The Potential Use of Polymeric Nanomaterials Against the Spread of the SARS-Cov-2 and its Variants: A Necessary Briefing

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Abstract: Regarding its evolutionary scale, mankind has made important achievements in a short period of time. The last 50 years have been fundamental for the development of technologies that currently allow human beings to make safe journeys in the orbit of the planet, study and accurately analyze the universe, build smart cities, propose more sustainable production processes, etc. The technological leap of the last decades has influenced practically all sectors, from engineering to medicine. There are many factors that allowed for technological evolution, and one of them refers to the development of new materials. Herein, polymers stand out. The versatility of these materials reinforced their relevance during the SARS-CoV-2 period. In the period when many medical and hospital supplies were exhausted, polymers were useful for manufacturing items such as face shields, general purpose masks, and swabs, helping to counter the spread of the virus. Two years after the pandemic peak, the challenge is to fight the viral variants and make the methods of diagnosis and treatment more effective. In this regard, nanotechnology and nanoscience seem to be promising for this purpose. Through a review study, the present work aims to identify technologies already available or under development that allow for the use of polymeric nanomaterials against the spread of the new coronavirus and its variants.

Keywords: COVID-19, SARS-CoV-2, Nanotechology, Virus, Nanopolymers.

INTRODUCTION

The last two years have been remarkable for mankind. The rapid spread of a virus with a high lethality rate impacted several production and consumption sectors around the world [1-4]. The pharmaceutical, automotive, beverage and food, transportation [5], tourism and leisure [6] industries were some of them, along with the financial sector [7-9]. Simultaneously with the race to secure supplies to maintain important production chains, there has been a relentless search for materials and methods to ensure rapid and effective diagnosis of Covid-19 as well as its treatment. The development and production of vaccines against the new coronavirus, combined with large-scale vaccination campaigns [10] and prevention mechanisms - such as the use of alcohol gel, social isolation, and the use of masks for the population at large [11-14] - were decisive to keep the disease under control. After this period of turbulence and having passed the pandemic peak, the economies of some countries seem to be finding their way back to pre-pandemic levels [7].

It so happens that, because it is a virus whose nature is to replicate and be constantly mutating [15], the new identified and currently circulating variants are still a matter of concern for both health authorities and infectious disease specialists. The variants spread more easily [16, 17] and could at some point become immune to the vaccines hitherto applied [18, 19] and even non-identifiable by valid diagnostic kits developed against the original version of SARS-CoV-2. For those reasons, the battle against Covid-19 is not yet over and is currently in an upgrade stage.

By all indications, technologies based on nanostructures can help in the treatment and diagnosis of Covid-19, since nanoscience is already present in many health treatments. In this sense, the present work aims to address the potential application of polymeric nanomaterials and nanoscience in the fight against the new variants of SARS-CoV-2.

METHODOLOGY

Collection of information and data related to the topic was carried out using internet search engines – those with free access - as well as specialized academic platforms (ScienceDirect). The search terms used were: ‘nanotechnology’/‘virus’, ‘nanopolymers’/ ‘virus’, ‘nanotechnology’/‘diagnosis’. No filter was used for the search period, and the collection of publications ended in Aug 2022.

RESULTS AND DISCUSSION

Figure **1** illustrates the sequence of actions involved in the search for scientific publications on the topic of nanopolymers and nanotechnology in fighting viruses.

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Figure 1: Steps in the process of collecting and selecting academic publications.

Table **1** shows the relationship between the search terms used and the number of retrieved articles, prior to the sorting.

When the search expression related *nanotechnology* to *virus* (Group I) and *nanotechnology* to *diagnosis* (Group III), the number of publications was higher than those containing *nanopolymers* (Group II and Group IV). At first glance, it is observed that the articles preferred to address aspects of nanoscience applied to diagnosing and/or fighting the virus, with no particular attention to the use of nanopolymeric material. It is worth pointing out that the use of the word *virus* retrieved publications related to the fight and/or treatment of any virus, not exclusively SARS-CoV-2.

The results reveal that, although the topic of nanotechnology has been associated to viruses since the 1990s, the number of publications has had a considerable increase since 2020, the year when the SARS-CoV-2 pandemic period was declared by the World Health Organization [20]. Although there are many definitions of nanotechnology, it can be considered as Molecular Level Engineering. Nanotechnology is a multidisciplinary area of applied science and engineering that aims at the design and manufacturing of extremely small components and systems. In other words, on a nanoscale. Such structures are built at the molecular levels of matter, characterized by their large surface areas in relation to volume, and exhibit behaviors governed by quantum mechanics [21]. Years 2020 and 2021 accounted for 30% of publications related to Group I search terms. However, when year 2022 is considered, this percentage reaches 49%. This significant increase may be attributed to the need to develop new technologies to fight viruses in general, stimulated by the spread of SARS-CoV-2 [22] and its variants of concern, currently known as Alpha (B.1 .1.7), first identified in the UK; Beta (B.1.351), discovered in South Africa; Gamma (P1), first identified in Brazil; Delta (B.1.617.2), first reported in India; and Omicron (B.1.529). There are also variants of interest in public health, known as Eta (B.1.525), Epsilon (B.1.427/B.1.429), Zeta (B.1.1.28.2), Theta (B.1.1.28.3), Iota (B.1.526), Kapa (B.1.617.1), and Lambda (C.37) [23]. Given this scenario, the scientific community emphasizes the importance of adopting public health strategies against the SARS-CoV-2 variants, seeking to develop and consolidate active systems for monitoring these variants, implementing resolute responses that can cause the least harm to the community.

A little more than 90% of the total publications in that period were articles and chapters in books. According to the criteria established by the search platform itself, the main areas of interest were *Immunology* and *Microbiology*; *Biochemistry*, *Genetics,* and *Molecular Biology*; *Materials Science*; *Medicine* and *Dentistry*; *Pharmacology*, *Toxicology,* and *Pharmaceutical Science*.

The wide range of publications in distinct areas of knowledge reinforces the multidisciplinary character of the subject. This highlights the importance of integrating different fields of knowledge [24, 25] in order to fight the current pandemic and future pandemic cases [26, 27].

The publications on the subject of nanotechnology as applied to diagnostics have also increased since the 1990s. However, 32.5% of the total number of publications concentrated in the pandemic period. This figure increases to 47% when one considers the publications already available for 2022.

Table 1: List of Search Terms and Number of Retrieved Publications

Group	Search terms	Number of articles
I	Nanotechnology, virus (including SARS-Cov-2)	404
II	Nanopolymers, virus (including SARS-Cov-2)	02
III	Nanotechnology, diagnosis	910
IV	Nanopolymers, diagnosis	04

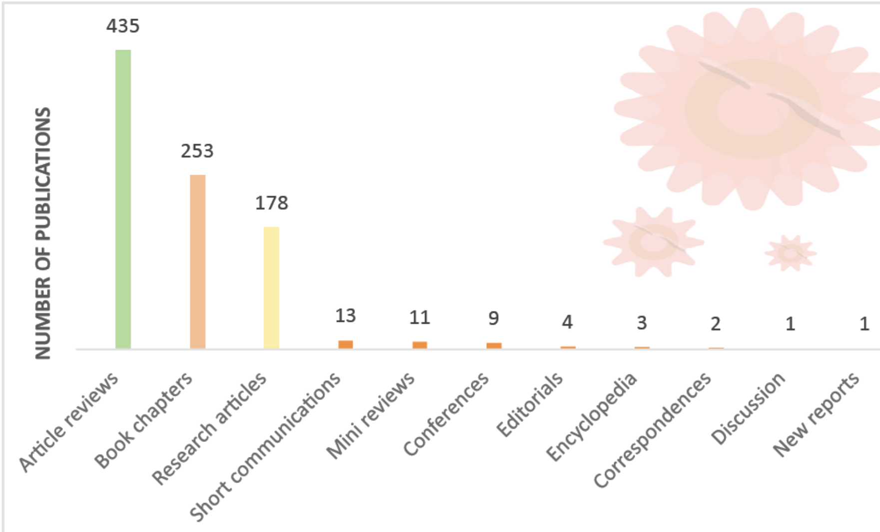

Figure 2: Type of publications available on the specialized search platform, using Group III search terms.

Figure **2** shows the types of publications.

Most published materials are articles - review articles and research papers - and chapters in books.

When using the search terms from Group II and Group IV, one notices a much smaller number of published documents, as shown in Table **1**. What these Groups have in common is the word *nanopolymers*. Regarded as a material consisting of a single polymer molecule at the nanoscale, nanopolymers [28] stand out for their variety of applications and properties. They can be classified based on self-assembled nanostructures, non self-assembled nanostructures and, number of nanoscale dimensions. In this last situation, nanopolymers can be thin films (1-D); nanofibers, nanotubes or nanostructures on polymeric surfaces (2-D) or; nanospheres, nanocapsules, dendrimers, hyperbranched polymers, porous, nano objects (3-D) [29]. Therefore, they are a specific type of nanomaterial. Shiri *et al.* (2019) [30] developed a nanopolymer synthesis method for the transportation of silibinin and silymarin extracts, for neurotrophic applications. As pointed out by the authors, one of the most commonly used methods for nanopolymer production is through the emulsion polymerization process. In this case, factors such as the type of solvent used, the nature of the emulsifying agent, its concentration, the type of initiator, and the reaction temperature are crucial for the success of the polymerization. Even though publications on research related to nanopolymers date back to the 1990s [31-33] - used even in medicine and in the development of drugs -, it seems that their applications are still limited when considering the fight against viruses. This is reinforced by the nature of the publications collected by Group IV. None of the papers are related to the diagnosis of virus-borne diseases. And the publications, however few, started only in 2008 in the specialized search platform adopted here in the present review. This does not mean that there is no research on the subject. The complexity in the development and selection of nanopolymers combined with the time required for approval of drug and antiviral testings [34-37] are probably factors that justify the small number of publications on the subject.

Nanoscience and Antiviral Technologies

A few decades ago, the use of nanostructures as tools to aid in medical and clinical treatments was a fertile environment for science fiction storylines. Nowadays, however, this is already happening. Nano-scale antiviral drug carriers can significantly improve their pharmacokinetic profile with decreased toxicity to the human organism [38].

Current therapeutic approaches employ drugs designed to inhibit aspects related to the viral lifecycle. These drugs, however, can bring serious side effects to the patient [39-44] and lose their effectiveness over time due to virus resistance [45-47]. Nanoscience-based treatments allow antiviral drugs to be encapsulated in nanoscale structures raising their bioavailability, increasing efficacy, and maintaining the therapeutic window for longer periods [48, 49].

One of the advantages of nanostructures is that they can remain in the circulatory system for a long time and can be amalgamated with a given drug, which is then released according to a specified dose. This results in less fluctuation in the plasma, with reduced side effects [50]. In addition, the diffusion of nanostructures into cells and tissues is greater, thus rendering the treatment more effective.

Nanotechnology has proven to have a potential role in the development of new treatments combining viral biology and nanotechnology to create therapeutic approaches for the treatment of diseases [51]. This include new treatments and diagnosis for SARS-Cov-2 [52].

One of the main goals of nanomedicine is to promote, through nanotechnological resources, a targeted attack against diseased cells and tissues. In this case, viruses could be employed as carriers of nanoparticles capable of acting selectively on certain cells, preserving the healthy ones. For this to happen, some studies have been conducted in order to change the original structure of the virus through genetic manipulation or by maintaining the integrity of the virus and using it only as a structure for nanofabrication [51]. This is possible thanks to the naturally nanometric dimension of these biological entities that, once modified, can be exploited to form molecular scale structures [53], as well as palladium and platinum crystals, useful for manufacturing biosensors [54].

Figure **3** shows a schematic illustration of how metal nanoparticles can be manufactured from a viral structure. Biological macromolecules, when in their crystal state, allow the production of nanomaterials with an ordered architecture [54]. In their studies on using viral capsid as a basis for nanomanufacturing, Falkner and coauthors (2005) [54] used the crystal structure of the cowpea mosaic virus (CPMV) to produce palladium and platinum nanoparticles. The nanoproduction is due to the large number of nanocavities and channels present in the CPMV structure, which represent almost 50% of the total volume of the virus. As seen previously, nanoparticles could be an important barrier against entering of viruses in the cell. But this will work appropriate if these particles have the perfect geometry for interact to virus structure, for example. The domain of the biofacturing of nanoparticles can be applied for new therapeutic treatment against SARS-Cov-2 and its variants.

Based on the nanofabrication process, Thangavelu and coauthors (2020) [55] produced gold and silver nanoparticles from the structure of the *Squash leaf curl China virus* (SLCCNV), measuring 32 nm. One of the goals was to obtain a hybrid nanostructure capable of conducting electricity for biomedical applications, including more accurate diagnoses [55].

Perhaps the biggest challenge for the application of vironanotherapy lies in the partial understanding of the mechanisms associated with the early stages of recognition and anchoring of the viruses to host cells, although they are known to be governed by the proteins of the viral capsid [56]. And, in the case of SARS-CoV-2, by the spike (S) glycoprotein, that seems the key target for production of vaccines, for example [52].

Nanopolymers for Treating, Diagnosing, and Fighting Covid-19

Polymeric materials have proven to be crucial in controlling the spread of the new coronavirus as early as 2020. The polymers were widely used to produce masks and faceshields, as well as individual protection equipment needed by health professionals [13]. As nanomaterials, polymers also were used in nanofibers

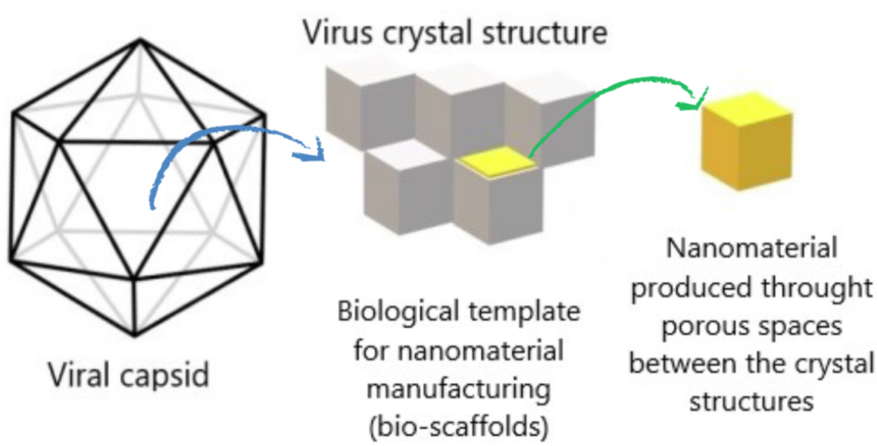

Figure 3: Area in the crystal structure of the viral capsid where metal nanomaterial is produced.

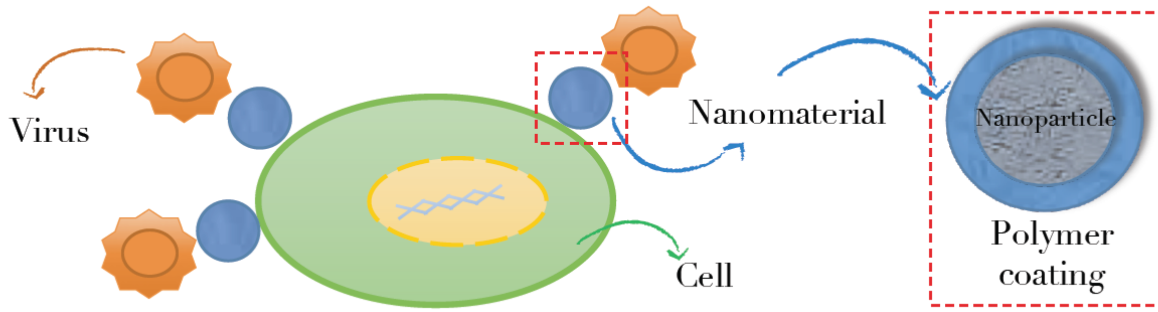

Figure 4: Schematic illustration of cellular protection against the action of viruses, provided by nanostructures able to block access to receptors present on the membranes.

scale with potential to produce filter material and to retain virus particles in the air [57, 58].

After two years coexisting with the disease, knowing better the dynamics of contagion and infection in the human body, polymers may be useful, once again, in the fight against this virus. The battlefront, however, is at nanometer level [49, 59-61]. Polymer nanoparticles (nanospheres or nanocapsules) have already been produced by solvent evaporation syntheses and through emulsion. And, when applied to medicine, they can contribute to a further integration between therapy and diagnosis [48], resulting in more accurate treatments.

The recent pandemic period mankind went through was an important driver for the development of vaccines and kits for diagnosing the disease. During these years, many non-randomized clinical trials have been conducted at different scales. These studies evaluated the performance of drugs such as Remdesivir, designed to fight the Ebola virus (EBOV); Chloroquine (CQ) and Hydroxychloroquine (HCQ), used against malaria; and Lopinavir/Ritonavir (LPV/r), used to treat the acquired immune deficiency syndrome [62]. Despites prescribed by the medical community, and with some side effects [63, 64], the effective control of the spread of Covid-19 has occurred thanks to the development and widespread application of vaccines.

The viral particles of SARS-CoV-2 have a diameter in the range of 60 to 140 nm, having a spherical crown shape when observed by electron microscope [65, 66]. For nanotechnology to be employed against this and other viruses, one of the strategies adopted is to ensure the blocking of viral particles from entering the cells. Figure **4** illustrates the action of nanoparticles blocking the entry of viruses into the cell. Nanoparticles (coated by a polymer structure) interact to virus before they enter the cellular.

The synthesized nanostructures would compete with viruses, inhibiting their entry into the cell and hindering the consequent infection [67]. Regarding the use of polymers for vaccine development, those that use polymeric nanostructure to coat the antiviral agents themselves stand out. In this case, the poly-lactic-co-glycolic acid - (PLGA) [68] is used, which is the most extensively studied for this purpose due to its classical clinical application, its degradability, and its approval by the United States Food and Drug Administration Agency (FDA) [69].

Jeremiah and coauthors (2020) [70] used polyvinylpyrrolidone (PVP) - a polymer widely employed by the pharmaceutical industry for ophthalmic formulations - to coat silver nanoparticles and evaluate its effectiveness in extracellular inhibition of SARS-CoV-2. Its molecular structure is shown in the Figure **5**. PVP was chosen because, among many available and studied coating agents [71], it does not hinder the antiviral action of silver nanoparticles [72], which have already shown excellent antiviral activity against the respiratory syncytial virus (RSH) [73] and the human immunodeficiency virus (HIV) [74]. The researchers observed a significant protection of infected cells and a suppression of the SARS-Cov-2 viral load.

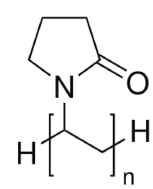

Figure 5: Molecular structure of polyvinylpyrrolidone (PVP).

Nanoparticles made from polyethyleneimine (PEI) [75] and polyethylene glycol-poly(ε-caprolactone) copolymer (PEG-PCL) [76] have also been studied as adjuvants in immunotherapeutic treatment for different diseases, acting as drug carriers, what could also be useful for the treatment of cytokine storm in COVID-19 patients [59, 77]. Figure **6** shows the molecular structure of the PEG-PCL copolymer.

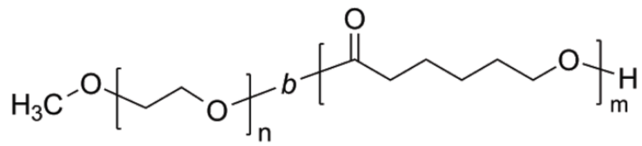

Figure 6: Basic structure of the polyethylene glycol-poly(ε-caprolactone) copolymer, PEG-PCL.

In the PEG-PCL copolymer, polyethylene glycol is responsible for ensuring the hydrophilicity of the material. Polycaprolactone, on the other hand, is hydrophobic. This combination of characteristics makes PEG-PCL - an amphiphilic material - generate highly stable micelles and nanoaggregates, which makes them well suited for the development of controlled release systems for pharmaceuticals [78]. Furthermore, they are partially biodegradable, biocompatible molecules with low immunogenicity [79], and can be structured in linear form, 4-arm or brush block [80].

PEI molecules consist of cationic groups and, since the 1990s, have become non-viral vectors employed for the transfer of nucleic acids into the cells [81]. They are water-soluble and easily modified polymers, allowing for the formation of chemical complexes [82, 83]. Since then, many *in vivo* and *in vitro* studies have been conducted showing the feasibility of the polymer for this purpose [84]. Figure **7** shows the molecular structure of PEI.

At the biological level, the presence of amino groups allows PEI macromolecules to chemically bind to the phospholipid layers of cells. This occurs as a result of the possibility of ammonium ion generation depending on the pH of the medium, which confers cationic nature to the polymer [85], favoring its transport along the cell membrane, as well as any other molecule that may eventually be complexed with the carrier polymer [84]. While studying the action of PEI as an intranasal vaccine adjuvant agent against *Streptococcus*, Dai and coauthors (2021) [86] observed its potential application. As a cationic polyelectrolyte, PEI in its linear or branched form, is able to be used as vaccine adjuvants, helping to stabilize the liposomes. They have found that the adjuvant properties were not improved with an increase in the molecular mass of PEI.

Nanotechnology can also be employed for manufacturing equipment and devices that can reduce the proliferation of viral particles, and this is not restricted to clinical use alone. Woon and coauthors (2020) [87], for example, developed an air filtration system based on polyvinylidene fluoride (PVDF) nanofibers. By obtaining nanofibers with defined dimensions and morphology, the researchers were able to trap aerosols up to 100 nm in size, with efficiency levels as high as 94%, reducing the transmission rate of SARS-CoV-2.

Nanomaterials have also proven promising for Covid-19 diagnosis. The combination of nanotechnology with genetic detection techniques is considered an efficient tool for identifying a particular pathogen. The advantage of using nanomaterials lies in a reduction in analysis time, an improvement in virus sensitivity [88], the use of small samples for analysis [89], as well as a reduction in the amount of consumables [90]. Numerous studies have been published reporting the use of gold nanoparticles (AuNPs) as biosensors. This is because gold particles have unique properties that cause them to have molecular interaction with a wide range of biomolecules, including antibodies and DNA strands [91]. Although the first applications of nanomaterials for

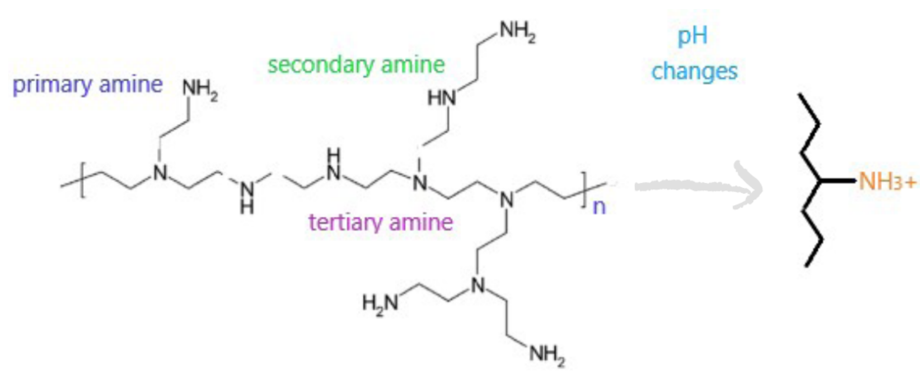

Figure 7: Molecular structure of the mer unit present in the polyethylenimine and the ammonium salt generated from the pH changes.

virus detection are associated with the use of nanometals - such as gold and silver [92]- silicon nanoparticles, quantum dots (QD) [93], and nanopolymers [69] are currently being studied, although there is very little information available in the literature on the latter.

Among the polymeric materials used in nanobiosensors, antibody mimic protein molecules (AMPs) stand out. These macromolecules are developed by *in vitro* selection techniques aiming to improve properties such as selectivity. Under a wide range of pH and electrolyte concentrations, they are more stable than typical antibodies. These characteristics allow AMPs to be used as capture agents for nanobiosensors [94]. In their studies related to the use of fibronectin as binding agents, Ishikawa and coauthors (2009) [94] were able to selectively detect the N-protein of the SARS biomarker, thus enabling its use in the diagnosis regarding this virus.

Prospects and Challenges

Despite being a promising field for treatment and diagnosis of viral infections, the development of nanopolymers requires more knowledge about their behavior in the human body, so that cellular and subcellular structures are kept intact. Because of this complexity of studies involved from the development and selection of the polymeric nanostructure to its test in the antiviral component, the scarce number of publications relating nanopolymers with diagnosis and fighting the virus and its variants is explained.

The use of polymeric nanostructures for treatment and diagnosis of diseases is a path with no return. However, it is vital that research be conducted to evaluate the toxicity of nanoparticles in the biological organism to ensure a safe use of nanotechnology-based treatments. Such studies should consider factors like hydrophobicity, size and shape of nanostructures, surface changes, among others. Opportunities to turn feasible and disseminate the use of nanopolymers in SARS-CoV-2 diagnostic techniques and vaccine development may depend on the development of chemical modification processes based on the generation of dynamic covalent bonds (DCBs).

CONCLUSIONS

Polymers - very versatile materials with a broad spectrum of applications - once again demonstrate their ability to help in the fight against SARS-CoV-2 and its variants. Whereas in the first two years of the Covid-19 pandemic they were useful in ensuring the supply of individual protective equipment to health professionals and to the general population, now they can contribute to more effective diagnosis and treatment. In this context, nanoscience has been useful.

The application of polymers (synthetic or natural) in nanomedicine - for the treatment and diagnosis of SARS-CoV as for any other viruses - requires the integration of professionals from different areas of knowledge. Without forming a multidisciplinary team, the development of vaccines or diagnostic devices may have only a partial efficacy.

However scarce, the literature on the use of nanopolymers in devices for diagnosing SARS-CoV-2 and its variants is now available mainly thanks to the recent pandemic period, where the knowledge about the infection dynamics, performance, and behavior of the virus is still under construction. However, nanopolymers show a potential application in the construction of biosensors because they are relatively easy to be chemically modified, allowing for the establishment of links with any type of biostructure.

DECLARATION OF COMPETING INTEREST

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in the present paper.

DECLARATION OF NON USE OF ARTIFICAL INTELLIGENCE

The author declares that he did not use any artificial intelligence tools for text and/or data production.

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