclusters on polymeric films and it was shown that the silver was released in a controlled manner which led to the antibacterial effect against a broad spectrum of bacteria. In addition to that, the coatings were compatible with the osteoblast cells.

- 2.11.1.3 Wound Healing Activity

AgNPs hydrogel derived from *Arnebia Nobilis* root extract demonstrated positive wound healing activity in an excision animal model due to its antimicrobial ability, providing a promising pharmacological direction for wound treatment in clinical research. In animal models, AgNPs mediated by *Indigofera aspalathoides* were screened for wound-healing applications after excision. AgNPs obtained from *Chrysanthemum morifolium* were discovered to have bactericidal activity when incorporated to clinical

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ultrasound gel used with an ultrasound probe, going to contribute to instrument's sterilisation [188]. As with any complex pathophysiological mechanism, the wound-healing process consists of several stages, including coagulation, inflammation, cellular proliferation, as well as matrix and tissue remodelling. Extracellular AgNPs derived from the fungus *Aspergillus niger* have been shown to modulate cytokines associated with wound healing in the excision rat model. The AgNPs embedded onto the cotton fabric and dressings resulted in a substantial decline in wound healing through an average time of 3.35 days, and bacterial clearance from infected wounds was however enhanced without any negative effects. Silver nanoparticles have antimicrobial properties that cause wound inflammation to decrease and fibrogenic cytokines to be modulated [189].

- 2.11.1.4 Silver Nanoparticles for Bone Healing

Human bone, dentin, and dental enamel are mostly made up of the calcium-phosphate salt hydroxyapatite (HA). Considering the biocompatibility of biosynthesized and synthetic HA, such a material and even its derivatives are also being extensively researched for the development of potential osseous-related restorative and regenerative schemes, such as artificial bone grafts or coatings for metallic implants [190]. When it comes to superficial modification of various metallic implant surfaces, biocompatible HA incorporated to silver (whether metallic or ionic form) seems to be an interesting candidate for fabrication of bioactive as well as antimicrobial bone implants [185]. The antimicrobial efficacy of HA-based coatings integrated with nanosilver against Gram-positive or even Gram-negative bacterial strains is being revealed [191].

- 2.11.1.5 Anticancer Activity

Only 40% of breast cancer cell lines are inhibited by silver nanoparticles synthesised with *Acalypha Indica Linn* (MDA-MB-231). MCF-7 cells to lose 50% viability when exposed to AgNPs formed by *Dendrophthoe falcata* at 5 g/mL. (L.f) Ettingsh is an abbreviation for Ettingsh [192]. Silver-(protein-lipid) nanoparticles processed from the seed extract of *Sterculia foetida* (L.) fragmented cellular DNA in HeLa tumor cell lines. At 20 g/mL, Datura inoxia-AgNPs suppressed 50 percent proliferation of the MCF7 breast cancer cell line by resisting growth, arresting cell cycle phases, as well as helping to reduce DNA synthesis to induce apoptosis. At such concentration of 25 g/mL, Chrysanthemum indicum-AgNPs had shown no toxic effect to 3T3 mouse embryo fibroblasts [193].

2.12. Zinc

Zinc is known as a fundamental supplement, implying that your body is unable to store or deliver it. Therefore, you should have a steady stockpile of zinc daily. Zinc is an omnipresent minor component fundamental for development. Zinc has various organic capacities in fixing injuries known from old occasions [194]**.** Zinc is a fundamental minor component needed for some cell catalysis, skeletal, and administrative cycles [195] and is basic for ordinary development, immune capacities, and wellbeing of the nervous system [196]. Zn is additionally perceived as a cell reinforcement and mitigating specialist that may have huge remedial advantages against a few constant infections, for example, malignancy, neurodegeneration, atherosclerosis, and immunological issues [197]. It has for quite some time been realized that zinc is needed for bone development and improvement and that its lack can prompt numerous sorts of skeletal variation from the norm in fetal and postnatal turn of events, including bone development hindrance, anomalous mineralization, and osteoporosis as shown in Figure 13C [3,5,200]**.**

2.12.1. Properties and Applications

Zinc is required for various processes in your body, including Quality articulation, Enzymatic responses, Immune operations, Protein blend, DNA union, curing of injury, Development, and advancement. Biomaterials having zinc fundamentally incorporate metallic Zn compounds, zinc earthenware nanoparticles, and Zn metal–natural systems

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(MOFs). Metallic Zn inserts debase at an attractive rate, coordinating the mending speed of nearby tissues, and animating renovating, and making of new tissues. Zinc ceramic nanomaterials are fruitful for tissue designing and treatment because of their nanostructural and antibacterial properties as depicted in Figure 13E [200]. Metal-organic frameworks (MOFs) have enormous surface zones and are effectively functionalized, making them ideal for drug distribution and disease treatment [199,200]

Y Su et al. [199] found that biomaterials made up of zinc have significant applications in the recovery of tissues and medicines. Ceramic Zinc biomaterials are being created as synergistic nanocomposite stages fit for joined malignancy focusing on, bioimaging, and responsive medication distribution as shown in Figure 13D [200]. Biodegradable zinc metals have great corruption rates and biocompatibility, and their automated power and flexibility can be upgraded by the process of alloying, in this way they will become promising for circulatory and muscular use. Figure 13A,B shows the Zn based metallic implants for cellular adhesion and proliferation for smooth muscle cells and plaque for stents [200].

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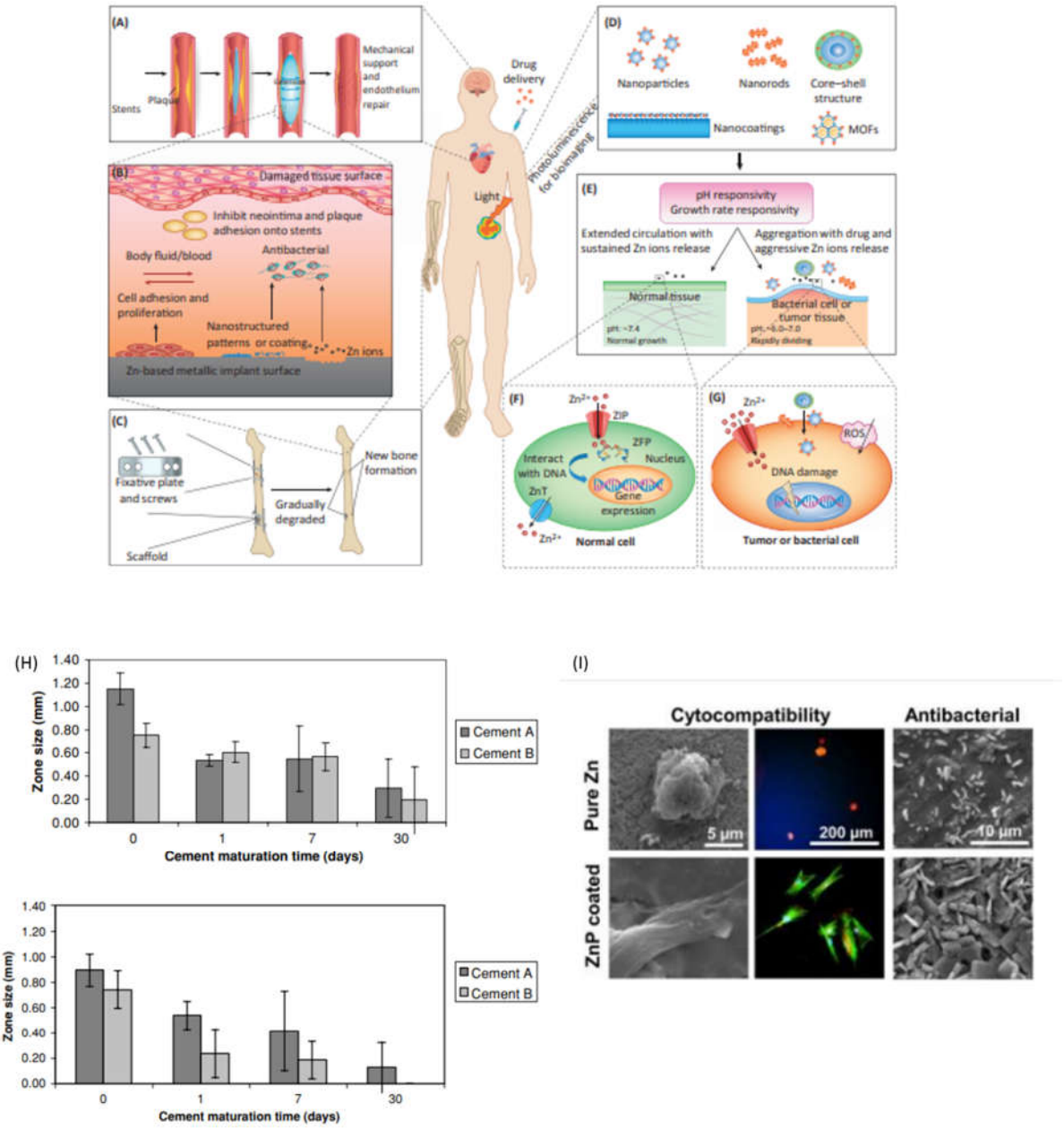

Figure 13. (A) Metallic Zn-based coronary stents reinforce the artery wall physically as well as aid endothelium reconstruction by removing plaque to prevent thrombosis and stent restenosis. (B) In vivo interactions of the Zn-based metallic implant surface against damaged tissues: an optimal nanostructured pattern / coating on the surface, as well as releasing Zn ions from the degradation process, can promote cellular adhesion and proliferation whilst suppressing bacterial cell adhesion and proliferation (such as smooth muscle cells and plaque for a stent). (C) Metallic Zn-based orthopaedic implants (fixative plates, screws, & porous scaffolds) provides temporary mechanical support to bone tissue regeneration during the biodegradation and development of new bone in a parallel phase. (D) Nanostructured Zn-based ceramic and organic biomaterials have a high surface/volume ratio for drug delivery and good photoluminescence for in vivo bioimaging. (E) Nanostructured Zn-based ceramic and organic biomaterials have pH and cell growth rate-sensitive responses, separating their circulation or aggregation activities on natural tissues, bacterial cells, and tumour tissues. (F) Normal cells are unaffected by comparatively low Zn ion concentrations, and in some cases, benefit from them. (G) In tumours and bacterial cells, high Zn ion concentrations, vigorous release of Zn ion, cellular surface aggregation of Zn-based nanomaterials, including induced ROS can destroy the cell surface and DNA. Adapted from [200] Reproduced with permission from Cell press. (H) Top: Inhibition of growth of A. viscosus. Bottom: Inhibition of growth of S. mutans . Adapted from [201] Reproduced with permission from Elsevier. (I) Cytocompatibility and

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Antibacterial Activity of Pure Zn and ZnP coated of Zn based biomaterials. Adapted from [202] Reproduced with permission from Elsevier.

- 2.12.1.1 Total Hip arthroplasty (THA)

Bacterial disease after complete hip arthroplasty is a genuine problem of hip substitution medical procedure that now and then requires amendment in previous medical procedures. D. Boyd et al. [203] integrated and portrayed zinc-containing glass polyalkenoate concretes to examine their expected use in THA. Y Su et al. [202] arranged Zinc-Phosphate covering on the natural Zn by a basic chemical transformation covering technique. The covering morphology could be restrained by changing the pH estimation of the 24/49 covering solution [204]. The zinc Phosphate covering controlled deterioration rate and fundamentally improved compatibility of blood, cytocompatibility, and antibacterial capability for the Zn biomaterials [205]. The measure of delivered Zn particle collected in the nearby climate and the surface morphology was demonstrated to be essential for the cytocompatibility and antibacterial performance of Zn material as shown in Figure 13(I) [201,202,205].

- 2.12.1.2 Antibacterial material

Zinc oxide (ZnO) nanoparticles can be chosen as an antibacterial material due to their astonishing properties, for example, high explicit surface territory and high action to hinder a wide extent of pathogenic specialists [207]. Earlier investigations had recommended the fundamental antibacterial poisonousness workings of ZnO NPs depended on their capacity to prompt overabundance reactive oxygen species (ROS) age, for example, superoxide anion, hydroxyl revolutionaries, and hydrogen peroxide creation. Figure 13F,G,H shows different concentrations of Zn ion released and their effect on bacteria [201,208]. The antibacterial action may include the gathering of ZnO NPs in the external layer or cytoplasm of bacterial cells and trigger Zn^{2+} discharge, which would cause bacterial cell film deterioration, layer protein harm, and genomic uncertainty, bringing about the demise of bacterial cells [209].

2.13. Iron

Fe ions are present in trace amounts in the body and used in the proper functioning of many proteins. Bodily processes regulate the amount of iron inside the body and keep them within defined limits as too little iron can lead to anaemia and suboptimal cellular function, while excess iron (hemochromatosis) can damage cells and tissues by catalyzing the production of reactive oxygen species [210]. Iron is abundantly available in our environment and can undergo redox reactions because of which the metabolism largely depends on Iron. Iron is also a cofactor for many proteins or enzymes which are involved in the key reactions of life such as cell division (synthesis of deoxyribose from ribose by ribonucleotide reductase), respiration, oxidant protection (ferritin, peroxidases), and O_2 transport (globins) [211]. Iron is the central component of blood cells and participates in redox reactions of metalloproteins and oxygen carrier proteins due to its ability to readily accept and lose electrons. These reactions occur in hemoglobin present in red blood cells and myoglobin present in muscle cells [212].

2.13.1. Properties and Applications

Iron ions can be incorporated with different agents to perform various functions depending upon application [213]. Ferric ions were incorporated by Machida Sano, (2009), in alginate films as a cross-linking agent to form Fe+ alginate films instead of Ca which is typically used for cross-linking. These films were used for the growth of Normal Human Dermal Fibroblasts-(NHDF). (NHDF) cells were found to attach and proliferate more substantially to Fe+ alginate films in comparison to Ca^{+2} alginate films. On Fe-alginate [214] films, cell spreading was evident at 4 h after cell seeding (Figure 14(a)), definite cell spreading was observed at 1 day after seeding (Figure 14(b)), and the cells had proliferated, and their numbers increased by day 3 (Figure 14(c)). The reason was that Fe-alginate

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film adsorbed a significantly higher amount of proteins, including vitronectin and fibronectin, which are critical for cell adhesion [215]. Moreover, these films had a higher surface hydrophobicity than Ca-alginate film. The results of the study suggest that Fe-alginate is a good option for a scaffold for human fibroblast cells and can be useful for tissue engineering research and other biomedical applications as they show better response than calcium alginate films and their response is comparable to calcium triphosphate [216]. Chitosan has good biocompatibility and metal-binding properties which is why Iron (III) ions have been used in conjunction with chitosan [217]. In-vitro tests performed by Burke (2000) on human blood serum indicated that chitosan is capable of adsorbing iron (III) ions in the body fluid medium and maybe a suitable iron-adsorbing agent in biological systems [218]. The interaction of iron (III) with Chitosan is used for the treatment of iron overload or the removal of iron (III) [219]. Spherical iron(III) oxyhydroxide nanoparticles have been stabilized by chitosan in an aqueous solution [220]. Using a transmission electron microscope, pictures were taken of the samples obtained from solutions containing iron(III) and Chit. Isolated FeOOH nanosphere particles of size 5–10 nm diameter in the solution were observed in the micrographs and are shown in Figure 14(C) [221-223].

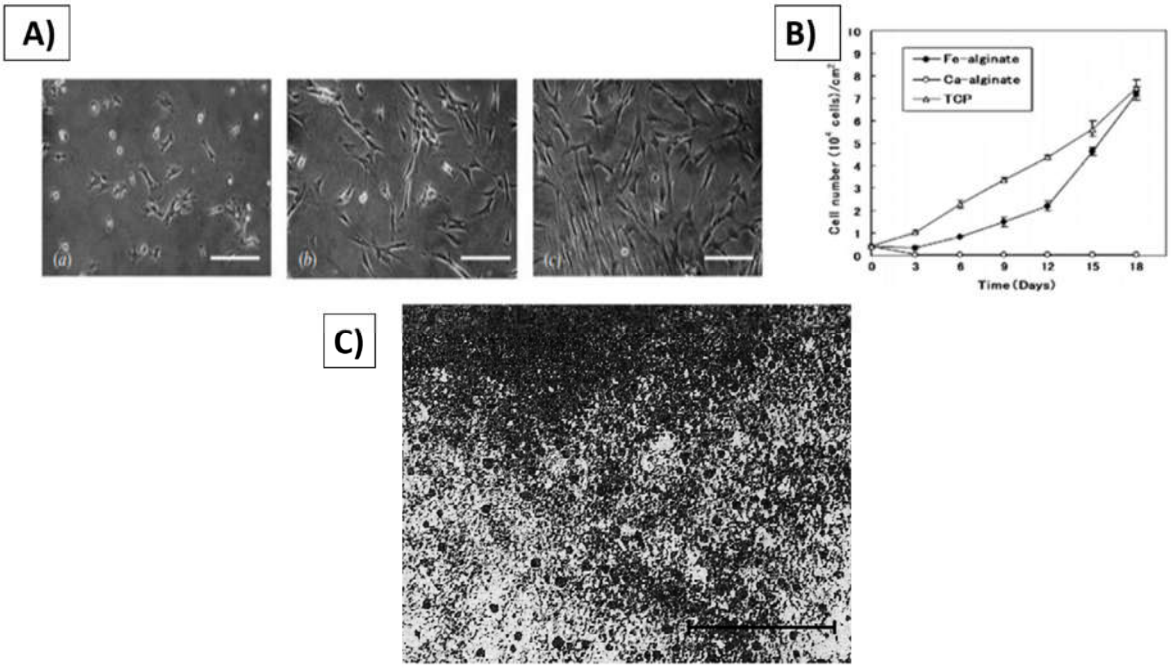

Figure 14. (A) shows photomicrographs of NHDF cultured on Fe-alginate films. Phase-contrast micrographs were taken at 4 h (left,), 1 day (middle), and 3 days (right) after cell seeding. Bar equals 200 μm in micrographs. B) shows the proliferation of NHDF on Fe-, Ca-alginate films and TCP. The numbers of attached cells were counted at 3, 6, 9, 12, 15, and 18 days after cell seeding. Adapted from [222] Reproduced with permission from IOP Science. C) shows a transmission electron micrograph of a Fe(III)–chitosan compound obtained from a solution of pH 4.6, at a metal-to-ligand ratio of 1:1, showing electron-dense spheres of FeOOH, with particle sizes ranging from approximately 5 to 10 nm. The scale bar represents 100 nm. Adapted from [223] Reproduced with permission from ACS.

- 2.13.1.1 Antimicrobial Activity

Antimicrobial resistance is indeed an old and major concern for healthcare which has expanded at rapid pace, going to spread the economic preoccupation [224]. Antimicrobial properties of gold, silver, aluminium, and iron oxide have long been noted. Nanomaterials can exhibit antimicrobial activity by damaging cell membranes, going to release toxic substances (that can react with proteins, resulting in protein loss), and damaging DNA, RNA, and proteins through reactive oxygen species generation [225]. These mechanisms cause microorganisms to be inhibited or killed [226].

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2.14. Cobalt

Cobalt(Co) ion exists as Co^{2+} and Co^{3+}. In the Co^{3+} state, it acts as a Lewis base and in the Co^{+2} state, it participates in catalytic processes without any tendency toward oxidation [227]. These can be highly toxic because they may produce reactive oxygen species and because they may occupy the binding sites of proteins that are for other metals [228]. So, it needs to be highly regulated in the body. It is a component of vitamin B12, which is necessary for the regulation of the production of red blood cells, DNA synthesis in cells, and the formation of the myelin sheath, protecting the cells of nerves and neurotransmitters [229].

2.14.1. Properties and Applications

- 2.14.1.1 Hypoxia mimicking agent

Co ions were released at the site of cells by treating cells with $CoCl_2$ by Fan (2010). CoCl2 was used as hypoxia mimicking agent, which can activate the hypoxia-inducible factor-1 (factors that respond to decreases in available oxygen in the cellular environment) in mesenchymal stem cells and subsequently activate HIF α target genes which include vascular endothelial growth factor (VEGF). The release of pro-angiogenic factors induces the growth of blood vessels into the bone substitutes and hypoxia-treated bone marrow stromal cells (BMSC) increased the expression of these factors such as VEGF. BMSC was treated with CoCl2 to induce hypoxia before being embedded in a collagen scaffold to facilitate the vascularization of blood vessels [230]. Figure 15A shows the comparison between the VEGF expression of treated and untreated cells. Co ions have also been recognized for their antibacterial effect. Co^{+} ions were stabilized in the form of complexes or nanoparticles to perform antibacterial functions [231].

- 2.14.1.2 Antiviral effects

Cobalt (III)-complexes derived from the N, O donor ligand were shown to have antibacterial and anti-viral effects [232]. Promising Co(III) complexes containing N, O donor ligands include CTC series of complexes based on a chelating Schiff base [233]. In viruses such as the herpes virus [234], Cobalt ions targeted maturational protease which contains large amounts of the amino acid, histidine. CTC complexes bind strongly to the histidine molecule and on reacting with the histidine molecule, they disrupted the normal function of the virus and ended up killing the virus [235]. Series of other cobalt ligand complexes have also shown to fight off certain viral diseases e.g., Hexamminecobalt(III) chloride, $[Co(NH_3)_6]Cl_3$ (2, "*Cohex*") [236]. Cohex inhibits viral replication via the inhibition of viral structural protein synthesis. Cohex significantly inhibited Sindbis virus replication in baby hamster kidney (BHK) cells in a dose and time-dependent manner. *Cohex* treated cells showed significantly less viral spread Figure 15B (right) as compared to untreated cells Figure 15B (left) [237].

- 2.14.1.3 Anti-bacterial effect

Furthermore, mesoporous cobalt ferrite (CF) nanoparticles were used to provide an anti-bacterial effect in desired surfaces or environments [238]. They exhibit antibacterial activity because of membrane perturbation and ROS production which lead to bacterial membrane damaging and loss of cell integrity [239]. CF nanoparticles were found to interact with the arginine protein in bacteria as shown in Figure 15C [240-243]. Hence, CF nanoparticles influence the functionality of certain proteins (as shown in Figure 15D) by leading to faulty or non-assembly of the bacterial membrane which results in cell death [241].

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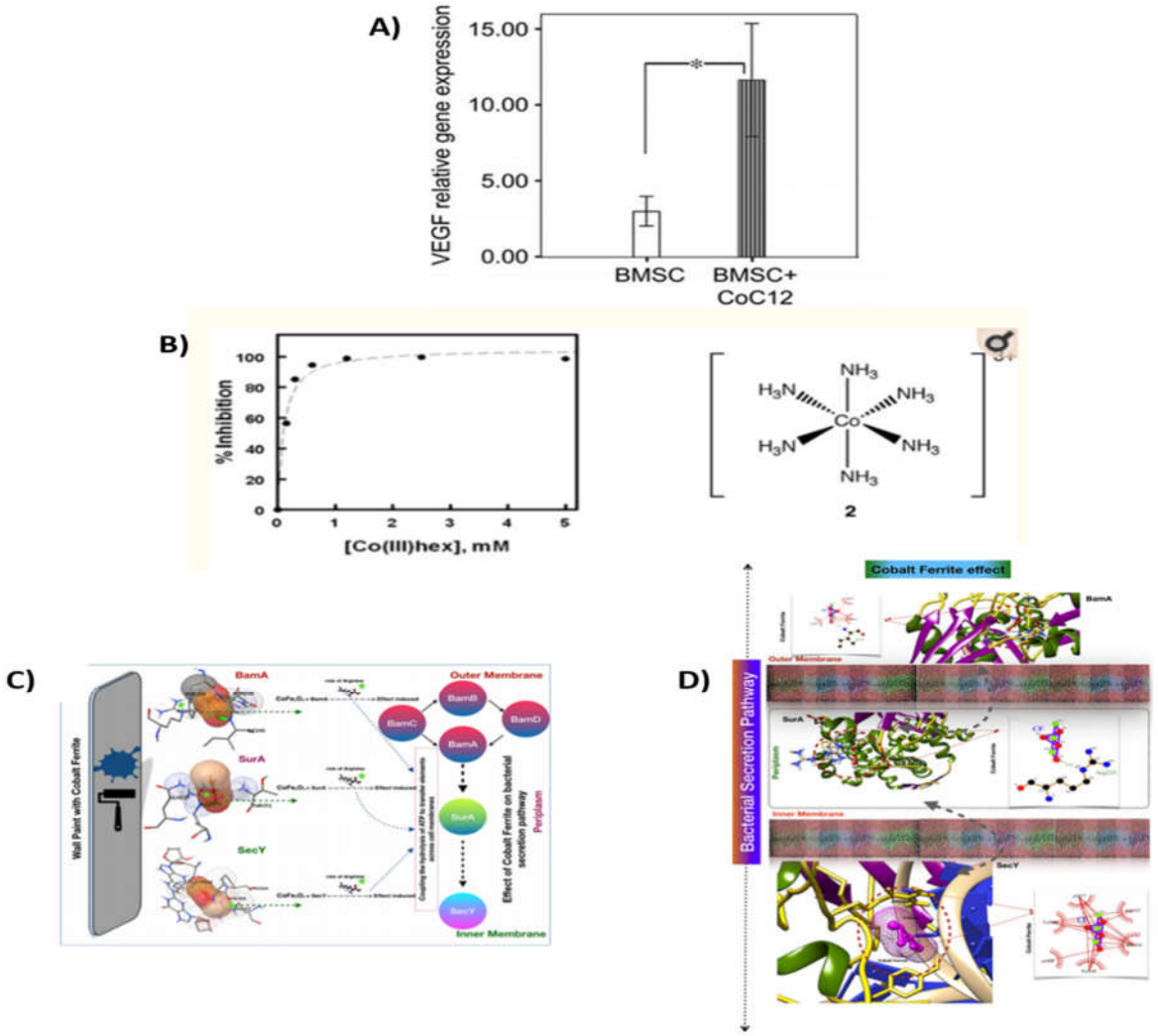

Figure 15. A) showing VEGF expression of CoCl2-treated BMSCs vs untreated BMSC cells B) (right) showing the inhibitory effect of viruses on BHK cells treated with cohex and Fig B (left) shows the structure of Cohex. Adapted from [242] Reproduced with permission from MDPI. C) shows the interaction of cobalt ferrite with BamA, SurA, and SecY proteins and their effects on bacterial metabolism. D) shows the effect of cobalt ferrite on bacterial secretion pathway through interaction with BamA, SurA, and SecY proteins as depicted by molecular docking and Ligplot. Adapted from [243] Reproduced with permission from Elsevier.

2.15. Copper

Copper(Cu) is involved in a large number of metabolic processes, so it is an essential ion for the majority of living organisms. The amount of copper that is introduced into the biological system needs to be taken under consideration as the high concentration of copper ions can produce toxic effects due to their ability to generate ROS. Copper ions can be released into the biological system by being incorporated in different mediums. Hydroxyapatite doped with copper is found to have higher antibacterial activity. It is believed that copper ions form strong bonds with hydrophilic groups such as thiolic, imidazole, amine, and carboxylic groups of proteins. This changes the structure of proteins and results in membrane transport dysfunction and cell death [244]. Another antibacterial mechanism is that copper ions, when they are released from the Cu/HA crystal in body fluid, form bonds with amine groups, amide groups, and disulfide bridges of proteins and enzymes of bacteria, structurally damaging their DNA and RNA and resulting in the inhibition of the reproduction of bacteria or their death [245]. Du et al. loaded chitosan

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nanoparticles with copper ions to test their antibacterial activity and reported that the chitosan nanoparticles loaded copper ions interacted with bacterial cell membranes of E. coli (K88) by initially causing structural change and then cell death [246].

Hydroxyapatite without doped Cu and Zn ions showed some initial cell reduction as well. This suggests that the adhesion of microorganism cells to the particles of HAP may be the underlying cause of the reduction of cell number [247]. Studies have reported that the presence of copper ions in the coatings of the implant can significantly prevent or minimize initial bacterial adhesion to the site of the implant. In vitro tests performed in direct surface contact with tissue cells and bacteria onto a copper-containing sol-gel derived titanium dioxide coating (Cu-TiO2) and non-filled titanium dioxide coating showed that the best cell growth was found on the Cu-TiO2 coatings. Moreover, excellent antibacterial properties with good cytocompatibility could be observed on the fourfold Cu-TiO_2 coatings [248]. Furthermore, copper ions stimulate the vascular endothelial growth factor (VEGF) which is involved in vessel formation and maturation and is also responsible for the angiogenesis effect in the body. Human umbilical vein endothelial cells were incubated for 48 h with 500 microM $CuSO_4$ in a serum-free medium in the absence of exogenous growth factors which resulted in a twofold increase in cell number [249]. In the study performed by Vojislav (2010), two samples of Cu doped hydroxyapatite nanopowders were synthesized. CuHAP1 had a 0.04 weight fraction of Cu ions while $CuHAP_2$ had a 0.40 weight fraction. Cu ions substitute Ca sites in the HAP and since copper cations are smaller than calcium ions, there is a shrinkage in unit cell parameters and particle size, while structural strain increases [250].

2.15.1. Characterization techniques

The XRD analysis shows sharp peaks Figure 16A, which indicated that HAP was well crystallized and lattice parameters a and c decreased with increasing Cu concentration. SEM micrographs and TEM micrographs of $CuHAP_1$ and $CuHAP_2$ have been shown in Figure 16B and Figure 16C, respectively. Scanning electron microscopy (SEM) shows fine agglomerates which are interconnected and cannot be seen individually due to small particle size. These particles are visible in TEM micrograph and are uniform in size. They are approximately 15–25 nm in diameter and about 70 nm in length. The antimicrobial disk diffusion test results showed that CuHAP1 did not affect E. Coli (Figure 16D upper part) while $CuHAP_2$ showed a significant antimicrobial effect (Fig 16D middle part). The same trend was observed in the case of C. albicans (Fig 16D lower part) [201,251].

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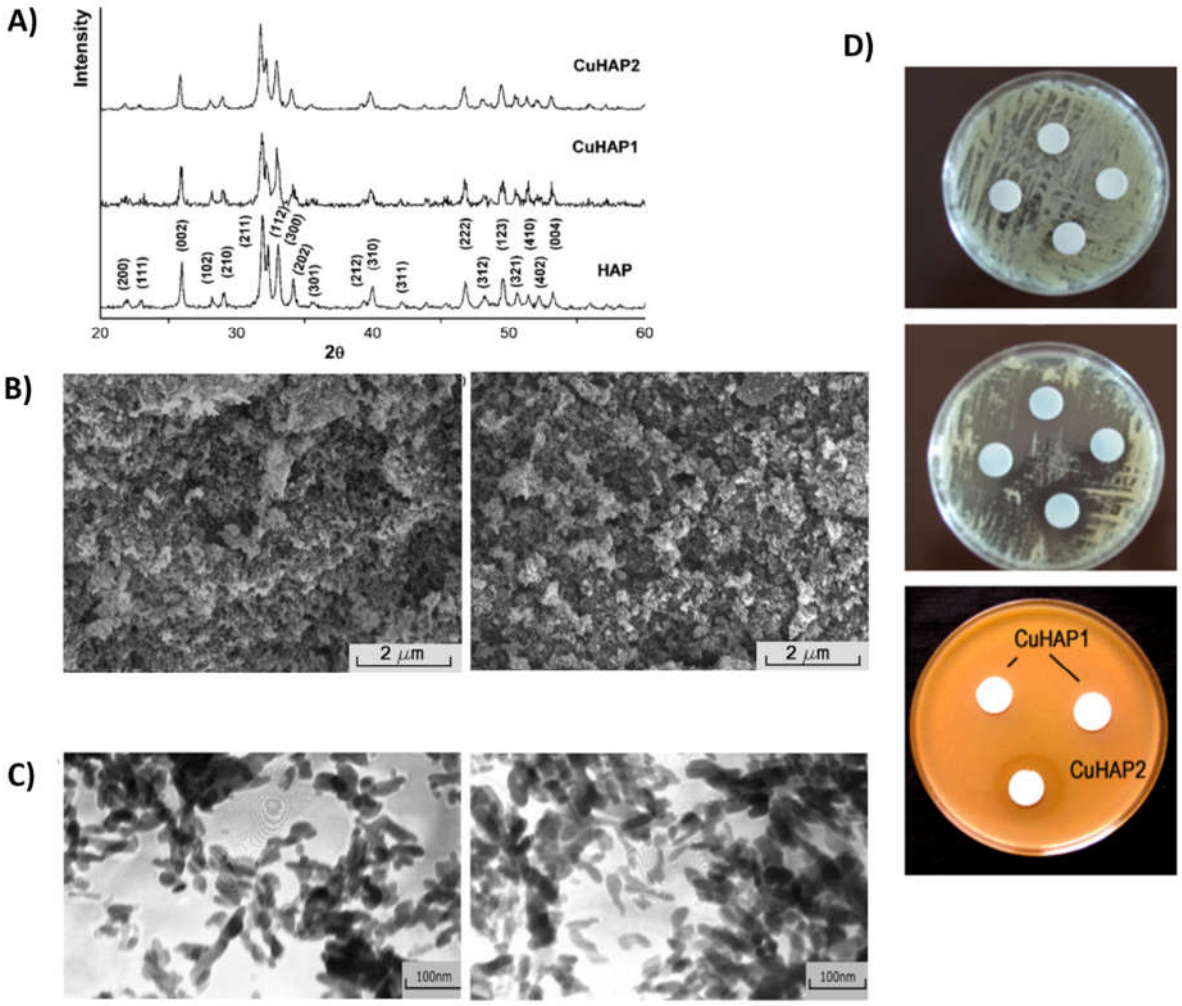

Figure 16. shows different characterization techniques of Cu Ion. A) shows the XRD patterns of the HAP and Cu doped samples. B) shows scanning electron micrographs of CuHAP1(left) and CuHAP2 (right). C) shows transmission electron micrographs of CuHAP1 (left) and CuHAP2 (right). Fig D (upper and middle) shows photographs of antimicrobial test results of CuHAP1 and CuHAP2, samples against E. Coli respectively. Fig D (lower) shows antimicrobial test results of CuHAP1 and CuHAP2 against C. Albicans. Adapted from [201] Reproduced with permission from Elsevier.

2.15.2. Properties and Applications

- 2.15.2.1 Inflammation

After already being oxidised in the air, Hostnek et al. (2006) discovered that metallic copper could indeed penetrate the skin. Cu's anti-inflammatory effect has been related to modulation of prostaglandin synthesis (Sakuma et al. 1996; Franco and Doria 1997; Sakuma et al. 1999), interleukin IL-2 expression (Hopkins and Failla 1999), and neutralisation of reactive oxygen radicals by Cu/Zn-superoxide dismutase, among other things. Although copper deficiency is widely acknowledged to impair immunity, the precise mechanism is unknown (Huang and Failla 2000). Several studies revealed copper(II) complexes with potential anti-inflammatory properties over the last decade. Chelating agents which can promote the transport of Cu(II) ions to sites of inflammation were studied in the treatment of rheumatoid arthritis [252].

- 2.15.2.2 Cancer

Since, introduction of cisplatin for cancer treatment, researchers have been looking for several other transition metal complexes with anti-proliferative activity. NSAIDs or Schiff bases were reported to be most widely known ligands for numerous copper(II)

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complexes, which were observed for being cytotoxic [253]. Many Cu(II) complexes have catalytic activity against reactive oxygen species and thus can cause DNA strand breakage. Guo et al. (2010) proposed that salicylaldehyde-amino acid Schiff base copper chelates induce apoptosis in cancer cells by downregulating overexpressed mutant type P53 protein. Disulfiram, a drug to treat alcoholism, forms a copper complex in vivo that behaves as a proteasome inhibitor and preferentially induces apoptosis in breast tumours (Chen et al. 2006). Disulfiram as well as copper gluconate are currently being explored in phase I trials for the treatment of solid tumours with liver metastases [254].

- 2.15.2.3 Antimicrobial

Copper, including both its metallic form and even in some chemical compounds, has antimicrobial activity that has been used since ancient times. Cupric ions have non-specific biocidal activity, however it is weaker than that of silver. Many hospitals use copper-silver electrolytic ionisation systems to reduce the number of Legionella in hot water pipes. To lessen the risk of complications after prosthetic surgery, metals and alloys used in orthopaedic implants can be doped with copper ions [255]. Based on non specific toxicity, copper should indeed be administered as complex compounds instead of simple inorganic salts to be used as an antibacterial therapeutic. The nature of the chelating agent, on the other hand, is critical, because there is no simple correlation among both antibacterial activity and complex stability [256]. Several distinct Cu(II) complexes with various ligands have been shown to have antibacterial and antifungal activity (Gölcü et al. 2005; Shakir et al. 2006; Singh et al. 2008; Sreedaran et al. 2008; Kumar and Arunachalam 2009; Suksrichavalit et al. 2009). Singh et al. (2008) used a strategy that involved using ligands which already had antimicrobial activity as well as enhancing it through complexation with copper [257]. While complexed with Cu, the antihypertensive drug pindolol (complex stability constant log = 11.28 in water-dioxan 40:60 at 25 °C) possesses significant antimicrobial activity against certain bacterial and fungal strains (Gölcü et al. 2005). A water-soluble polymeric complex with antimicrobial activity and also the binding ability DNA (Kumar and Arunachalam 2009). The complexes were only tested for antibiotic properties, but no further evaluations for medical applicability were performed, to best of knowledge [258].

Copper (I)-Cl-(nicotinic acid)2 (polymeric) can dramatically reduce gastrointestinal mucosa lesions caused by nonsteroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid [259]. The complex has antioxidative, antiapoptotic, secretolytic, as well as antihemorrhagic properties and it might be a promising idea to effectively utilised antiulcer drugs, proton pump inhibitors, that further raise gastrin levels (Tuorkey and Abdul-Aziz 2009). It seems to be a classic case of a Cu(I) compound that's been suggested for diagnostics. Toyota et al. (2005) portrayed a class of copper and iron complexes that functioned as thrombin inhibitors [260]. The Cu(II) complex with 4-formyl-3-hydroxybenzamidine and D-tryptophane would have the maximum inhibitory effect (Ki value 2.7 108 M), relative to the certified anticoagulant drug argatroban (Ki 1.9 108 M) (Toyota et al. 2005). Tian et al. (2009) proposed copper-taurine as a potential compound capable of promoting wound healing by boosting tissue regeneration and preventing infections [261].

2.16. Manganese Ion

Manganese(Mn) ions play an important part in metabolic activity of living organisms as it is a cofactor for a variety of enzymes in the body such as oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases, lectins, integrins and glutamine synthetase) [262].

2.16.1. Properties and Applications

- 2.16.1.1 Antibacterial property

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Mn ions have been incorporated with Hydroxyapatite in many studies due to their bio-tolerant and antibacterial properties [263]. Mn ions in low concentration, exhibit antibacterial effect against a broad spectrum of Gram-positive and Gram-negative bacteria [264]. Mn ions were incorporated in zinc oxide (ZnO) nanoparticles for antibacterial studies [265]. Mn ions bind to the thiol groups of protein, thus altering their structure and causing dysfunction [266]. This causes the rupture of bacterial walls and prevents DNA replication and division, hence, killing the bacteria [267].

Furthermore, Mn ions being incorporated in hydroxyapatite improves bone mineralization, extracellular matrix remodeling, and it promotes cell adhesion [40]. The presence of Mn in biphasic calcium phosphate powders was found to increase the crystallinity of powders due to progressive densification of particles [268]. In the study conducted by Luthen (2007), human MG-63 osteoblastic cells were treated with Manganese(II) chloride ($MnCl_2$) and their behavior showed that the release of Mn cations needs to be thoroughly adjusted in the surface of a biomaterial for them to be effective, as they can be toxic for cells in higher concentration as shown in Figure 17A [269]. The proliferative phase was found to be maximum when (Magnesium chloride) $MgCl_2$ was added to DMEM solution in a concentration range of 0.03% [270]. In vitro experiments conducted by Fujitani (2010) on osteoblast-like cells (MC3T3E1) showed that Mn-doped hydroxyapatite showed higher cell adhesion potential than pure hydroxyapatite [271]. The addition of Mn improves bio response as Mn ions in hydroxyapatite activate integrins, [272], which play a part in the cell adhesion potential of MC3T3E1 cells to the surface of Mn-doped HA [273]. In the study performed by Barrioni et al. on Mn-doped in sol-gel bioactive glasses, it was found that Mn enhanced cell proliferation and viability of osteoblastic cells while maintaining acceptable bioactivity and showing an antibacterial effect [274]. The antibacterial effect of Mn-doped sol-gel bioglass was studied in physiological conditions against relevant bacterial strains. Furthermore, it was found the Mn release levels after immersion in simulated body fluid (SBF) could be adjusted within therapeutic limits, and cytotoxic analysis showed that the ionic products of Mn-doped sol-gel bioactive glass did not pose a threat to the cell environment. Sol-gel-derived glasses offer adjustable composition, sizes, and morphologies [275]. Also, it is a good technique for the synthesis of nanoparticles such as MBGNs [276]. Also, they have improved bioactivity due to the high surface area. In the study performed by Nawaz et al.[277], it was observed that a concentration of Mn greater than 5mol% affected the morphology of MBGNs Fig 17C-17D shows the morphology of synthesized BG particles of different concentrations. In antibacterial studies, MBGNs and Mn-MBGNs were found to slow down bacterial growth. Slow-release of Mn ions can provide a long-term antibacterial effect to MBGN [277]. The therapeutic limit for Mn ions is reported to be 5.49 ppm from the literature [278]. Furthur characterization results have been shown in the Figure B,E-G [277,280]. Table 1 summarizes the functions and effects of different metallic ions in the biological system.

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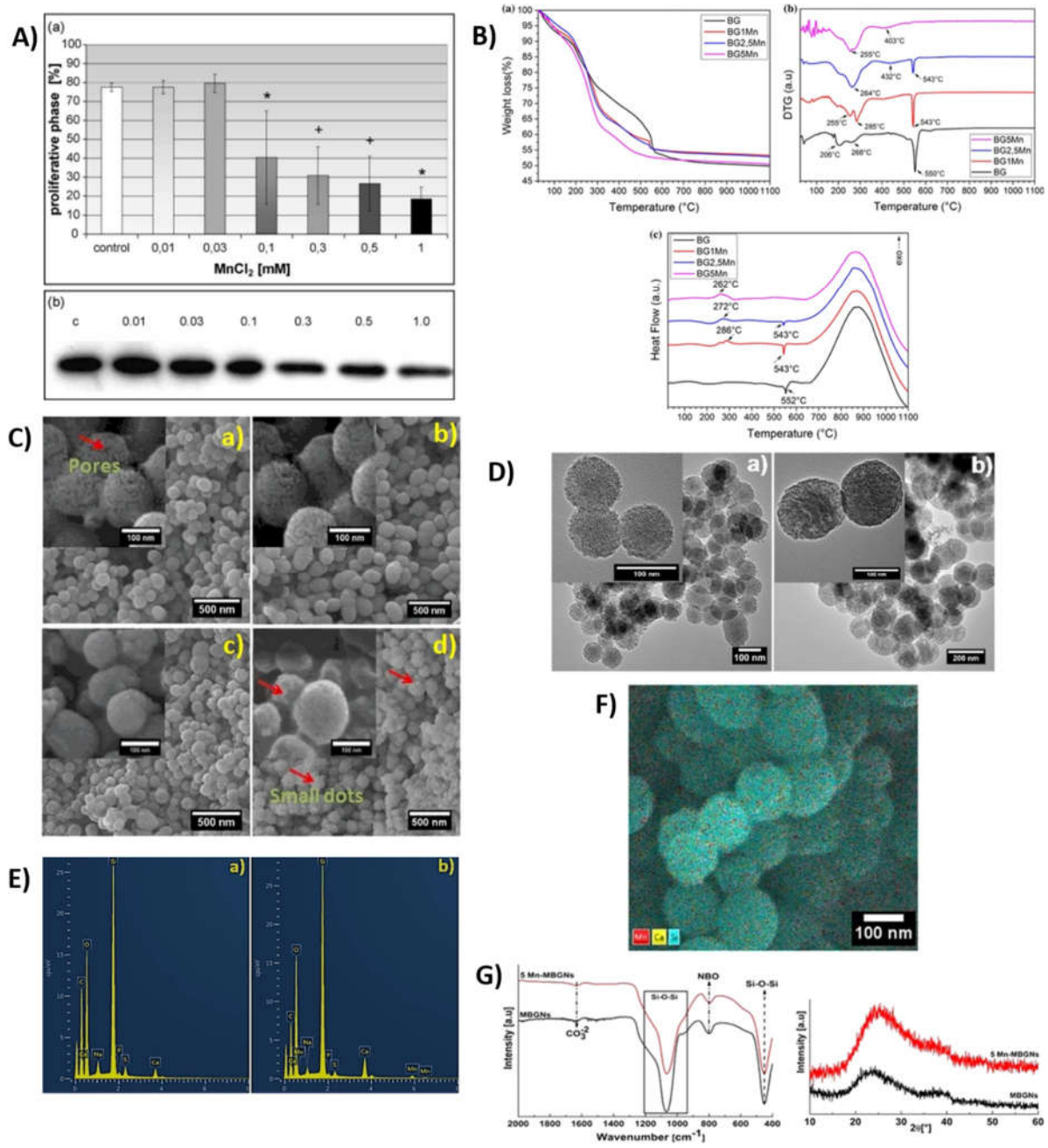

Figure 17. A) shows the proliferation of osteoblast cells treated with varying concentrations of MnCl2. Manganese ions with in range of 0.1 mM to 1.0 mM prevent osteoblast proliferation. After 24 hours, the cell cycle's proliferative step (S+G2/M) is greatly decreased (flow cytometry, U-test, p 0.05, n = 8). Adapted from [279] Reproduced with permission from Elsevier. B) shows (a) Thermogravimetric analysis (TGA), (b) derivative thermogravimetric (DTG), and (c) differential scanning calorimetry (DSC) of bioactive glasses. Adapted from [280] Reproduced with permission from Sage. C) shows SEM images depicting the morphology of the synthesized BG particles: (a) MBGNs, (b) 3 Mn-MBGNs, (c) 5 Mn-MBGNs, and (d) 7 Mn-MBGNs. D) shows TEM images of (a) MBGNs and (b) 5 Mn-MBGNs. E) shows EDX spectra of the synthesized BG particles (a) MBGNs and (b) 5 Mn-MBGNs. the presence of an Mn peak in addition to the Ca, P and Si peaks correspond to the addition of Mn in MBGNs. F) shows EDX mapping analysis of 5 Mn-MBGNs showing that Ca (yellow), Mn (red), and Si (blued) are uniformly distributed in the nanoparticles. G) shows XRD analysis (right) and FTIR spectra (left) of the synthesized BG nanoparticles doped with various concentrations of Mn. XRD analysis revealed the amorphous structure of MBGNs and 5 Mn-MBGNs indicated by the broad halo in the range of 20°–34° . Adapted from [277]. Reproduced with permission from Springer.

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Table 1. Review list of metallic ions' along with their potential biological effects.

Metallic ion	Ion Function in Biological system	Ref
Ga	• alterations in the permeability of the plasma membrane as well as mitochondrial activity	[281]
	• immunosuppressive activity	[32]
	• Both in vivo and vitro, it's indeed effective for the treatment of hypercalcaemia associated with tumour malignancy in the bones.	[270,271]
	• inhibits bone resorption and lowers concomitant elevated plasma calcium	[284]
	• significantly reduces concomitantly increased plasma calcium and prevents bone resorption	
	• inhibit Pseudomonas aeruginosa, Staphylococcus aureus methicillin-resistant, and Clostridium difficile in vitro	[236,273]
	• anti-inflammation properties	[11,27] [29.274]
Bi	• prevents tumour development (possibly anticancer action against malignant tumour cell lines), as well as lymph node metastases	[287]
	• Bi-TPC, a water-soluble bismuth cyclen-based drug, has anticancer effects 100 times stronger than cisplatin, owing to interactions with DNA under physiologically specific conditions	[288]
	• In vivo studies indicate bismuth oxide has proven cytotoxicity as well as antimicrobial activity.	[289]
	• proved successful in treating *H.pylori* infection by inhibiting metallo-B-lactamase through replacing the Zn(II) cofactor.	[290]
	• dental repairing applications	[291]
	• development of dextran-coated bismuth/iron oxide nanostructures in Mr applications	[292]
	• drug delivery system	[293]
	• Bismuth salts are being used to produce numerous complexes/medicines to treat gastrointestinal disorders like peptic ulcers (for example colloidal bismuth subcitrate (CBS), bismuth subsalicylate, and bismuth subnitrate), dyspepsia (bismuth subsalicylate, bismuth subnitrate, etc), elimination of *H. pylori*, or even other tumours and diarrhoea (bismuth subsalicylate, bismuth nitrate etc) used in radiotherapy for their exceptional antitumor properties	[294]
	• relieves gastritis and reduces inflammation	
	• It was reported to be a far more effective antiulcer agent because it contains ranitidine, an H2- receptor antagonists that suppresses the secretion of excessive stomach acid.	
	• used for a tissue engineering application	[45,281]
	• Bismuth thiolates are a type of antimicrobial (antibacterial, antileishmanial, anticancer, antiviral, and antifungal) agent that is frequently used.	[296]
	• Bismuth-based compounds as well as associated metallodrugs have the ability to be a new category of MBL inhibitors..	
	• BiZn, a bismuth-citrate-based complex, has the ability to mimic the formation of antioxidative biomolecules.	[297]
		[298]
		[299]

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		[300]
Mg	• Because of its association with phosphate ions, it is important for living cells (ATP) • It acts as a coagulant. • usually exists as a chelate in cells • cofactor for a variety of enzymes (catalytic action) • in vitro/in vivo modulation of new bone tissue growth and osteoblastic cell adhesion • Antacids	[60] [67] [301] [65] [63] [302]
Ca	• Bone contains 99 percent of the calcium in the body. • Forms hydroxyapatite when combined with phosphate • Behave as an ionic messenger • act as a signal for a variety of cellular processes • In vitro, it monitors neurite elongation and growth cone motility • Triggered bone cell differentiation, osteoblast proliferation, bone metabolism and its mineralization • Antacids • antimicrobial properties	[69] [70] [301] [82] [71] [303] [304] [305]
Ge	• antibacterial, antiviral, anti-inflammatory, anticancer or antitumor functions, as well as eradication of the free radicals, anticipation of cell aging, regulation of immunity • Spirogermanium have antitumor, antiarthritic, antimalarial and immunoregulatory activities (by inhibiting the synthesis of DNA or RNA and enhancing the immune responses) • play biologically important roles in lymphocyte atrophy or degeneration, as well as nucleus fragmentation and suppress protein synthesis as well as the growth and proliferation of *Fusarium*, *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*, and thus play a significant role in cell lysis. • As a protective agent • It acts as an antioxidant. The beneficial radio-protective function of this antioxidant agent is shown by the germanium L-cysteine a-tocopherol complex. • Activating the hematopoietic system. Increase oxygen uptake in the blood, which can be mixed with blood cells and absorbed directly by blood vessels, promoting RBC production. • Ge-132 controls hematopoietic activity in the body by increasing the expression of cell stimulating factor IL-3 in multifunctional hematopoietic stem cells (HSCs) and by controlling the differentiation and proliferation of multifunctional hematopoietic stem cells (MHSCs) and progenitor cells.	[306] [307] [93,96] [91] [92.93]. [66] [306]
Cr	• MRI contrast agents • Help for better glucose and insulin regulation that is both safe and economical • Mutagenicity triggered by metabolism of Cr(VI) by a biologically reducing agent is dominated by Cr(III)-DNA adducts.	[105]

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		[112]
		[124]
		[308]
	• has a small therapeutic index, meaning there isn't much space between therapeutic and toxic thresholds.	[119]
	• Lithium levels can influence dermatological effects.	
	• a long-term successful therapy for decreasing the risk of mortality and morbidity in people with bipolar disorder (expected higher overall mortality in patients with mood disorders using lithium is decreased)	[123]
	• Lithium acts synergistically with signal transduction via G-protein-coupled receptor (GPCR) routes or through inhibiting particular targets in signalling systems such as inositol monophosphatase and glycogen synthase kinase-3 (GSK-3)	
Li	• N-methyl-D-aspartate receptor (NMDAR)/nitric oxide (NO) signalling can activate certain lithium-induced responses in the brain and peripheral tissues (antidepressant actions of lithium in the FST, its effects on cognitive performances like memory, several animal models of BPD, PPI of the auditory startle response, and seizure threshold).	[119]
	• lithium's antiviral and immunomodulatory effects	
	• neuroprotective properties	
	• Lithium-associated hypercalcemia/hyperparathyroidism is done in the same manner as primary hypercalcemia/hyperparathyroidism..	
	• promotes in wound healing	[116]
	• seems to have anti-inflammatory properties	[132]
		[129,130]
		[124], [309]
		[136]
	• Dramatically lower blood pressure (BP) both in hypertensive and nonhypertensive patients in a dose-dependent fashion	[134]
	• A 10-mmol rise in daily potassium consumption resulted in a 40% decrease in stroke-related mortality.	
	• The OGR7 receptor on osteoblasts detects acid levels, causing intracellular Ca^{2+} liberation and thus receptor activator of nuclear factor kB ligand expression, that leads to bone resorption.	[310]
K	• It's also been shown that increasing potassium consumption reduces the chance of kidney stones.	[311]
	• The DASH (Dietary Approaches to Stop Hypertension) research found that increasing dietary potassium (even decreasing calcium) decreased blood pressure, urinary calcium excretion, and bone resorption in the immediate future, and a longer-term DASH/osteoporosis mitigation research is now desperately needed.	[300-301]]
	• keep an electrolyte balance	
	• function in nerve functioning	[135]
		[137]
		[140]
	• retained as in skeleton through exchanging with Ca^{+2} in the hydroxyapatite crystal lattice, generally in current trabecular tissue, with differences depending on skeletal location (Sr+2 material rises with in diaphysis of femur, lumbar vertebra, as well as iliac crest)	
Sr	• Improved bone growth and decreased bone resorption among normal animals and humans, resulting in increased bone density and improved mechanical properties.	
	• Increased differentiation & role of osteoblasts, reduced differentiation & functionality of osteoclasts, and disturbance of actin cytoskeleton organisation	[146]

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		[147]
		[310]
		[244]
		[173]
B	• Increases TNF-alpha release by modulating ECM turnover. • The influence of boron on healing process seems to be indirect, resulting from the fabrication of wound-healing cytokines (that is TNF-alpha) or even the free radical formation (or even other compounds) and indeed the stimulation of transcription factors like NFk*B*. • TNF-alpha is the most common form of tumour necrosis factor (TNF-alpha). VEGF, a powerful angiogenic factor, is most likely to be induced. • The effects of B-nHAp, nHAp composites, as well as boric acid on bone cells were explained using molecular pathways. Wnt and TGF signalling pathways were affected by B-nHAp composites, therefore stress response was increased. • As a result, B-nHAp may be a potential candidate for bone tissue regeneration. WTIP gene expression is linked with stress response, and B-nHAp composites enhance it. B-nHAp composites also influence cell differentiation (GO:0030154), Wnt and TGF signalling pathways (P00057 and P00052, respectively), and stress response (GO:0006950) • B might benefit with improvements in certain biochemical parameters in experimental diabetes. • MC3T3-E1 cells' osteoblastic activity is regulated • Boronated compounds were shown in vitro and in vivo for being effective anti-osteoporosis, anti-inflammatory, hypolipemic, anti-coagulant, and anti-neoplastic agents.. • B interacts with several other essential vitamins and minerals, like calcium, magnesium, & vitamin D, as well as hormones that seem to be essential for bone growth, to play a significant role in bone metabolism. Bone morphogenetic proteins (BMPs) are multi - functional growth factors that belongs to transforming growth factor b (TGFb) superfamily and facilitate bone and cartilage development. • Glu-BSH tended to be superior to BSH in terms of increased tumor:normal tissue ratios and an increased tumor: blood ratio. • Albumin-linked functionalized dodecaborate became successful in cancer therapy and improved effectiveness towards subcutaneous implants of murine C26 colon carcinoma after intravenous administration. • • effective for extracranial tumours including head/ neck cancer and melanomas as just a transmission agent	[156] [153,314] [315] [163] [10,11] [173] [159] [316]
		[163]
		[316]
Ag	• exhibits antibacterial property • attachment with microbial DNA (prohibiting replication) or sulfhydryl classes of bacteria enzymes (inhibiting cell respiration and hindering essential substances from being transported through the cellular membranes and inside the cell) • breast cancer cell lines be repressed • development of bioactive and antimicrobial bone implants	[317] [318]`

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	• possesses wound healing activity	[193] [319] [189]
Zn	• The zinc ion (Zn^{+2} with copper) is a part of superoxide dismutase (SOD) and helps in an increase in aminoacyl-tRNA synthetase activity • It's attributed to growth hormone (GH) or insulin-like growth factor 1 in bone metabolism (IGF-1) • The relative extent of zinc-induced DNA increase appeared close to the relative extent of zinc-induced ALP activity increase since zinc was added to tibial cultures • promotes neural development • improving osteoblast differentiation to promote bone development • Boosts Runt-related transcription factor 2, which is believed to be a bone-forming stimulant. • exhibits anti-inflammatory properties. • prevents bacterial development and facilitates wound healing at the surgical site	[320] [321] [16] [197] [187,322] [323,324] [207][209] [207]
Fe	• Iron-containing biphasic scaffolds (ferrogels) for muscular TE • In leukemia, the expressions of certain iron metabolism-related proteins are abnormally regulated, and iron alters a number of signalling mechanisms and physiological processes, indicating the crucial role of iron in cancer growth. • USPIOs improve drug delivery, gene therapy, radiosensitization, MRI-assisted radiation therapy preparation, tissue regeneration, detoxification, & magnetic fluid hyperthermia targeting. • Ferumoxytol is a drug that is being used to treat anaemia in chronic kidney disease patients. • M1 macrophages, which are both pro-inflammatory and anti-tumor; and M2 macrophages, which are both anti-inflammatory and pro-tumor. • Magnetic drug targeting is commonly used to improve the aggregation as well as effectiveness of iron oxide nanoparticles that are being filled with chemotherapeutic agents. • induces various types of programmed cell death, such as ferroptosis. Many biological processes, such as oxygen delivery, energy production, and DNA synthesis, involve iron. • DFO in the suppression of bone formation caused by iron overload. Furthermore, DFO therapy reduced the downregulation of osteoblast-specific genes that occurred during FAC treatment. DFO was shown to be effective in treating iron-related bone formation inhibition.. • possess antimicrobial properties	[204,211]] [325] [326] [212] [315-316] [329] [330] [210]
Co	• a component of vitamin B12 that aids in the development of red blood cells • trigger hypoxia inducible factor-1 (HIF-1) in mesenchymal stem cells, which then activates HIF-a target genes including VEGF, EPO, and p21. • Hypoxia-treated bone marrow stromal cells (BMSCs) were successfully used in animal studies to help re-vascularize ischaemic or infracted muscles. • upregulation of pro-angiogenic growth factors (VEGF) expression in various cells, particularly BMSCs • Antitumor as well as antioxidant properties • act as an antibacterial agent • antiviral properties	[229] [222,319] [231] [222.320]

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	• • provide hypoxic tumour cells as a target for cytotoxicity	[223,233] [232]-227] [219] [231]]
Cu	• Act as a stimulant for proliferation of human endothelial cells • in vitro, it's a component of super oxide dismutasa (SOD), lysyl oxidase, ceruplasmin (CP) and cytochrome c oxidase (COX) • inhibiting DNA synthesis and altering its 3D structure Protein synthesis can be altered. Several enzymes have been shown to be inhibited (such as ATPase, DNA polymerases, ribonucleotide reductase and tyrosine-specific protein phosphatase) • regulation of human mesenchymal stem cellular proliferation and differentiation into osteogenic lineage • intending for developing cells to release growth factors and cytokines • antibacterial effects (Staphylococcus epidermis) • participates in the operation of a number of transcription factors (both through HIF-1 and proline hydroxylase) and binds to the cell membrane, generating a complex • activation of endothelial growth factor and increased angiogenesis stimulation in combination with FGF-2 • MRI contrast agents • Anti-tumor, Antioxidant, as well as DNA-binding properties • possess anticancer properties	[249] [252] [316,308] [334] [250] [235-236] [245-247]] [335] [319,324] [337] [248,326]
Mn	• a cofactor for a wide range of enzymes (oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases, lectins, integrins and glutamine synthetase). Superoxide free radical detoxification is impossible without it. • MRI contrast agents • • antibacterial and bio-tolerant properties	[262] [2] [265]

3. Results

The above discussion is a clear indication of the importance of metallic ions in biological research. Ranging from anti-allergy to anti-cancer all types of treatments, cures, and breakthroughs are possible in the research world of metallic ions. These ions find the profound potential of growth in the field of tissue engineering, due to their therapeutic abilities especially targeted delivery to the site of injury. The general advantages which attract attention for more application-oriented research are the low-cost, higher safety, availability, and stability of ions. These ions and their complexes can stabilize, modulate, destabilize, inhibit and transform biological molecules, altering the behavior and nature of their function. The efficacy of these metallic ions is extremely dependent on the mutual compatibility of the ions and the matrix in which they are doped. In the right compositions, they can produce synergistic effects and generate 100% results. The benefits of these ions are well-known however, the exact nature of their performance and the mechanisms are still partly vague and have not been studied with concrete evidence. Through this review, we have aimed to highlight the new era of therapeutic biomedicine and encourage development and in vivo research for the systemic toxicity, mechanism of action, efficacy,

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scaffold-ion relationship, and other realms of metallic ion therapy which lack explicit evidence still.

4. Future Prospective

Metals in medicine are bridging the gap between inorganic and organic chemistry. The synthesis, structure, and general properties of metal-based materials, metallodrugs, and agents for treatment and detection of diseases, as well as biomedical applications on cellular and living systemic levels, are indeed critical. These metal compounds' mechanisms of action and functions in cellular control and signaling in health and disease are of particular concern. There is a need for researchers with a detailed understanding of inorganic chemistry to engage in medically applicable research ties these fields together. This special issue contains a series of papers on various compounds/materials that have been studied for antitumoral, antimicrobial, and antifungal activity, along with DNA binding.

Metal ions have long been used in medicine. The development of better predictive methods for metal-based bioactive drugs is one of the field's challenging issues. Most metal ions are often not essential nutrients, but they're still pretty popular components of diagnostic and therapeutic agents used to research and cure a wide range of diseases and metabolic disorders. The list of metal ions that qualify for critical status is still being compiled; it encompasses not only anticipated members like zinc, copper, and manganese, but also those that were previously considered to be toxic, like selenium and molybdenum. Arsenic, nickel, silicon, and vanadium are among the surprising choices on the “possibly essential” list.

While it is unlikely that these metal ions will be deficient in the general population, it is conceivable that they may have harmful physiological effects in severe circumstances. Toxicology has no counterargument to essentiality and vice versa. Metal ions induce responses in biological systems that vary from deficiency to toxicity. The threshold for toxicity, whether necessary or not, maybe very low. One of its difficulties in developing metal-based drugs is balancing the possible toxicity of an active formulation with the significant benefits of these highly used therapeutic and diagnostic aids. For metal-based therapeutics or diagnostics, tissue targeting is a pretty valuable objective. As a consequence, proper metal-based therapeutic dosages must be precisely described. Metal ions found inside well-designed molecules are indeed a huge help to the medicinal pharmacopeia. Transition metal complexes' therapeutic applications are an undeveloped field of research with plenty of space for advancement. Biologists, material scientists, pharmaceutical technologists, tissue engineers, and biomedical researchers are expected to collaborate on much of the work. The review's ultimate goal was to promote research that bridged the gap between materials chemistry and medicine to build innovative therapeutic approaches based on regulated metal ion release in the biological system. For decades, there has been empirical proof of the efficacy of metal-based therapies; theoretical understanding will inevitably follow. Metal ions are needed in biology, but their function as pharmaceutical drugs is quite well known. Pt (cisplatin) and Au (auranofin), mainly two drugs based on metals with no known biological activity, are commonly used to treat genitourinary and head and neck tumors and rheumatoid arthritis, respectively. Furthermore, radioactive metal ion compounds such as 99mTc and paramagnetic metal complexes such as Gd(III) are now commonly used as imaging agents for disease diagnosis. Many patients admitted to a hospital in the United States for the night will be given a 99mTc compound injection for radio-diagnostic purposes. Despite the apparent success of metal complexes as diagnostic and chemotherapeutic agents, several pharmaceutical or chemical companies have serious in-house research programs focused on these critical bioinorganic aspects of medicine.

Conflicts of Interest: The authors declare no conflict of interest.

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