# Chapter 13
# Recent Advances in Biomedicine: Diatomaceous Applications

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**Abstract** At global scale, biomedical industry being one of the major drivers of economic and social development requires continues advancements to cope up with the changing needs of the society. Consequently, the future demands that the growth and development in present time must not compromise with the needs of future generation. In this context, the applications of microbes in the medicine sector become inevitable. The recent advances suggest the prospective sustainable utilization of diatoms in drug delivery, hemorrhage control as biosensors, anticancer agents, antimicrobial, etc. The uniqueness of diatoms by the virtue of its silica-based nanostructure has offered a great opportunity for efficient applications in medicines. Moreover, diatomaceous properties viz. nano size, chemical inertness, thermal stability, porous nature, and modifiable surface makes diatoms promisable tool for interdisciplinary applications. Another significant aspect of diatom utilization is its eco-friendly nature. Being the natural cosmopolitan microbe, diatoms have overcome the environment contamination problems posed by the use of chemicals. In this chapter, an attempt has been made to present the significant improvement in the utilization of diatoms in biomedical applications.

**Keywords** Diatoms · Surface modification · Biomedical application · Drug delivery · Biosensor

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## 13.1 Introduction

The social and economic trends of the Anthropocene are now diverted towards sustainable development to cope with the changing health and climatic scenario. Various interdisciplinary approaches are now being employed to address this vital issue for attaining sustainable growth.

For example, a significant research input in biotechnology, in terms of capital and time, has helped humans to explore the microbial potential for consumption. Moreover, industrial microbes' uses and the improvised techniques had supported excellent gain on capital input. Evidently, the published scientific literature in this century reflects diverse applications of microbes, such as yeast, bacteria, and microalgae in research (Sharma et al. 2021).

Certainly, owing to its silica-based shell walls, many scientists have gained attention towards the fine architecture of microalgae, such as diatoms. The advances in microscopy have revealed the amazing characters of these microorganisms. Currently, material research is focusing on the utilization of their potential as nanomaterials (Ragni et al. 2017). Unlike artificial nanomaterials, biological nanostructures are a worthy choice due to their lower impact on the environment, scalability, greater structural reproducibility, and low cost of production (Ragni et al. 2018). In the living world, from microbes to vertebrates, many organisms produce minerals which in turn contribute to the development of features such as teeth, shells, exoskeleton, and bones. This phenomenon of biomineralization involves more than 62 biominerals, chiefly phosphates and calcium carbonates, ferric hydroxides/ oxides, and silicates (Kumari et al. 2020). In contrast to synthetics, at physiological conditions, biomineralization allows obtaining nanostructured materials showing superior properties without the requirement of high pressure and high temperature for its synthesis (Livage 2018).

The silica micro-/nanoparticles offer numerous advantages compared to other nanomaterials by the virtue of their properties like chemical inertness, particle size, ease of surface modification, greater surface porosity, biocompatibility, and thermal stability (Albert et al. 2017; Chao et al. 2014; Maher et al. 2018; Rea et al. 2017; Simovic et al. 2011; Terracciano et al. 2018). The artificial synthesis of mesoporous silica utilizes toxic chemicals, needs advanced skill, generates nonrecyclable by-products, etc. (Maher et al. 2018; Delasoie and Zobi 2019). As a solution to these issues, Morse (1999) proposed the production of mesoporous silica by employing natural microbe, diatoms.

The biomedical uses of diatoms and research in pertaining areas have gained a lot of research interest since the last decade (Panwar and Dutta 2019). The very differentiating character of diatom is the frustule, a distinctive three-dimensional structure of its shell (Tramontano et al. 2020). Once the frustules are obtained from living algae or fossil remains, called diatomaceous earth (DE), it offers a unique possibility for drug delivery, theranostics, micro-/nano-devices, and many other medical applications (Delasoie and Zobi 2019). The traditional drug delivery system is limited by many aspects such as uncertainty in solubility, poor targeting, high

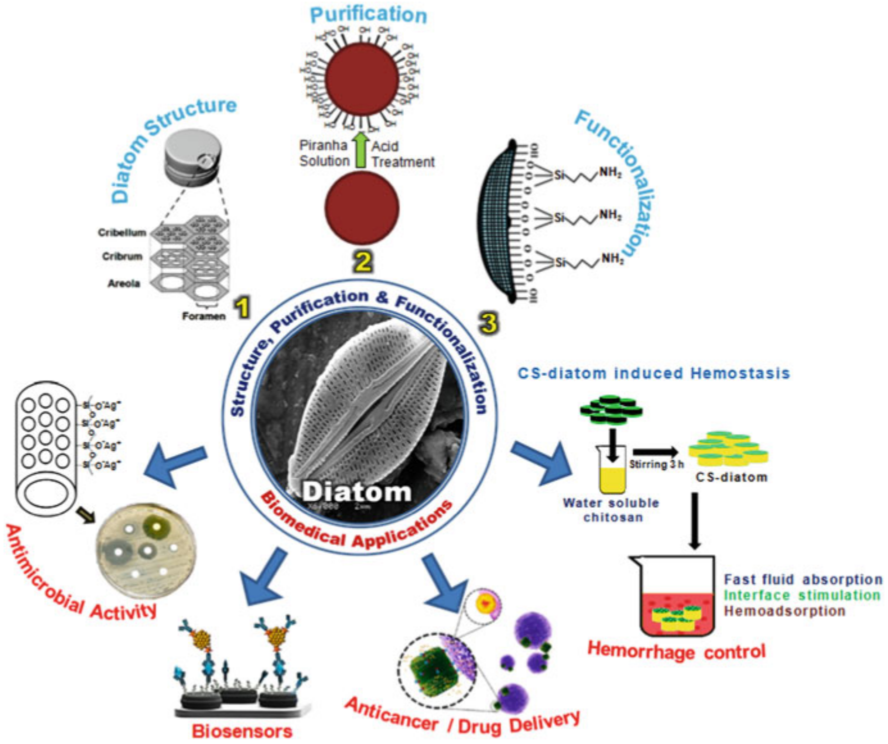

**Fig. 13.1** Overview of diatom structure and its biomedical applications. (Modified after Rabiee et al. 2021; Ragni et al. 2018)

toxicity, and less stability. In this scenario, the natural biomineralization process is considered as a role model for the elaboration of artificial materials and competent drug carriers (Maher et al. 2018).

In this chapter, we attempt to enlighten the recent advances in biomedicine by emphasizing the potential application of the diatom biosilica-based system. This chapter is purely based on the recently published scientific literature. This approach deals with the structure and modification of diatom silica, the function of diatom-based nanoparticles (NPs) in drug delivery, and the role of biosilica in advanced medical applications (Fig. 13.1).

## 13.2 Diatom or Diatomite Silica: Structure, Purification, and Surface Modification

### 13.2.1 Diatom Structure

Diatoms are unicellular eukaryotic algae, which are cosmopolitan in aquatic environments having considerable biological, ecological, and geochemical effects on the development and sustenance of life on earth. Diatoms are microscopic nanofabrication industries that employ simple self-assembly procedures to produce complex porous 3D silica shells called a frustule. The frustules exhibit various shapes such as triangular box, drumlike, circular box, and many more. Although frustules show different kinds of shapes, there are also some common characters like the void pill-box structure formed by two overlying valves closed together by girdle bands. The primary role of silicaceous porous shell is physical protection nevertheless; external characters of frustules exhibit multiple properties like nutrient sieve, antibacterial, optimized energy, and light-harvesting functions and movements (Maher et al. 2018).

Diatom frustules have numerous distinctive structural, mechanical, optical, excellent biocompatibility, photonics properties, and high surface area with micro-/nanoscale porosity that ensures its utility for a wide range of applications. Diatom frustule’s hollow porous microcapsular structure makes them perfect for the improvement of micro-/nanodrug carriers for a range of medical treatments like microrobotics and theranostics (Rea et al. 2017; Maher et al. 2017). This biomaterial can be procured in two possible ways: firstly through cultivation, harvest, and isolation of frustules from living diatoms and secondly, via mining DE or diatomite (Jiang et al. 2014). DE is a significant tool for diverse applications in fields like drug delivery, nanofabrication, molecular separation, biosensing, energy storage, chromatography, water purifications, etc. (Maher et al. 2018).

### 13.2.2 Purification

The raw DE minerals possess impurities like alkaline metals, alkaline earth, organic materials, and iron that could obstruct the properties of frustules essential for a specific purpose. In the industries, DE is processed by crushing, purification, and separation based on the size. In crushing, milling equipment is used to get finely crushed DE with sub-micrometer to several micrometer particle size frustules and broken pieces. Later, the purification step is done to eliminate the unwanted impurities. It involves both chemical and physical purification methods.

The physical purification procedure involves burning the impurities, i.e., calcination of the raw DE at high temperatures (greater than 600 °C). But, such calcination of raw DE consists of toxicity and is thus not suitable for commercial uses. While the chemical methods are preferable as they utilize the acid treatment of a raw

DE in a hot medium, herein, it is noteworthy to mention that the time required for acid leaching treatment is greatly reliant on the source of raw DE (that includes a type of impurity) (San et al. 2009). Such treatment makes the purified frustules appropriate and secure for biomedical uses (Terracciano et al. 2018). The purification process developed by Rea et al. (2017) is based on crushing, sonication, and filtration. These steps, in turn, help to get NPs for drug delivery uses. Later, for purification, a piranha solution (10% hydrogen peroxide, 2 M sulfuric acid for 30 min at 80 °C) was employed on the nanopowder along with 5 M hydrochloric acid (overnight treatment at 80 °C). The techniques such as dynamic light scattering (DLS) along with SEM and TEM confirmed the porous nature and nanometric size (300 nm) of the powder. Furthermore, after the purification treatment, EDXS analysis, FTIR spectroscopy, and photoluminescence confirmed the enhancement of the silica nanopowder (Aw et al. 2011).

### *13.2.3 Surface Functionalization*

Intrinsically, the purified DE surface presents the potential of the DE surface for the generation of novel bioengineered materials for applications in biomedicine. The hydroxyl group constituted by the silica over the DE surface could be used to gain functionalized chemical modification strategies. The most familiar method of surface modification is based on functionalizing the reactive silanol (SiOH) groups on diatom surface with reactive species (e.g., -SH, -CHO, -COOH, and -$NH_2$). These modifications built concrete bonding sites for the arrest of chemical or biological entities such as sensing probes, aptamers, enzymes, antibodies, proteins, DNA, drugs, etc. Along with that silanization is another popular method which forms the covalent Si-O-Si bonds for stable binding of various active entities on the diatom surface. After that surface modification with the required terminal chemical group arrests various biological moieties like nucleotides, antibodies, etc. This enables improved drug loading for biosensing and drug delivery. The commonly used methods for arresting active biomolecules on the surface of chemically modified diatomaceous earth include both covalent and non-covalent interactions. The key issue while employing the non-covalent interaction is dependence on the solution, such as a change in ionic strength or pH may change the bond strength. Thus, it may lower or strengthen the non-covalent bond's stability. Therefore, covalent binding is more preferable in terms of reproducibility and stability (Maher et al. 2018; Tramontano et al. 2020).

## 13.3 Biomedical Applications of Diatom Silica

### *13.3.1 Drug Delivery Systems*

The need of the hour for the pharmaceutical industry is the delivery of specific drug at a defined concentration to target in the human body, wherein causing minimal or no side effects on the healthy tissues/part of the body (Ferrari 2005; Wagner et al. 2006). The choice of the perfect drug is limited due to some undesirable limitations such as uncertain solubility, less stability, high toxicity, poor targeting, and, thus, side effects. Consequently, recent years have witnessed a rise in research and developmental activities pertaining to advanced drug delivery systems (aDDS). Unlike traditional drugs, the enhancement in the physicochemical properties of advances achieved in the aDDS system has overcome the different barriers (Yan and Chen 2014).

The potential of diatom's biological structure for the construction of raw material was realized by Morse (1999). He suggests that the precision in biological silica synthesis is genetically controlled and far from the competence of human engineering. The first attempt at deliberate use of diatoms as a delivery system was shown by Rosi et al. (2004). The report demonstrates the controlled loading and release of gold nanoparticles from the DNA-functionalized surface of the diatom. The available reports also suggest diatomaceous microcapsules as efficient carriers in both implant and oral applications (Ragni et al. 2017).

In recent drug delivery reports, antihyperalgesic effects of ibuprofen were demonstrated (Janicijevic et al. 2018). The delivery system used aluminum salt-modified diatomite for carrying the drug ibuprofen. The modified system showed greater drug loading ability and increased drug release in in vitro conditions. Unlike pure ibuprofen, in vivo experiments on rats confirmed the enhanced efficiency of the ibuprofen-diatomite complex for the same doses. In another report, natural silica obtained from diatom *Amphora subtropica* was used for doxorubicin drug delivery (Sasirekha et al. 2019). Results revealed that, unlike artificial nanomaterials, *Amphora* frustules are the superlative alternative for drug delivery. Furthermore, studies on lung cancer cell line (A549) showed low toxicity and persistent drug delivery.

It is established that drug quantity and the approach of encapsulation govern the efficacy of the drug delivery system. A recently published report suggests the enhanced efficacy of porous carriers in drug encapsulation. Wherein biogenic silica from frustules of *Cyclotella* sp. was employed for encapsulating Isorhamnetin with the help of a silicon microfluidic device (Mancera-Andrade et al. 2019). The frustules showed 48% drug release in the first hour and the residual drug release in the later 3 h. In 2019, curcumin drug delivery was achieved by diatom modified with polydopamine (Uthappa et al. 2019). It was proved to be an efficient catalyst for dye degeneration and systematic drug release. The results reported that the diatom-curcumin-polydopamine-ligand folic acid complex could serve as an excellent system for drug delivery in tumor therapy. Additionally, the diatom-polydopamine complex was modified with silver NPs for anionic (Congo red) and cationic (methylene blue) dye degradation.

Recently, an inventive approach for drug delivery over cancer tissues expressing transcobalamin (II) receptor present in the colon was published (Delasoie et al. 2020). The delivery system utilized in this approach was based on the vitamin B12-modified diatom frustules. Moreover, microparticles could be photoactivated to produce free radicals or carbon monoxide, which in turn stimulated apoptosis in the tumor cell.

In cancer treatments, Kabir et al. (2020) reported to devise self-assembled micro-/NPs from diatomaceous earth to overcome the failure of the combined chemotherapy and multidrug resistance. They employed dual delivery of chemotherapeutic drugs and supersede the antagonistic effect by taking different molar ratios of drugs. Saxena et al. (2021) loaded the curcumin drug onto the *Thalassiosira weissflogii* frustules. The study indicates that unlike acidic conditions, the rate of drug discharge was quicker at physiological conditions. During cell viability testing, they observed no lethal effects of curcumin-loaded biosilica, while toxicity was observed against human renal adenocarcinoma cell lines.

The applications of diatom silica structures for nucleic acid delivery in gene therapy are also astonishing. Thus, consequently, small interfering RNA (siRNA) delivery is now recognized as a successful approach for cancer treatment. The pioneering attempt in using diatoms for delivery of siRNA constitutes a binding of poly-D-arginine peptide/siRNA complex to diatom with APTES (3-aminopropyltriethoxysilane) surface-modified (Rea et al. 2014). The delivered siRNA acts to suppress the expression of a cancerous gene, known as gene silencing. Eventually, this leads to cell death (Maher et al. 2018; Tramontano et al. 2020). Similarly, Martucci et al. (2016) reported amino-silanization-modified diatomite nanoparticle for siRNA delivery to lymphoma cells. The kinetics of internalization of diatomite nanoparticles deduced via Raman imaging explained the cytosolic location of nanoparticles bound to RNA interference (Manago et al. 2018). It was supposed that internalization occurred through endosmosis, and NPs co-existed in lipidic vesicles.

### *13.3.2 Biosensors*

Recent reports suggest the probable exploitation of biosilica for getting a variety of biosensors (Rabiee et al. 2021). The low cost of making and efficiency in filtration are suitable choices for biosensor designs. Such perceptive devices possess a biomolecular detection element associated with a transducer, capable of inducing a signal with respect to the altering concentration of the target molecule to be sensed. As the porous nature of frustules could be optimized, it has the ability to integrate into frustule-specific sensing chambers of biosensors. This would help to achieve a selective transport of the molecules. By virtue of its enormous refractive property, frustules magnify signals and therefore could be utilized as fluorescent probes

**Table 13.1** Some recent studies on diatom-based biosensor applications in medicine

| Sr. No. | Diatom species | Methods used | Biomedical application | References |
|---|---|---|---|---|
| 1. | *Chaetoceros* sp. | Iron oxide NPs | Differentiate breast cancerous and normal cells from each other | Esfandyari et al. (2020) |
| 2. | *Amphora* sp. | APTES (3-aminopropyltriethoxysilane) | Detection of bovine serum albumin | Viji et al. (2014) |
| 3. | Diatom biosilica | Photonic crystal-enhanced fluorescence imaging immunoassay | Clinically relevant detection of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the facile screening of heart failure | Squire et al. (2019) |
| 4. | Biosilica | Gold NPs integrated into biosilica-based ultrasensitive surface enhanced Raman spectroscopy (SERS) immunoassay | Interleukin 8 detection in human blood | Kaminska et al. (2017) |
| 5. | DE biosilica | Silver NPs | Biomedical studies for molecular detection | Kong et al. (2016) |
| 6. | *Amphora* sp. | Covalent immobilization of *Salmonella typhi* antibody onto the crosslinked diatom substrates via glutaraldehyde | Diagnosis of typhoid | Selvaraj et al. (2018) |

(Mishra et al. 2017). Here, Table 13.1 exemplifies different examples of biosensors in medicinal use.

### *13.3.3 Tissue Engineering with Biosilica*

Silicon plays a very significant function in osteogenesis and bone maintenance. It stimulates mineralization and enhances osteoblast cell functions. Abnormal long bone and bone deformation is often linked to silicon/silica deficit (Le et al. 2016).

In nature, diatomite serves as a rich and cheap source of natural silica that possesses applications in regenerative medicines (Maher et al. 2018). By the virtue of biocompatibility and greater stability, biosilica is utilized in on-site and in vivo bone repair (Rabiee et al. 2021), where silica shells of the diatom *Thalassiosira weissflogii* were utilized to augment propagation and linking of human osteosarcoma cell line MG63 and L murine fibroblasts. Two drugs, first antibiotic ciprofloxacin and second antioxidant cyclic nitroxide 2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), were used to modify the diatom silica surface. The antibiotic was supposed to heal allied bacterial contamination, while the antioxidant avoids inflammation by dealing with the reactive oxygen species. After the incubation period as compared to the control, results confirmed enhanced cell viability for both cells (Cicco et al. 2015). Moreover, for bone tissue engineering, the production of diatomite and chitosan biocomposite as the origin of biosilica was achieved by the lyophilization technique (Tamburaci and Tihminlioglu 2018).

### *13.3.4 Hemorrhage Control Using Biosilica*

In hypovolemic shock, unrestrained hemorrhage if not cured early could result in death. Currently available hemostatic drugs have many limitations, such as the drug QuikClot zeolite may consequently cause tissue burning because of high heat that may reach 95 °C. Alternatively, silica diatom agents are nonimmunogenic, noncytotoxic, and cheap hemostatic drugs that are reported to surmount limitations (Feng et al. 2016). Unlike zeolite, no heat generation was observed in silica diatoms due to greater plasma absorptivity.

Feng et al. (2016) coated two purified frustules, commercially available diatomite and lab-cultured diatoms, with chitosan in various concentrations. Later, modified frustules were tested for in vivo blood clotting and in vitro hemolysis. Results revealed that in contrast to uncoated diatom, chitosan-coated frustules showed insignificant hemolysis. Conversely, unlike QuikClot zeolite and gauze in rat-tail amputation, much-reduced blood clotting time was attained for chitosan-coated frustules. Furthermore, the chitosan-dopamine-diatom biosilica complex showed appropriate biocompatibility for hemostasis, where dopamine acts to fasten diatom biosilica with chitosan and developed porous structure leads to quick hemostasis due to adsorption of a high amount of water (Wang et al. 2018). In another case, *Coscinodiscus* sp. frustule-derived calcium-doped biosilica having many hemostatic properties was obtained (Li et al. 2018). In a rat-tail amputation experiment, it was reported that modified frustules of Ca-biosilica have strengthened the blood coagulation process. The quicker hemorrhage potential of modified frustules was attributed to the rich calcium and silanol group interface. The main advantages of Ca-biosilica were simple eco-friendly preparation process, efficacy, and superior biocompatibility.

### *13.3.5 Anticancer Effects*

The treatment of cancer is continuously evolving. Diatom-based drug delivery of therapeutic agents is showing much potential for applications. Moreover, some of the modified diatom-based agents reported having effective anticancerous activity, such as marennine, oxylipins, polysaccharides, monoacylglycerides, haslene lipid, chrysolaminarin fucoxanthin, fatty alcohol esters, stigmasterol, and adenosine (Hussein and Abdullah 2020).

In diatom *Skeletonema marinoi*, isolated monoacylglycerides showed cytotoxic activities by activating 3/7 apoptotic pathways in hematological and colon cancer cell lines (Miceli et al. 2019). Lauritano et al. (2016) cultured different diatoms in variable conditions. Later, the extracts were checked for any potential activities. Eventually, antibiofilm activity against *Staphylococcus epidermidis*, anti-inflammatory activity, and anticancer activity was found in six diatom species. It was noteworthy that experiments on normal human cells showed a nontoxic nature against all the six evaluated diatoms.

### *13.3.6 Antimicrobial Effects*

The natural diatomaceous earth is an excellent compound material against microbes. It is believed to be effective for water treatment (Sherief et al. 2021). The diatom extracts showed antibacterial activities against Gram-positive as well as Gram-negative bacteria (Lauritano et al. 2016). Moreover, NPs synthesized from diatom *Skeletonema* sp., *Chaetoceros* sp., and *Thalassiosira* sp. were reported to have antibacterial properties against *Aeromonas* sp., *Streptococcus pneumonia*, *Staphylococcus aureus*, *Bacillus subtilis,* and *Escherichia coli* (Mishra et al. 2020). In the conducted study, silver NPs were supplemented over a diatom surface to prepare the silver-diatom NPs complex. Such modified complex was reported to possess more antimicrobial potential against *Aspergillus Niger* and *Staphylococcus aureus* than diatomaceous earth (Sherief et al. 2021).

## 13.4 Conclusions and Future Prospect

In recent years, diatoms were proven to be a cost-effective natural source of nanostructured silica. Diatom's porous frustules having properties like greater surface area and easy chemistry of the surface proved its value as a cheap substitute for the improvement of the multifunctional silica system. The current research trend on diatoms concludes that chemically modified and biofunctionalized frustules have potential future aspects in biosensing, drug delivery, cell proliferation, and adhesion. Moreover, the benefits of modified frustule's silica surface also include biomedical applications such as increased drug solubility, enhanced biocompatibility, and more drug encapsulation at the specific target site. However, prospects of diatom research should include biodegradability and long-term studies for possible toxicity, although current studies found no or negligible toxicity. More research should be undertaken to explore other areas of research by virtue of its cheap and eco-friendly nature.

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