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Fabrication, Properties, and Biomedical Applications of Calcium-Containing Cellulose-Based Composites

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Calcium-containing cellulose-based composites possess the advantages of high mechanical strength, excellent osteoconductivity, biocompatibility, biodegradation, and bioactivity, which represent a promising application system in the biomedical field. Calcium-containing cellulose-based composites have become the hotspot of study of various biomedical fields. In this mini-review article, the synthesis of calcium-containing cellulose-based composites is summarized via a variety of methods such as the biomimetic mineralization method, microwave method, co-precipitation method, hydrothermal method, freeze-drying method, mechanochemical reaction method, and ultrasound method. The development on the fabrication, properties, and applications of calcium-containing cellulose-based composites is highlighted. The as-existed problems and future developments of cellulose-based composites are provided. It is expected that calcium-containing cellulose-based composites are the ideal candidate for biomedical application.

Keywords: cellulose, composites, hydroxyapatite, calcium carbonate, biomedical application

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1 INTRODUCTION

Cellulose received considerable attention due to its properties of mechanical strength, biocompatibility, and biodegradation and its wide applications in clothing, paper, biofuel, and biomedical fields (Eichhorn *et al.*, 2010; Moon et al., 2011; Huang et al., 2020,2022; Wang et al., 2021; Kang et al., 2022). There are more than 30,000 studies that used "***cellulose***" as the "***title***" on the Web of Science over the last 10 years, indicating that cellulose has become a hot research topic. Calcium-containing inorganic functional materials mainly included hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, HA), $CaCO_3$, calcium silicate, and $CaSO_4$ (Tran and Webster, 2009). HA is used in the fields including drug delivery, toothpaste additive, and dental implants because of its biocompatibility, bioactivity, and biological properties (Suchanek and Yoshimura, 1998; Chu et al., 2002; Ma et al., 2006; Ma and Zhu, 2009; Ma, 2012). Moreover, carbonated hydroxyapatite (CHA), containing carbonate ions of 6~8 mass%, shows high bioactivity in comparison to that of HA (Gibson and Bonfield, 2002; Landi et al., 2003; Morales-Nieto *et al.*, 2013). $CaCO_3$ is abundant in organisms (Politi et al., 2004). The calcium-containing cellulose-based composites combined the characteristics of cellulose and calcium-containing inorganic materials, producing new properties by synergistic effect

(Hokkanen et al., 2016). Therefore, it is expected that calcium-containing cellulose-based composites meet the requirements of applications. As early as 2010, the progress in the fabrication of calcium-based inorganic biodegradable nanomaterials was reviewed by Ma and Zhu (2010). Qi *et al.* (2018) reviewed the synthesis and properties of calcium-based biomaterials for diagnosis, treatment, and theranostics. In the previous review study, we summarized the recent development of multifunctional cellulose and cellulose-based nanocomposites adsorbents (Shi et al., 2022).

In recent years, there are rapid demands for biomedical materials (Habraken et al., 2016; Hu et al., 2018; Fu et al., 2019c; Yi et al., 2020; Yuan et al., 2021). For example, the disabled and bone injury patients need a lot of bone repair materials, the patients with cardiovascular disease need artificial heart valves, and the patients with renal failure need kidney dialyzers. It was reported that the composites, consisting of inorganic materials such as HA, $CaCO_3$, calcium silicate, SiO_2, and polymer including collagen, chitosan, chitin, hyaluronic acid, cellulose, poly lactic acid (PLA), poly glutamic acid (PGA), and poly caprolactone (PCL), were the new generation biomedical materials in the 1990s, which had the features of bioactivity and biodegradability to meet the clinical needs (Kaur et al., 2015; Liu et al., 2020). Chan *et al.* (2002) reported the synthesis of polypropylene/calcium carbonate nanocomposites. In fact, it is believed that cellulose is an organic biomedical material, meanwhile, calcium-containing inorganic functional composites are inorganic biomedical materials. The calcium-containing cellulose-based composites are promising biomedical materials to meet the requirements of applications (Oprea and Voicu, 2020).

This current mini-review study gives an overview of the synthesis, properties, and applications of calcium-containing cellulose-based composites. In section two, various methods including the biomimetic method, the microwave method, the co-precipitation method, the hydrothermal method, the freeze-drying method, the mechanochemical reaction method, and the ultrasound method were summarized for the synthesis of calcium-containing cellulose-based composites. In section three, the properties of calcium-containing cellulose-based composites such as mechanical properties, degradation, bioactivity, biocompatibility, feasibility, viability, cytocompatibility, cell-guiding property, antibacterial properties, and ion-exchangeability were also reviewed. In addition, the applications of these composites were described in the tissue engineering scaffolds, histological, drug delivery, and wastewater treatment. Finally, the future developments of calcium-containing cellulose-based composites were suggested.

1.1 Synthesis of Calcium-Containing Cellulose-Based Composites

1.1.1 Biomimetic Mineralization Method

Biomineralization refers to the generation process of inorganic minerals by the biological macromolecules of the organism (Addadi, Raz, and Weiner, 2003). In comparison to general mineralization, the process of biomineralization involved the biological macromolecules, cells, and organic matrix (Gower, 2008). Based on the biomineralization mechanism, the biomimetic synthesis method is an important route for creating biomedical materials by imitating the synthetic process of natural reaction and structure (Dorozhkin, 2011). The biomimetic synthesis method was developed to fabricate biomedical materials (Tas, 2000). Addadi, Raz, and Weiner (2003) reviewed the amorphous calcium carbonate by the biomineralization method.

Fang *et al.* (2009) prepared bacterial cellulose (BC)/HA nanocomposite scaffolds *in vitro* biocompatibility by the biomimetic technique. As for the fabrication of cellulose/HA composites via the biomimetic method, Wan and coworkers had done system work. In 2006, they developed the biomimetic precipitation of CHA with low crystallite size and crystallinity on BC from simulated body fluid (SBF) (Hong et al., 2006). Then, the biomimetic method was reported to synthesize CHA/BC composites by soaking phosphorylated and $CaCl_2$-treated BC fibers in the SBF (Wan et al., 2006). After that, they applied the biomimetic method to fabricate CHA/BC nanocomposites with a three-dimensional (3D) network and crystallinities below 1% (Wan et al., 2007). It found the formation of HA on BC in the existence of phosphorylation. Furthermore, HA/BC nanocomposites were also carried out via the biomimetic route (Zhang et al., 2009). It carried out the growth of calcium phosphate via phosphorylation reaction.

Generally, HA has a ratio of 1.67 for Ca/P. However, calcium-deficient HA is always obtained with a ratio of Ca/P below 1.67 in nature. Hutchens *et al.* (2006) first synthesized calcium-deficient HA in the BC hydrogel. BC was used as a template for the biomimetic fabrication of apatite. Shi *et al.* (2009) synthesized calcium-deficient HA/BC nanocomposites with improved mineralization efficiency by combining the alkaline treatment and biomimetic mineralization process. Zimmermann and coworkers (Zimmermann et al., 2011) designed calcium-deficient HA/BC nanocomposites using the biomimetic approach in dynamic SBF for bone healing applications. Hammonds *et al.* (2012) prepared calcium-deficient HA/BC composites.

It reports that SBF is a very important media for the formation of HA during the process of biomimetic mineralization. The synthesis of cellulose fabrics with hydroxy carbonated apatite using the biomimetic method in SBF was reported by Hofmann *et al* (2006). Cromme et al. (2007). In Cromme's study (2007), regenerated cellulose (RC) films were obtained with hydrochloric acid vapors, in which the calcium phosphate was formed in SBF. Yin *et al.* (2011) prepared HA/BC nanocomposites by the biomimetic mineralization method. It found that CHA nanorods were grown *in vitro* along with the network of BC via the dynamic SBF treatment. Rodriguez, Renneckar, and Gatenholm (2011) used the electrospinning method to produce cellulose acetate (CA) scaffolds. Li *et al.* (2012) synthesized electrospun cellulose nanofiber (CNF)/HA composites with micro-, meso-, and macro-pores in SBF. It achieved the growth of HA along the fibers in the composites. Petrauskaite *et al.* (2013) developed biomimetic mineralization using the cellulose porous matrix in the SBF solution. It achieved

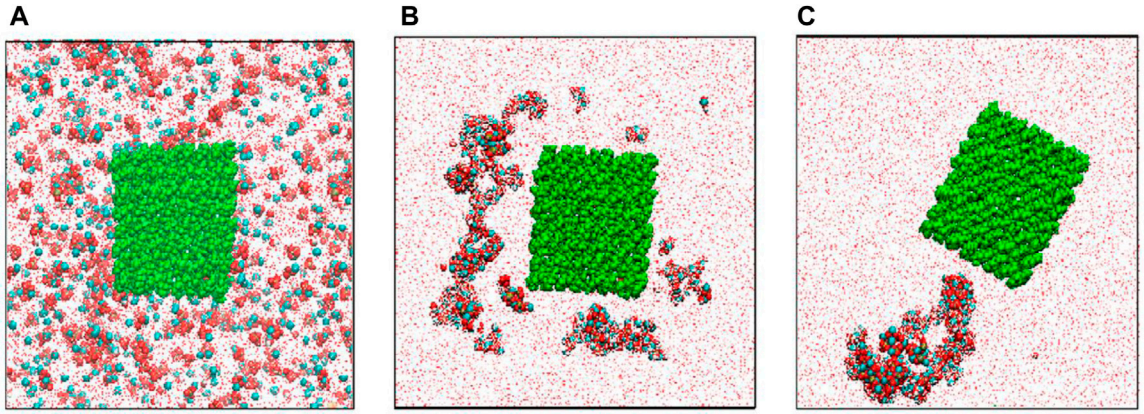

FIGURE 1 | Distributions of ions in the modeling cell: **(A)** in the initial state, **(B)** in 12 ns, and **(C)** at the end (100 ns) of simulation. Red balls-O atoms, cyan balls-Ca^{2+} ions, yellow balls-P atoms, white balls-H atoms, green balls-cellulose atoms (Lukasheva and Tolmachev, 2016).

the improved cell adhesion and growth rate on the porous cellulose matrix. Garai and Sinha (2014) reported the biomimetic synthesis of 3D micro/macro CMC/HA nanocomposites. 3D nanocomposite structures were due to the ionic/polar or electrostatic interactions of HA impregnated CMC matrix. It obtained compressive strength of 1.74–12 MPa and a compressive modulus of 157–330 MPa.

Lukasheva and Tolmachev (2016) presented biomimetic synthesis and molecular dynamics simulation of HA/BC nanocomposites. The CP crystals nucleate initially in solution, and then adsorbed on the surfaces of BC nanofibrils (**Figure 1**). Yang *et al.* (2016) applied the biomimetic process to prepare oxidized BC/HA/gelatin nanocomposites with the 3D network for a potential bone scaffold material. The nanocomposites have a tensile strength of 0.3 MPa and a complete degradation time of approximately 90 days in SBF. Kim *et al.* (2018) fabricated 3D pore-structure biomimetic cellulose/calcium-deficient HA composite scaffolds for bone tissue engineering. It found bone mineralization in the composite scaffold via cellular responses using preosteoblasts (MC3T3-E1). Liu *et al.* (2019) used BC hydrogel to synthesize biomimetic multilevel HA. It observed the weak coordination between the hydroxyl groups of BC molecule with Ca^{2+}. Okuda *et al.* (2022) applied the biomimetic approach to preparing the CMC/HA composites with a stable interface. It achieved the flexural strength of 113 ± 2 MPa and the elastic modulus of 7.7 ± 0.3 GPa. It found an ionic interaction between Ca^{2+} and COO-.

Li and Wu (2009) reported the monodisperse rosette-like calcite mesocrystals in CMC by the biomimetic gas-diffusion method. Xiao *et al.* (2011) prepare calcium carbonate on RC fibers in ethanol-water mixed solvents by the mineralization method. It found that twin-sphere-based vaterite, zonary, and rod-like calcite were embedded in fibers. Liu *et al.* (2011) used electrospun CA fibers modified by poly acrylic acid (PAA) as scaffolds for the mineralization of $CaCO_3$. It showed the calcite film coatings with needle-like shapes on the surfaces of CA fibers. The carboxylic groups of acidic PAA molecules interacted with the OH moieties of CA, then bent with Ca^{2+} ions on the surfaces of CA fibers. Rauch *et al.* (2012) synthesized calcite with minor fractions of aragonite on and in RC gel membranes by a diffusion-driven mineralization approach. The experimental result indicated that the calcium carbonates were assembled from building blocks. Liu *et al.* (2013) fabricated BC/lamellar $CaCO_3$ hybrid induced by egg white *in situ* by the biomimetic mineralization method. The hybrid had a rough surface and an elaborate 3D structure with controllable porosity. Vyroubal *et al.* (2013) fabricated $CaCO_3$ in BC by the biomimetic method. Paulraj *et al.* (2017) used $CaCO_3$ as a template to fabricate microcapsules with controllable permeability properties by the layer-by-layer method in plant polysaccharides of pectin, cellulose nanofibers, and xyloglucan. It obtained the spherical $CaCO_3$ with 16 ± 4 μm (**Figure 2A**), the $CaCO_3$ $(AP/CNF)_5AP/XyG$ microparticles with a thickness of ~60 nm (**Figures 2B, C**), and hollow microcapsule structures after complete core removal (**Figure 2D**).

The biomimetic mineralization method was widely used to synthesize biomaterials, induce bioactive materials, and investigate the synthetic mechanism. However, it needs long reaction times, complex reaction procedures, and precise control conditions. Recently, Qi *et al.* (2019) used the biomolecule-assisted green method for the synthesis of nanostructured calcium phosphates and investigated their biomedical applications.

1.1.2 Microwave-Assisted Method

The microwave-assisted method is a greener technology due to its characteristics of reduced energy consumption, short reaction time, and high yield (Zhu and Chen, 2014). Over the past years, the microwave-assisted method was used to fabricate metals, metal oxides, and metal sulfides (Ma et al., 2014; Meng et al., 2016). In the several review articles, one can find the applications of the microwave-assisted method (Tsuji et al., 2005; Polshettiwar et al., 2009; Baghbanzadeh et al., 2011). For example, Tsuji *et al.* (2005) reviewed the development of the microwave-assisted synthesis of metallic nanostructures in solution. Polshettiwar *et al.* (2009) described the applications of the rapid and sustainable microwave-assisted route to synthesize organics and nanomaterials.

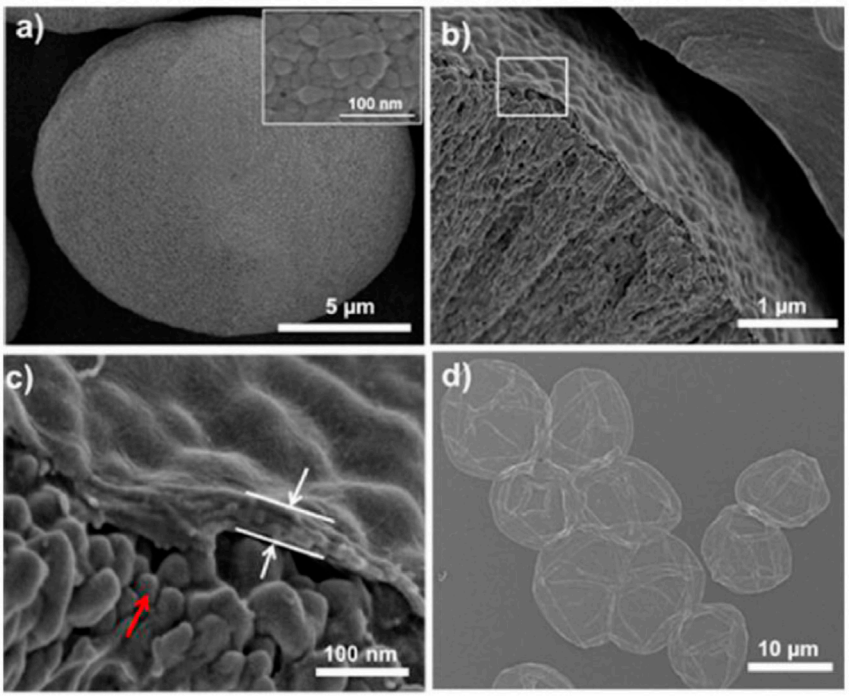

FIGURE 2 | The SEM images of **(A)** spherical $CaCO_3$ microparticles. The inset: details of the $CaCO_3$ surface. **(B)** Cross-section of $CaCO_3$ $(AP/CNF)_5AP/XyG$ microparticles, and **(C)** is a higher magnification of **(B)**. The red arrow points to the surface morphology of $CaCO_3$ microparticles. The white arrows point to the AP/CNF multilayer. **(D)** The SEM image of $(AP/CNF)_5AP/XyG$ microcapsules after core removal (Paulraj et al., 2017).

In the earlier studies, the cellulose/HA nanocomposites were fabricated by the microwave-assisted method (Ma et al., 2010). It found the homogeneous dispersion of HA nanoparticles with a narrow size distribution in the cellulose matrix. The cellulose/CHA nanocomposites were also obtained via the microwave-assisted method in the NaOH/urea solution (Jia et al., 2010b). The cellulose/CHA nanocomposites with a rough surface and aggregated CHA nanorods were also carried out in ionic liquid (IL) by the microwave-assisted method (Ma et al., 2011). It noted that F-substituted HA could enhance the acid resistance and stability of HA. The cellulose/F-substituted HA nanocomposites were also obtained in ILs via the microwave-assisted method (Jia et al., 2012a). It found the increased number of F-substituted HA with increasing heating time. The lignocellulose/HA nanocomposites were also carried out via the microwave-assisted rapid synthesis method (Fu et al., 2015). Both the morphologies and sizes of HA in the nanocomposites were adjusted via heating time. Fu *et al.* (2016) developed the microwave-assisted hydrothermal method for the synthesis of cellulose/HA nanocomposites using sodium dihydrogen phosphate dihydrate or adenosine 5-triphosphate disodium salt, creatine phosphate disodium salt tetrahydrate, or D-fructose 1,6-bisphosphate trisodium salt octahydrate. All the phases, sizes, and morphologies of the nanocomposites were affected by phosphate sources. It obtained various HA morphologies of nanorods, pseudo-cubic, pseudo-spherical, and nano-spherical particles.

The preparation of calcium sulfate nanowires was reported by thermal transformation of calcium dodecyl sulfate in the ethylene glycol and *N,N*-dimethylformamide mixed solvents (Li et al., 2008). The synthesis of cellulose/calcite composites was group explored using alkali extraction cellulose and MCC using the microwave-assisted method (Ma et al., 2012a). It achieved composites with better crystallinity using MCC than that of alkali extraction cellulose. Moreover, it found cellulose fibers and $CaCO_3$ particles using alkali extraction cellulose, and irregular cellulose and $CaCO_3$ microspheres using MCC. The cellulose/$CaCO_3$ nanocomposites were formed in the alkali extraction of cellulose by the microwave-assisted IL method (Ma et al., 2013). IL acted as the solvent for absorbing microwave, dissolving cellulose, and synthesizing cellulose/$CaCO_3$ nanocomposites, and it was found that the change morphologies of $CaCO_3$ from polyhedral to cube to particle occurred with increasing cellulose concentration. Cytotoxicity experiments demonstrated the cellulose/$CaCO_3$ nanocomposites with good biocompatibility. Cheng *et al.* (2016) used the microwave method to fabricate cellulose/$CaCO_3$ composites in an IL/ethylene glycol mixed solution within 10 min. It was found that ILs favored the synthesis of composites. The microwave IL method was reported for the fabrication of cellulose/calcium silicate nanocomposites in ethylene glycol (Jia et al., 2011a). ILs had an effect on the composite of cellulose and calcium silicate. After that, the cellulose/calcium silicate nanocomposites were obtained by the microwave method in ILs and recycled ILs (Jia et al., 2011b). Both the size and microstructure of cellulose/

calcium silicate nanocomposites were influenced by starting ILs and recycled ILs.

In general, the microwave method is green, rapid, and environmentally friendly for the synthesis of cellulose-based nanocomposites. In particular, considerable study should be carried out on the fabrication, structure, and property of cellulose/HA nanocomposites by the microwave-assisted method. This rapid microwave-assisted method is completely different from the aforementioned biomimetic synthesis method, but it could significantly shorten the reaction time and improve the reaction selectively and the yield, and be suitable for the large-scale synthesis in modern industrial production.

1.2 Co-Precipitation Method

As a traditional synthesis method, the co-precipitation method is an important strategy to obtain homogeneous composites with small size and narrow size distribution (Doerner and Hoskins, 1925; Park et al., 2003). The co-precipitation method is similar to the precipitation method, which is cumbersome and time-consuming. As early as 1925, the co-precipitation method was applied for the preparation of radium and barium sulfates by Doerner and Hoskins (1925).

Zakharov *et al.* (2005) obtained HA/CMC composites with a pore structure via the co-precipitation method for biomedical applications. Grande *et al.* (2009) synthesized the CHA/BC nanocomposite via a wet chemical precipitation method. In Kumar's study (Kumar et al., 2010), the co-precipitation method was developed for the preparation of biomimetic CMC/HA nanocomposites. Nunez *et al.* (2020) used *in situ* wet chemical precipitation technique to synthesize BC/HA nanocomposite adsorbent. It carried out a removal capacity of 192 mg g^{-1} in batch experiments and 188 mg g^{-1} in packed-bed column systems for Pb(II). Tabaght *et al.* (2021) developed a dissolving and precipitation technique for the synthesis of biocompatible HA/cellulose composite for bone substitute. Sivasankari *et al.* (2021) reported a chemical precipitation technique to prepare HA incorporated CA/polyetherimide membrane with biocompatibility for adsorption and biomedical applications. The co-precipitation method is an important route for the preparation of HA/cellulose nanocomposites. It is known that the synthesis of HA is a double decomposition reaction with rapid nucleation and growth rate. So it is not easy to obtain homogeneous cellulose/HA composites by the co-precipitation method.

Ciobanu *et al.* (2010) reported the cellulose fibers with $CaCO_3$ by the *in situ* precipitation method. $CaCO_3$ was precipitated into the lumen and wall pores of fibers by the *in situ* precipitation method. The cellulose/calcium silicate nanocomposites were carried out by the precipitation method (Li et al., 2010). Stroescu *et al.* (2012) deposed $CaCO_3$ on BC membranes using sodium dodecyl sulfate (SDS) and cetyl trimethylammonium bromide (CTAB) by a precipitation reaction. It obtained the calcium carbonate with rhombohedral and flower-like by adjusting the surfactant type and concentration. Zhu *et al.* (2020) prepared RC/calcium carbonate biocomposite films with flexibility, optical properties, mechanical strength, and thermal stability by *in situ* precipitation. It found a tensile strength of 84.7 ± 1.5 MPa for biocomposite.

1.3 Hydrothermal Method

The hydrothermal method refers to the synthesis of functional materials with water as the solvent in the vessel sealing at high temperature and high-pressure conditions. In the mid-19th century, geologists simulated the mineralization in nature and found the hydrothermal method. After 1900, the theory of hydrothermal synthesis was constructed. Then, the hydrothermal method was developed to synthesize the functional materials (Byrappa and Adschiri, 2007). It reported the hydrothermal synthesis of 0D, 1D, and 2D materials and composites (Feng and Xu, 2001).

The hydrothermal method of lignocelluloses had an effect on cellulose, hemicellulose, and lignin (Garrote et al., 1999). Jiang and Zhang (2009) prepared HA nanorods with well-controlled particle size and porosity through the hydrothermal method using phosphate ester as the structure-directing agent and sodium salt CMC as the template. The hydrothermal method was applied to prepare cellulose/CHA nanocomposites with CHA nanostructures dispersed in the cellulose matrix in a NaOH-urea aqueous solution (Jia et al., 2010a). In comparison with the biomineralization method, the hydrothermal method needs high temperature and high-pressure conditions, which restrain the wide application in the synthesis of biomedical composites. Moreover, Palaveniene *et al.* (2019) reported the hydrothermal synthesis of an osteoconductive 3D porous RC/HA composite scaffold with a porosity of 85% for bone tissue regeneration. The MG-63 cells proliferated well on scaffolds via *in vitro* cell culture. Pieper *et al.* (2020) prepared cellulose/HA biofilm with good thermal stability using a microwave-assisted hydrothermal synthesis at 140°C for 5 min.

The hydrothermal method was developed to obtain cellulose/$CaCO_3$ bio-nanocomposites with good biocompatibility in the NaOH/urea solution (Jia et al., 2012b). The urea was also used as the CO_3^{2-} source for the preparation of $CaCO_3$. Furthermore, the fabrication of wood powder/$CaCO_3$ composites was investigated by the hydrothermal method (Ma et al., 2012b). This work utilized all the main components of lignocelluloses, compared with cellulose-based composites.

1.3.1 Other Synthesis Methods

The freeze-drying method might be more suitable for the synthesis of biomedical composites, which spray the solution to the organic liquid, then freeze instantaneous, sublimate, dehydrate, and decomposed to produce the comparatively loose products. The freeze-drying method was applied to synthesize cellulose/HA composites by Jiang group (Jiang L. et al., 2008). They incorporated CMC into HA/chitosan to obtain HA/chitosan/CMC composite as 3D scaffold by the freeze-drying method. Then, they applied the freeze-drying method for the preparation of the HA/chitosan/CMC porous composite scaffolds with different weight ratios (Jiang L.-Y. et al., 2008). After that, HA/chitosan and CMC composite scaffolds with good cell biocompatibility and tissue biocompatibility were also carried out by the freeze-drying method (Jiang et al., 2009a).

Generally, the freeze-drying method has characteristics of eliminating 95–99% water, obtaining the loose and porous materials, maintaining the original structure and volume, and restraining microbial growth and enzyme function, which is widely used in the pharmaceutical industry, food industry, and biomedical fields. It noted that these are still some problems requiring improvement for this method. Moreover the requirement of expensive equipment, this method is just a means of posttreatment measure. Of course, this method always needs to combine with other synthetic methods. Chong *et al.* (2015) reported the preparation of calcite $CaCO_3$-loaded cellulose aerogel for removal of Congo Red (CR) from aqueous solution by freeze-drying. The aerogel had significantly enhanced adsorption capacity toward CR. It obtained the maximum adsorption capacity of 75.81 mg g^{-1} for the $CaCO_3$-cellulose aerogel. Narwade *et al.* (2019) used the one-directional freeze-drying technique to obtain flexible and lightweight HA/CNFs nanocomposite films. It observed the detection limit of ammonia at a concentration as low as 5 ppm, sensitivity up to 575%, and response/recovery (210/30s) for nanocomposite films.

The mechanochemical reaction method was also called the high-energy ball milling method. As an energy-saving and efficient technology for the preparation of materials, it significantly reduces the reaction activation energy, refines the grain, and enhances the bonding interface. Yoshida and coworkers (Yoshida et al., 2005) prepared the cellulose/B-type CHA composites through mechanochemical reaction. Then, they applied this method to synthesize cellulose/CHA composites with a bending streng of 10–13 thMPa and Young's modulus of 1.5–2.2 GPa (Yoshida et al., 2006). In general, the mechanochemical reaction method has the disadvantages of low efficiency and energy consumption, as a supplementary method.

The sonochemical method is a green methodology, which has characteristics of intense local heating, high pressures, and extremely rapid cooling rates (Gedanken, 2004; Bang and Suslick, 2010; Cravotto and Cintas, 2010; Chemat et al., 2011). The ultrasound had wide applications in organic and inorganic synthesis. Stoica-Guzun *et al.* (2012) investigated the $CaCO_3$ deposition on BC membranes by ultrasonic irradiation. It obtained the calcite in the presence of ultrasonic irradiation and vaterite in the absence of ultrasonic irradiation. Moreover, it found cubes of calcite to spherical and flower-like vaterite particles in the presence of ultrasonic irradiation. Fu *et al.* did a system study about calcium-containing cellulose-based composites by the ultrasound method. For example, the influences of synthesis strategies of the microwave method and ultrasound method were investigated on the $CaCO_3$ in the cellulose matrix (Fu et al., 2013a). It obtained the vaterite spheres with a diameter of about 320–600 nm by the ultrasound method. The $CaCO_3$ crystals with good biocompatibility on the cellulose substrate had biomedical applications. The growth mechanism of vaterite was explored on the cellulose matrix via the sonochemistry process (Fu et al., 2013b). It achieved the vaterite polymorph using Na_2CO_3 as a reactant in ethylene glycol in the cellulose by the sonochemistry method. Moreover, cellulose/HA nanocomposites with good cytocompatibility were obtained via the sonochemical synthetic method for application in protein adsorption (Fu LH. et al., 2019). It achieved a relatively high protein adsorption ability. Fu *et al.* (2019a) used the sonochemical method to obtain cellulose/vaterite nanospheres with a diameter of 206–246 nm. It found cytocompatibility and a relatively high protein adsorption ability for cellulose/vaterite nanocomposites. Nicoara *et al.* (2020) used the co-precipitation method and ultrasound exposure to *in situ* and *ex situ* design HA/BC/Ag composite with excellent biocompatibility, bioactivity, and antibacterial properties for tissue engineering. It carried out a homogenous porous structure and high water absorption capacity for the composites.

1.4 Properties and Applications of Calcium-Containing Cellulose-Based Composites

1.4.1 Properties and Applications of Cellulose/Hydroxyapatite Composites

It has been accepted that cellulose/HA composites are promising bone substitutes. Therefore, it is very important for cellulose/HA composites to have mechanical properties analogous to natural bone. Yoshida *et al.* (2006) synthesized cellulose/CHA composites with good mechanical properties and bioactivity through mechanochemical reactions. Pure CHA had a density of 1.26 g cm^{-3}, bending strengths of 5.4 MPa, and Young's modulus of 1.58 GPa. However, the cellulose/CHA composites displayed a density of 1.59 g cm^{-3}, bending strengths of 13.0 MPa, and Young's modulus of 2.18 GPa. By immersing in SBF for some time, HA with low crystallinity was carried out at the surface of cellulose/CHA composites, displaying good bioactivity. Undoubtedly, all the mechanical properties, bioactivity, and high chemical durability are very important for cellulose/CHA composites to use as bioactive bone substitutes.

As for HA/chitosan/CMC composites, Jiang and coworkers did system research on the mechanical property, swelling behavior, degradation, and bioactivity. Jiang L. Y. et al. (2008) prepared HA/chitosan/CMC composites by the freeze-drying method. It was found that the HA/chitosan/CMC composites with 30 wt% CMC had a pore size of 100–500 μm and porosity of 77.8%, the compressive strength of 3.54 MPa, and bioactivity *in vitro* in the SBF soaking. Then, the HA/chitosan/CMC composites with high bioactivity and adjustable biodegradation rate were carried out by the cosolution method (Jiang et al., 2009b). It achieved the value compressive strength of 85.03 74.91 MPa in the HA/chitosan/CMC composites for weight ratios of 70/15/15, compared with that of HA/chitosan (61.26 MPa). After that, they also prepared HA/chitosan/CMC composite membrane with the highest tensile strength of 40 MPa by self-assembly of static electricity. By soaking in 1.5 SBF, it observed the increased number of apatite particles on the surface of the HA/chitosan/CMC composite membrane. Generally, it is agreed that the HA/chitosan/CMC composites with mechanical properties, swelling behavior, adjustable degradation, and high bioactivity had applications in bone tissue regeneration.

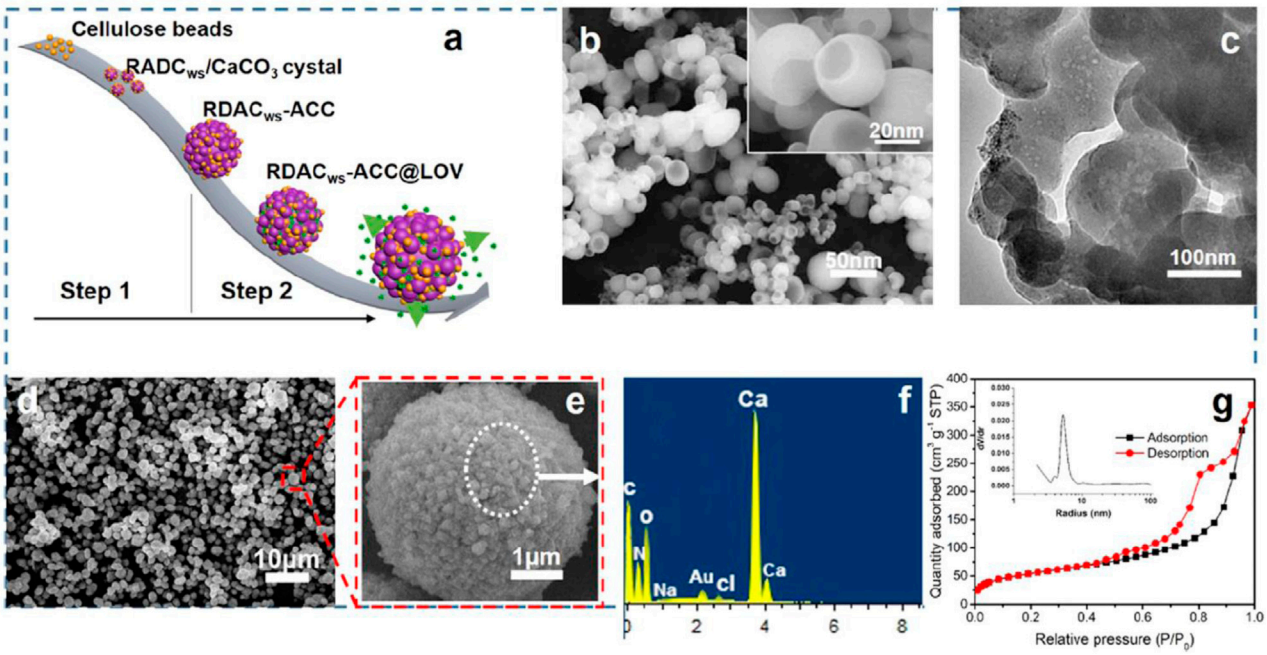

FIGURE 3 | (A) Schematic illustration for the preparation of $CaCO_3$ microspheres and drug loading and release procedures, **(B)** The scanning electron microscopy (SEM) image of the hollow cellulose-based NPs (DACws after aging for 10 days at 60 °C) and the corresponding magnification diagram (inset), **(C)** the transmission electron microscopy (TEM) image of the hollow cellulose-based NPs, **(D)** the SEM image of $CaCO_3$ microspheres with hollow cellulose-based NPs as the template, **(E)** the corresponding enlarged image of the $CaCO_3$ microspheres, **(F)** the corresponding energy-dispersive X-ray spectroscopy (EDS) pattern of the particles, and **(G)** the corresponding N_2 adsorption-desorption isotherm and pore size distribution (inset) of $CaCO_3$ microspheres (Yan et al., 2019).

1.4.2 Biological Properties as Tissue Engineering Scaffolds

Grande *et al.* (2009) prepared BC/calcium-deficient HA nanocomposites with biocompatibility and cell viability by a precipitation method. It found the cell viability of 97.2% for HEK cells in the BC/calcium-deficient HA nanocomposites, more than that of BC (86.8%). They suggested that all pore sizes, fiber diameter, and chemical bond of HA in nanocomposites influenced the cell viability of HEK cells. Saska *et al.* (2011) prepared biocompatible BC/HA nanocomposite membranes with biological properties for bone regeneration by *in vivo* tests. At 4 weeks, BC/HA composites displayed newly formed bone with several osteocytes, blood vessels, and bone matrix filled in bone defects. It found HA of low crystallinity with a Ca/P molar rate (1.5) similar to that of physiological bone.

Tazi *et al.* (2012) used BC scaffold to support osteoblast growth and bone formation and used BC/HA membranes to evaluate osteoblast growth. It observed the significantly increased cell growth and spreading on the surface of BC/HA membranes, compared with that of BC. They demonstrated that BC could sustain osteoblast adhesion and the HA enhanced osteoblast adhesion and spreading. Hammonds *et al.* (2012) investigated the feasibility of generating calcium-deficient HA from BC/calcium-deficient HA composites by thermal and enzymatic methods. The degradation method produced calcium-deficient HA, providing an example for the composites as a bone filler.

Tommila *et al.* (2009) found that cellulose sponges coated with HA attracted circulating hemopoietic and mesenchymal progenitor cells efficiently and contained calcium-sensing receptors-positive cells. It probably suggested that the stem cells were responsible for the richly vascularized granulation tissue formed in HA-coated sponges. Liu *et al.* (2010) used HA/polyurethane composite scaffold to generate an antibiotic drug delivery system with good cytocompatibility and antibacterial properties. It found a sustained release of the model drug for up to 60 days Wang *et al.* (2013) prepared a porous BC membrane with gelatin and CHA with low crystallite size and crystallinity via the laser patterning technique. It showed that the C5.18 cells survived after being cultured in the 3D BC scaffolds for 7 days. The chondrogenic rat cell could keep viability on scaffolds, which indicated the scaffolds with good cytocompatibility. It is known that chitosan possessed innate antimicrobial properties toward both Gram-positive and Gram-negative organisms, which could be used in the wound dressings without antimicrobial infections during the implants produce. Mututuvari *et al.* (2013) synthesized cellulose/chitosan/HA composite with good antimicrobial activity.

Yan *et al.* (2019) prepared biocompatible dialdehyde cellulose/$CaCO_3$ microspheres about 2–3.5 μm and a high specific surface area of similar to 363 $m^2\ g^{-1}$ for tunable pH-responsive drug delivery (**Figure 3A**). It observed a small and uniform template (**Figure 3B**) and a porous structure (**Figure 3C**). It obtained uniform microspheres by hollow cellulose (**Figure 3D**) formed by the aggregation nanoparticles (**Figure 3E**). A strong Ca signal was

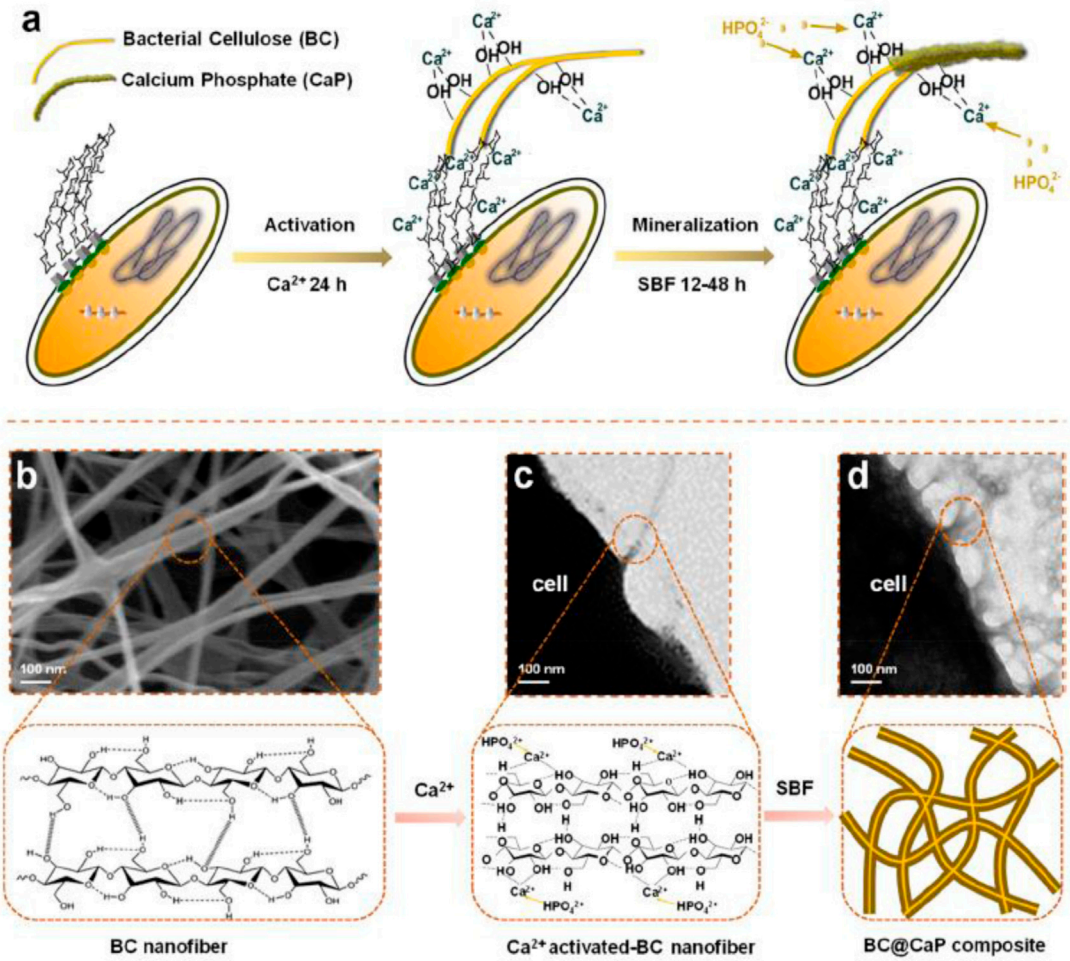

FIGURE 4 | In the experimental design of this study, hydroxyl-rich cellulose molecule chains capture free Ca^{2+} to initiate the nucleation of HAp. **(A)** Schematic diagram of the formation of HAp accompanying the production of cellulose by **(A)** x. **(B)** The representative SEM image of cellulose nanofibers secreted by bacterial cells. **(C)** The representative TEM image of cellulose nanofibers secreted by bacterial cells. **(D)** The representative TEM image of the BC@HAp composite was obtained under biological metabolism conditions. (Chen et al., 2021).

observed (**Figure 3F**). It carried out a surface area of ~363.1 m^2/g and a diameter of 10 nm for $CaCO_3$ microspheres (**Figure 3G**). It found encapsulation efficiency, pH responsiveness, and biocompatibility for the porous microspheres. Chen *et al.* (2021) reported the mineralization of biomimetic HA/nanocellulose nanocomposites with a higher Young modulus. It found the easier capture of Ca^{2+} by the abundant hydroxyl groups on the glucan chain before the formation of hydrogen bonding for the subsequent growth of HA crystals (**Figure 4**). Gao J. et al. (2022) developed flexible and superhydrophilic ultralong HA nanowire-based biopaper with tensile strength (2.57 MPa), porosity (77%), and specific surface area (36.84 m^2 g^{-1}) for a wound dressing. It found the proliferation, migration, and *in vitro* angiogenesis of HUVECs for the biopaper.

Nasrallah and Ibrahim (2022) reported physico-chemical, dielectric, and antimicrobial properties of the PVA/CMC blend films by silver doped HA nanoparticles using the casting technique. The films had antimicrobial properties for antibacterial activity against Bacillus subtilis, Escherichia coli, and Candida albicans. Nanocomposites had improved electrical conductivity and antimicrobial efficiency by doping silver/HA nanoparticles. Gao F. et al. (2022) prepared deacetylate 3D porous CA/HA/polydopamine microspheres coating with excellent attachment, adhesion, and proliferation as the scaffold for bone tissue regeneration. The microspheres coating was capable of differentiating osteogenically via *in vitro* mineralization.

2 FUTURE PERSPECTIVES

It is widely known that there are increasing demands in the biomedical fields. The calcium-containing cellulose-based composites included cellulose/HA, cellulose/calcium carbonate, and cellulose/calcium silicate composites in this review study. Obviously, the calcium-containing cellulose-based composites

had the characteristics of cellulose and HA/$CaCO_3$/$CaSiO_3$ and induced some new properties. As aforementioned, the cellulose/HA composites possessed high mechanical properties, good swelling behavior, adjustable biodegradation, high bioactivity, high chemical durability, good cytocompatibility, and excellent ion-exchangeability. Therefore, it is believed that these materials are promising candidates for the applications in the biomedical fields such as bone regeneration, bone tissue engineering, drug delivery, etc. In order to realize the realistic applications, based on the as-reported works in the literature, the following issues need to be explored in the near future.

First, the interaction mechanism between cellulose and inorganic calcium is still unknown and needs to be explored. There are a few reports on the interaction mechanism between cellulose and $CaCO_3$. As aforementioned, obviously, there exists a strong interaction between these two apartments. Halab-Kessira and Ricard (1996a), and Halab-Kessira and Ricard (1996b) investigated the interaction of $CaCO_3$ particles with cellulose grafted poly acrylate of trimethylaminoethyl chloride (PCMA) copolymers. Experimental results indicated that the retention of calcium carbonate particles was strongly dependent on the cationic content of the copolymer and electro-interactions make the adsorption easier. It obtained the maximum cover of about 750 mg g^{-1} for grafted fiber, and 280 mg g^{-1} for ungrafted fiber. As we all know, it is very important for the composites to display the applications by understanding the surface and interface properties. More importantly, as aforementioned, it showed that apatite particles grow on the surface of the cellulose/HA composites. The surface and interface properties are directly related to biomedical applications. Although some groups suggested the combination between cellulose and HA through hydrogen bonding, obviously, there is still a lack of experimental evidence and theoretical explanation. It assumed that the interaction is the hydrogen bond. The intramolecular hydrogen bonding or intermolecular hydrogen bonding, the strength of the hydrogen bonding, the hydrogen bonding be quantitative or semi-quantitative analysis should be investigated. We would like to know how the hydrogen bonding formed between cellulose and HA and whether the stability of cellulose is enhanced or weakened by hydrogen bonding. In addition to the hydrogen bonding, there exist other interactions such as electrostatic force, van der Waals, etc. Moreover, it is easy to observe the HA crystals dispersed on the surface of cellulose. The formation mechanism should be solved. Therefore, the intrinsic and detailed interaction mechanism between cellulose and HA needs to be further investigated. In fact, the research of mechanism is of great importance for the applications of both the cellulose/HA composites and other composites.

Second, the calcium-containing cellulose-based composites, especially cellulose/HA composites, should be explored for the industrialization application. Although calcium-containing cellulose-based composites are promising biomedical materials, there is a long road ahead for the industrialization application. Undoubtedly, it is a long process for the industrialization process of biomaterials. Obviously, the research on calcium-containing cellulose-based composites is at the initial stage. There are many problems that need to be solved. In comparison with other biomedical materials, the advantages of calcium-containing cellulose-based composites should be highlighted. For example, at present, there is a lack of comparative study of cellulose/HA composites and other biomedical materials. We should pay attention to the comparative study in the next stage. In addition, more biomedical properties including protein adsorption, gene carrier, adsorption/release, the performance of bone repair, and vascular properties should be explored.

Third, cellulose itself is certainly worthy of more attention. It reports that cellulose is extracted from sources including wood, plant, tunicate, algae, bacterial, etc. There are four polymorphs of crystalline cellulose (I, II, III, IV), which consist of crystalline and amorphous regions. Each polymorph has a different crystalline structure. The cellulose was extracted from cellulose sources via the mechanical treatment, acid hydrolysis, and enzymatic hydrolysis method by the complete or partial removal of matrixes (hemicellulose, lignin, etc.). In addition, it reports that there are nine particle types of cellulose. Each particle type has a characteristic size, morphology, crystallinity, and properties. Therefore, choosing an appropriate type of cellulose is important for the formation and applications of calcium-containing cellulose-based composites. For example, the existence of hemicellulose and lignin on the properties of composites should be researched.

As aforementioned, there are many methods for the synthesis of calcium-containing cellulose-based composites. Much attention has been paid to the biomineralization method. Indeed, HA is close to the natural bone in the cellulose/HA composites by the biomineralization method. This is a good method to investigate the mechanism of biomineralization. However, this method has the disadvantages of being time-consuming, low-productivity, and poor reproducibility. Obviously, it is not the best choice for the industrialization process of biomaterials. Moreover, the synthesis method should meet the principles of environment friendliness, economic friendliness, low cost, and high yield.

Finally, the calcium-containing cellulose-based composites itself is certainly worthy of more attention. As described in the literature, it is believed that the composites with specific porous structures could produce bone activity and osteoblast cells could have good adhesion and proliferation at the surface of composites (Yuan et al., 2010). It is reported that the histological evidence on the special micro or nanostructure induces bone regeneration (Zhu et al., 2009). It is well known that both cellulose and inorganic calcium have various morphologies and structures. Therefore, more attention should be paid to the pore and microstructure of calcium-containing cellulose-based composites. For example, cellulose/HA composites with 3D patterning should be fabricated by the electrospinning method and could be processed into film or bio-ceramic. Moreover, it is found that ions could promote cell proliferation and activate the gene expression (Lin et al., 2011). Nature HA also includes the chemical compositions of Na, Mg, Sr, Si, K, F, Cl, and CO_3^{2-},

which favored the improved biological properties of HA. The cellulose/HA composites with other chemical compositions should also be prepared.

3 CONCLUSION

In this mini-review article, we described the recent advances in the synthesis, properties, and biomedical applications of calcium-containing cellulose-based composites including cellulose/HA, cellulose/calcium carbonate, and cellulose/calcium silicate composites. The future developments and applications of calcium-containing cellulose-based composites were given. It expects that more attention is paid to the research of calcium-containing cellulose-based composites.

AUTHOR CONTRIBUTIONS

R-JS, TW, J-QL, NZ, and M-GM: investigation. R-JS, NZ, and M-GM: supervision. R-JS, TW, J-QL, NZ, and M-GM: writing the original draft. R-JS, NZ, and M-GM: writing—review and editing. All authors contributed to the article and approved the submitted version.

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