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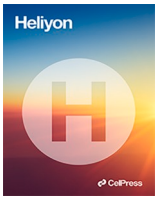

Review article

Polyrhodanine-based nanomaterials for biomedical applications: A review

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A B S T R A C T

Rhodanine is a heterocyclic organic compound that has been investigated for its potential biomedical applications, particularly in drug discovery. Rhodanine derivatives have been examined as the medication options for numerous illnesses, including cancer, inflammation, and infectious diseases. Some rhodanine derivatives have also shown promising activity against drug-resistant strains of bacteria and viruses. One of these derivatives is polyrhodanine (PR), a conducting polymer that has gained attention for its biomedical properties. This review article summarises the latest advancements in creating biomaterials based on PR for biosensing, antimicrobial treatments, and anticancer therapies. The distinctive characteristics of PR, such as biocompatibility, biodegradability, and good conductivity, render it an attractive candidate for these applications. The article also explores obstacles and potential future paths for advancing biomaterials made with PR, including synthesis modifications, characterisation techniques, and in vivo evaluation of biocompatibility and efficacy. Overall, as an emerging research topic, this review emphasises the potential of PR as a promising biomaterial for various biomedical applications and provides insights into the contemporary state of research and prospective directions for investigation.

1. Introduction

Rhodanine monomer is derived from thiazolidinone, which is one of the most vital heterocyclic rings in the medical applications. Rhodanine also holds an important position in the medicinal field due to its diverse array of biological effects, including antiviral, antibacterial, and anticancer properties [1,2]. In addition, rhodanine is a Lewis base. It is used in the synthesis of conducting polymers, such as polyalanine and polyrhodanine (PR). PR is a standard polymeric platform used in the medical field owing to its chemical reactive groups (amide, amine, carbonothioyl, carbonyl, sulphide, and dithiocarbamate), biocompatibility, and high electrical conductivity. Moreover, PR can be a good candidate for synthesising functionalised metal-based nanostructures for antimicrobial, anticancer, and biomedical sensing applications [3–5]. PR is synthesised through the oxidative polymerisation of the rhodanine monomer. Fig. 1 shows remarkable physicochemical properties of PR related to its structure. It can be observed that monomer rhodanine has four active sites. Additionally, free electron pair promotes the formation of coordination bonds with inorganic cations, while a high number of π bonds increases reactivity with organic matter [6,7].

Bacterial resistance towards antibiotics is one of the most impactful human health-related issues. Millions of deaths worldwide can

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be attributed to bacterial resistance, with an estimated ten million lives being affected yearly by 2050. The consequence of this problem is not only the infections that cannot be treated but also the lack of safe routine medical operations, such as surgeries and chemotherapy for oncological patients due to the failure of antibiotic prophylaxis [9–11]. Another key factor of human death worldwide is cancerous tumours. In 2020, the cancerous tumours led to ten million deaths. The leading causes of cancer-related fatalities included breast, colon, liver, lung, rectum, and stomach cancer [12]. With the increased global health burden, a new biotechnology approach is needed to place conventional treatments for microbial infections and cancer. A nanomaterials-based method can be one of the ways to prevent the resistance of bacteria and as a treatment for microbial infections. Furthermore, the new nanomaterial approach should have unique properties towards tumour cells, and at the same time can avoid the risks and downsides that result from conventional cancer treatments, such as chemotherapy.

Polymeric nanostructures have garnered the interest of researchers in the medical applications because of their cost-effective synthesis and the versatility they offer for surface modification. Additionally, polymeric nanostructures are sophisticated materials that incorporate various nanoparticles either by coating them with a polymer to develop a core-shell structure [4], bonding them covalently to form a functional nanostructure [13], or dispersing them in a polymer matrix [14]. Rhodanine and PR have versatile biological actions, such as antibacterial, antiviral, and antitumour properties [1]. Furthermore, their high surface area modification ability increases their interest. This review showcases recent advancements in the synthesis and characterisation of PR. Moreover, the review focuses on the biological applications of PR and PR-nanocomposites, demonstrating their properties as antibacterial, antiviral, antifouling, antiparasitic, anticancer, and others. Lastly, the review addresses the toxicity of PR as an important property in the medical field.

2. Synthesis of PR and its nanocomposites

In general, PR is synthesised through a process of chemical oxidation polymerisation. The functional groups on PR such as carbonyl, amide, and sulphide, take this polymer to another level and add other characteristics to its conducting behaviour. In addition to enhancing its biological and antibacterial performance, PR also forms stable conformations with other nanomaterials [15]. Therefore, in this section, pure PR synthesis, synthesis of superparamagnetic iron oxide and ferrite metals/PR, synthesis of metals and metal oxides/PR, and green approaches using curcumin and cellulose nanocrystals/PR will be discussed.

2.1. Synthesis of PR

Although PR has been used in different applications, the synthesis of freestanding PR polymer has rarely been reported. Nazaktabar et al. polymerised rhodanine monomers to assess their cytotoxicity and antiviral activity towards Newcastle virus in chicken embryo model [16]. Chemical oxidative polymerisation was employed for 20 h under severe stirring owing to high shear flow during polymerisation. Generally, after heating and dissolving the rhodanine in distilled water between 60 and 70 °C, the solution was cooled to a temperature range between 35 and 40 °C to avoid agglomeration. After polymerisation, which was initiated by the oxidant potassium permanganate ($KMnO_4$), the synthesised polymer was obtained by centrifugation and oven drying. As $KMnO_4$ is the most commonly used oxidant for the rhodanine polymerisation, a thin film composite (TFC) was developed by Rahimpour et al. utilising highly compatible PR nanoparticles into a polyamide active layer [8]. This film enhanced the antimicrobial, antifouling, and transport behaviours of the membrane.

An interesting study reported that utilisation of copper acetate as an oxidising agent in synthesis of PR nano-/microspheres. In this direct one-pot and green approach, its polymerisation happened under mild conditions, based on microwave synthetic protocol, as well as a green solvent involved in this transformation, such as water or ethanol [17]. The oxidative oligo-/polymerisation process was initiated and led to the formation of a complex of copper (Cu) with rhodamine. This formation occurred when the amide group was deprotonated, and Cu(II) ions formed coordination bonds with the nitrogen, sulphur, and/or carbonyl groups. The varnishing of NH-related peaks (1439, 3087, and 3172 cm^{-1}) led to NH bond being deprotonated, as indicated in FTIR analysis. Moreover, C═S band in rhodanine exhibited a red shift, moving from 1075 cm^{-1}–1018 cm^{-1} in the rhodanine−Cu(II). At room temperature, copper acetate was used to generate solid nanospheres containing rhodamine, resulting in the formation of PR core-shell nano-/microspheres. Although copper acetate exhibited slower formation processes and less quantity conversion of rhodanine to PR than the strong oxidant $KMnO_4$, a porous, non-spherical PR composite material was synthesised using $KMnO_4$. However, it was verified that the configuration of the resulting core−shell nanospheres changed when the potent oxidising agent $KMnO_4$ was used as a cocatalyst along with copper acetate in this synthesis method.

A study was employed with a green approach to prepare PR coated on cellulose nanocrystals (CNCs) and it was tested as an antimicrobial and an optical pH indicator [18,19]. Ferric chloride can be utilised as an oxidant to initiate the polymerisation of rhodanine on the negatively charged surface of CNC. In addition, various critical conditions were carefully controlled during the

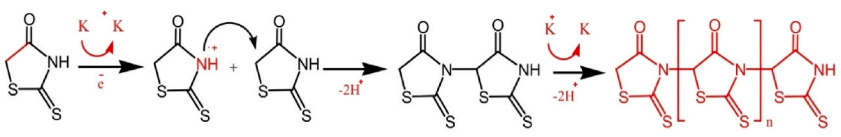

Fig. 1. Polymerisation mechanism of PR. Reprinted with permission from Rahimpour A et al. [8] Copyright 2018 American Chemical Society.

coating process to optimise its effectiveness. Initially, iron(III) chloride ($FeCl_3$) was dispersed into a evenly distributed CNC solution and stirred vigorously for 6 h. CNC–Fe (III) complexes were added to the prepared rhodanine monomer solution. Subsequently, the coordination bond between the ferric ions and nitrogen, oxygen, and sulphur atoms on the rhodanine monomers was established. Finally, the oxidative polymerisation of rhodanine continued for a duration of 24 h at which the final products were recovered using a 100 nm membrane filter via the ultrafiltration process. This process was used to repeatedly rinse the sample with Millipore-Q water until the filtrate became colourless.

Moreover, curcumin (C) was encapsulated by PR. Curcumin exhibited low water solubility in water, which deteriorates its performance in terms of excretion, limited absorption, maintaining physiological pH, poor bioavailability, and rapid metabolism [20]. To enhance the bioavailability and miscibility of curcumin in antimicrobial composites, PR was introduced. To induce a $FeCl_3/H_2O_2$ combination system, the oxidative polymerisation was initiated via a Fenton reaction. In this reaction, the hydrogen peroxides (H_2O_2) reduce iron (III) to iron (II), triggering the formation of a hydroxyl radical and proton. Two distinct oxygen radical species with water as a byproduct was formed by the disproportionation of H_2O_2. Then, the emulsified solution was formed via homogenisation, by using a rhodanine solution as water phase, and a curcumin solution as oil phase. Using the Fenton reaction has several benefits, including controlling the ratio of the oxidant to the monomer in the chemical oxidative polymerisation, which is usually maintained above a pH of 2.5. Over-oxidation occurs when the oxidant is overloaded, compromising the physical properties of the C/PR-NCs. Also, using a minimum amount of oxidant reduces the byproduct formation and avoids inactive material in the chemical transformation of the C/PR-NCs. Moreover, in this reaction, the curcumin/PR nano capsule shell thickness was manipulated by altering the ratio of the rhodanine monomer, which polymerised at the surface of the curcumin droplet. It was attributed to the ionic bonding between Fe^{+3} ions and sulphonate acid salt.

2.2. Synthesis of core-shell PR nanocomposites

The main challenge in synthesising a nanoscale polymer is controlling its size due to poor physical properties, which can lead to agglomeration or polymerisation to the bulk state of unstable nano-sized polymers [21]. Therefore, core-shell nanoparticles are widely used where a polymer coating is applied to solid inorganic nanoparticles, which serve as the core substrate. Besides, the core-shell structure offers the advantage of preventing agglomeration, resulting in numerous benefits. PR coating has antibacterial, antifungal, antiviral, and antitumour properties [22,23]. Moreover, other inorganic materials such as iron oxide, zinc oxide, cobalt, and nickel, have strong biological behaviour, thus the core-shell material adds value to the inorganic core with the polymer coating. PR shell also produces sufficient biocompatibility for biological applications by reducing the cytotoxicity of the inorganic materials [3].

2.2.1. Superparamagnetic iron oxide nanoparticles (MNPs)/PR

Superparamagnetic iron oxide nanoparticles (MNPs) have recently been accentuated in various fields, particularly in biology, owing to their exceptional properties. MNPs are a promising option for biomedical fields due to their resilience to chemical change, relative biocompatibility, simplicity of synthesis, and capability to be functionalised with other nanomaterials [24]. These biomedical applications include drug delivery [25], magnetic hyperthermia [26], and magnetic resonance imaging (MRI) and diagnosis [27].

Table 1
Magnetic nanoparticles/PR nanocomposites.

PR Nanocomposites	Synthesis	Properties	References
$PR/GO/Fe_3O_4$	Fe_3O_4 by coprecipitation approach, GO by modified Hummer's method, PR was the coating for the structure by chemical oxidative polymerisation using $KMnO_4$ as oxidant.	The core/shell structure improved the functional groups, increased the magnetization of the polymeric platform, and reduced the toxicity of the inorganic particles.	[4,5]
$CoFe_2O_4/PR$	Cobalt ferrite ($CoFe_2O_4$) was the first core material used for the oxidative polymerisation for PR using the oxidant $FeCl_3$.	As the quantity of polymerised rhodanine monomers increased, the size of the nanocomposite also grew, ranging from approximately 40 nm–150 nm. The particles had a spherical shape.	[3]
$NiFe_2O_4/PR$	Nickel Ferrite ($NiFe_2O_4$) was initially prepared via a coprecipitation method and later employed in the oxidative polymerisation of rhodanine monomers using $KMnO_4$.	Having a polygonal shape, the particles had a significant surface area to volume ratio, which is a crucial factor in biological applications, as it can contribute even at low concentrations. The size of $NiFe_2O_4/PR$ was roughly 15 nm, and the distribution of particle sizes was satisfactory.	[15]
$MnFe_2O_4/PR$	The resulting Manganese ferrites ($MnFe_2O_4$) stock suspension was further used to prepare $MnFe_2O_4/PR$ composites via an oxidation polymerisation process using $FeCl_3$.	The polymer layer provided effective coverage, as evidenced by a noticeable weight loss. The presence of $MnFe_2O_4$ had an impact on the thermal stability of the composite compared to pure polymer. The particles were small and had uneven shapes, occasionally appearing spherical, indicating a relatively random particle growth pattern with an average size of around 8.5 nm.	[30]
$MnFe_2O_4/PR$	The process of oxidation polymerisation was employed to manufacture binary hybrids of $MnFe_2O_4/PR$, with $FeCl_3$ serving as the oxidising agent.	With an average particle size of 8.3 nm and a narrow distribution, the product had an irregular morphology. The selected synthetic method permits the production of hydrophilic particles with moderate aggregation resistance, providing an accessible surface for future functionalisation	[23]

However, due to their inorganic nature, MNPs are not sufficiently biocompatible on their own. Therefore, one approach to enhance this compatibility is to envelop the magnetic nanoparticles with a biocompatible polymer [28]. Owing to the combination of the functional properties of magnetic core and polymeric shell in the nano or sub micro hybrid materials at the same time, these materials have a significant value in the novelty of nanocomposite [29]. However, magnetic iron oxide nanoparticles face some challenges in the biological environment, such as degradation and release of Fe^{2+} and Fe^{3+} ions, surface oxidation, and shortage of functional groups. Table 1 summarises the nanocomposites that include magnetic nanoparticle/PR as a core-shell combination. For instance, the production of PR/graphene oxide (GO)/iron oxide (Fe_3O_4) is employed as an anticancer and antibacterial agent. It is acted as an extremely sensitive biosensor for detecting doxorubicin hydrochloride in physiological fluids [5]. To produce the PR-coated Fe_3O_4 nanoparticles, a coprecipitation technique was adopted to generate the magnetic nanoparticles, and subsequently the polymerisation of rhodanine was performed using $KMnO_4$ as an oxidising agent. This alteration was carried out to improve the magnetization of PR and transform it into a recoverable magnetic polymeric platform. As part of this research, GO nanoparticles were used to coat the iron oxide, enhancing the morphology, functional groups, structural stability, and catalytic activity of PR.

Recently, researchers have shown an interest in developing ternary metal oxide structures by combining ferrite with metals like cobalt, copper, nickel, and zinc, due to their ferromagnetic properties for various biomedical applications [31]. For example, nickel-ferrite doped α-alumina nanoparticles were investigated for their bactericidal effectiveness towards *E. coli*, *S. aureus*, and *P. aeruginosa*. These were also observed to minimise the microbial proliferation activity of *S. aureus* and *P. aeruginosa* bacteria [32]. Compared to pure metals such as Co, Mn, and Ni, iron oxide exhibited limited saturation magnetization and negligible hysteresis losses. However, ferrite/metal combinations exhibited strong coercivity, elevated curie temperature, medium magnetization, and significant magneto crystalline anisotropy, making them an attractive alternative to Fe_3O_4 [33]. To regulate the cytotoxicity activity of the metal ferrite composites in biological environments, PR was used to coat nickel ferrite and cobalt ferrite for antibacterial purposes [3,15], and manganese ferrite for osteoporosis treatment, anticancer, and antibacterial [23,30].

The preparation of the hybrid nanoparticles containing metal ferrite coated with PR typically begins with the synthesis of the metal ferrite, which is subsequently used in the oxidative polymerisation of PR. For example, the preparation of $CoFe_2O_4$ coated with PR involved synthesising $CoFe_2O_4$ and resuspending it in 30 mL of water. A micro-scale approach was used for quantifying the concentration of magnetic particles. An oxidative polymerisation of rhodanine was occurred using $FeCl_3$ as an oxidant at room temperature to synthesise a $CoFe_2O_4$/PR. Specifically, a certain amount of rhodanine monomer was dissolved in water at 70 °C, and $CoFe_2O_4$ nanoparticles were subsequently added and stirred for 1 h. Next, $FeCl_3$ solution was introduced to the previous solution for further stirring for 24 h. PR nanocomposite was recovered by centrifugation. The described process produced a 1:1 wt ratio of $CoFe_2O_4$ to rhodanine. However, the hybrids with various amounts of rhodanine (1:1, 1:3, 1:5, 1:10) manipulated the thickness of the polymeric shell using the same synthetic technique [3].

2.2.2. Metal Oxides/PR synthesis

Among the inorganic core materials are metal oxides, such as zinc oxide, which have a bactericidal effect on many microorganisms. The biocide effect of ZnO is proposed in different techniques, including the of zinc ions (Zn^{+2}) liberation, reactive oxygen species (H_2O_2) generation, bacterial membrane disruption via exposure to ZnO, and Zn^{2+} ion interaction with cellular content [34]. Soleimani Lashkenari et al. used PR/ZnO in an antiprotozoal activity towards Trichomonas gallinae [35]. Owing to unique functional groups found in rhodanine monomers such as carbonyl, amine, thiol and sulphapyridine, polymerisation on ZnO nanoparticles resulted in the nanoparticles readily binding to parasite membranes and disrupting cellular functions. ZnO particles were prepared using zinc nitrate hexahydrate ($Zn(NO_3)_2.6H_2O$) solution and sodium carbonate (Na_2CO_3) solution. The process commenced with precipitation, resulting in the formation of a white solid that was subsequently rinsed with ethanol. These solids were then dried at 100 °C for 6 h and finally calcined at 250 °C for 2.5 h. Rhodanine polymerisation was conducted on ZnO nanoparticles. First, functionalised ZnO was formed using thiol (–SH) functional groups. ZnO–SH was added to ethanol for 20 min. Then, the suspension was filled with a dispersion of silver nitrate ($AgNO_3$) and mixed at 60 °C for 2 h. After that, rhodanine monomer was dispersed to the mixture under vigorous stirring and polymerisation occurred at 60 °C for 1 day. Following the centrifugation of the PR-coated ZnO suspension, it was rinsed multiple times with ethanol to eliminate residual materials. Ultimately, drying of precipitates was performed at 45 °C for 1 day. The results of FESEM illustrated a spherical morphology configuration with a low aggregation of nanoparticles. However, the size of nanoparticles became relatively larger from 66.1 to 161.9 nm when PR was coated on ZnO nanoparticles.

In another study, PR/ZnO was employed to modify the polysulfone (PSf) membrane by using a dip-coating technique to enhance the microbial inhibitory influence on the membrane [22]. ZnO/PR nanoparticles were synthesised using a similar approach to the previous preparation. Owing to the intense attraction between the silver and SH group, the rhodanine was involved in chemical oxidation polymerisation initiated by silver ions (Ag^+), which were situated on the functionalised ZnO surface via thiol (ZnO-SH). The presence of Ag^+ ions on the ZnO led to the polymerisation of the PR surrounding the ZnO. PR was also used in membrane modification as sulfonated-PSf/PR membranes to increase their antibacterial properties. Sulfonation of PSf was initiated to improve its hydrophilicity. Subsequently, the sulfonated PSf generated PR nanoparticles by in situ polymerisation of PR [36]. Another metal oxide combined with PR as a core-shell nanocomposites is titanium oxide (TiO_2). Using a lower cost with a simple procedure and no advanced equipment needed, Ozkan et al. prepared needle-like TiO_2/PR nanocomposites without altering the intrinsic structural configuration and electronic lattice of rutile TiO_2 [37]. First, TiO_2 was coated with Fe ions, and then 100 ml n-hexane, which had been dispersed with Fe^{3+} ions-treated TiO_2 nanoparticles, was sonicated for 30 min to obtain rhodamine through polymerisation. Further, with severe stirring at 25 °C for 24 h, the polymerisation of rhodanine was carried out on the surface of needle-like TiO_2 nanoparticles.

2.2.3. Metal/PR synthesis

Metallic nanoparticles have unique physical and chemical properties that are useful in various fields, including medical and healthcare applications. Silver nanoparticles, in particular, are known for their antibacterial, anticancer, and diagnostic properties [38]. Researchers have synthesised a PR-silver complex in the form of nanofibers, which were assessed for antimicrobial effectiveness towards Gram-positive and Gram-negative bacteria [39]. The PR-silver complex was prepared by adding $AgNO_3$ to ethanol and then adding rhodanine monomers to the solution at 60 °C with vigorous stirring. The SEM images showed that the spherical silver nanoparticles were affixed to the exterior of the tubular structure of the PR-silver complex. An average size of 40 nm was found in Ag nanoparticles coated in the PR tubes. Besides, silver/PR nanocomposites with a substantial unique surface area were synthesised by Song et al., featuring silica nanoparticle decoration. A strong affinity for metal ions was achieved by pre-treating the silica nanoparticles using Thiol-terminated silane [40]. Further, the dispersion of the functionalised SiO_2 in silver nitrate solubilised in ethanol was required to trigger metal binding on the surface of thiol groups in treated silica. Owing to this action, Ag^+ ions were favourable attached to the surface of the nanoparticle. Subsequently, rhodanine monomers were added and underwent their polymerisation using an oxidising catalyst (Ag^+ ions). This was attributed to polymerisation on the silica surface with Ag^+ ions resulting in the formation of metallic silver nanoparticles by the reduction of Ag^+ ions. The resulting silica nanoparticles decorated Ag/PR-nanocomposite had a dark colour due to the presence of PR. Finally, Song et al. fabricated silica/PR core-shell nanoparticles as an antibacterial agent by coating silica with Fe ions as an initiator and polymerising for 12 h on the surface of silica nanoparticles [41]. Since silica nanoparticles serve as the core, their various size could manipulate the size of the nanoparticles core-shell.

Generally, the main synthetic route for PR is chemical oxidation polymerisation, which involves the utilisation of chemical oxidants, such as $KMnO_4$ and $FeCl_3$. Typically, in PR nanocomposites, the nanoparticles attached to PR are prepared first, followed by the polymerisation step. The selection of the appropriate synthesis method for PR nanocomposites depends on the specific application being targeted. For instance, the polymerisation on metal oxides requires the functionalisation of thiol groups on ZnO and the initiator Ag^+ ions. A green approach to synthesising PR is the best route as it is a mild and environmentally friendly method that can be carried out under mild conditions. PR is a polymer that has attracted considerable attention in the biological field. Therefore, it is highly significant to emerge a green method that can increase its biocompatibility in these applications, in addition to reducing harm to the environment. Microwave-assisted synthesis has been identified as a green one-pot method. The ethanol-based synthesis produced spherical Cu-PR complexes ranging in size from 20 to 200 nm, while water-based synthesis produced smaller and visually more porous particles. When $KMnO_4$ was used as the oxidant instead of copper acetate, the reaction was faster, but the PR nanosphere configuration did not resemble that of microspheres, as seen in TEM analysis. This template-free method was simple and conveniently scaled up in the industrial production of PR nanosphere.

3. Characterization

Since many PR-nanocomposites can be synthesised for different applications as mentioned in the previous section, it is essential to comprehensively understand their impact on the physical and mechanical characteristics of PR nanocomposites. Structural and morphological details of the synthesised PR and its nanocomposites can be generated by various kinds of microscopic and spectroscopic methods. Therefore, characterisation is done using a plethora of analysis techniques, such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), thermal analysis, UV–vis spectroscopy, Vibrating-sample magnetometry (VSM), and X-ray diffractometry (XRD). In this section, the characterisation methods for PR and its nanocomposites will be presented.

3.1. Fourier transform infrared spectroscopy (FTIR)

FTIR is commonly adopted to investigate the molecular structure of the synthesised PR, indicate the polymerisation of rhodanine monomers, and provide evidence of the successful development of PR nanocomposites. Table 2 shows the most common peaks found in PR that were generated through oxidation polymerisation, as analysed by FTIR spectra [16]. A $C \equiv C$ stretching vibration (1667 cm^{-1}) and a $C = N^+$ stretching (1438 cm^{-1}) were observed in the PR spectra. However, there was the absence of $C = O$ stretching of rhodanine monomer, which is usually indicated in an intense peak at 1710 cm^{-1}. Additionally, $C - O$ stretching vibration (1195 cm^{-1}) increased compared to the peak of rhodanine monomer [40,41]. One possible interpretation is that the polymerisation process of rhodanine

Table 2
Characteristic peak wavenumber of PR. Reprinted from toxicity assessment and antiviral effectiveness of polyrhodanine nanoparticles by adopting the chicken embryo model in vivo [16], Copyright (2017), with permission from Elsevier.

Wavenumber, cm^{-1}	Assignments
3412	$O - H$ bending of water
2353	Atmospheric CO_2
1667	$C \equiv C$ stretching vibration in the polymer chain
1576	Amino group
1438	$C = N^+$ stretching
1317	$C - H$ aromatic stretching
1195	$C - O$ stretching vibration

operated via an autocatalytic mechanism, which involved the formation of a polymer chain across carbon and nitrogen atoms by linking rhodanine molecules [41]. As shown in Table 2, the successful polymerisation of rhodanine monomers was confirmed by the peak 1576 cm^{-1}, indicating the amino group of rhodanine. One of the most prepared hybrid compounds with PR is superparamagnetic nanoparticles. For example, the intense Fe − O absorption peak around 450 and 594 cm^{-1} confirmed the formation of magnetite [29]. Moreover, the peaks of PR and Fe_3O_4 showed a slight shift, indicating the interaction between PR and magnetite nanoparticles, as illustrated in FTIR spectrum of Fe_3O_4/PR core/shell [30].

3.2. Scanning electron microscopy and transmission electron microscopy

Scanning electron microscopy (SEM) is an advanced approach to investigate the surface morphology of the synthesised PR and their nanocomposites. SEM is generally well-suited for capturing surface details across relatively large areas, while transmission electron microscopy (TEM) is applied for assessing the internal details of small samples at near-atomic resolution. The diameter of spherical PR nanoparticles typically ranges from 50 to 200 nm on average, with the majority of particles being less than 80 nm in diameter [16]. The spherical shape of PR offers a high surface area-to-volume ratio, which is a crucial element in biological applications due to its impact even at low concentrations.

In the previous section, different modifications will be discussed that result in different particle morphologies. SEM is often used to confirm the presence of PR coatings in hybrid compounds, and the dimensions of these hybrid particles depend strongly on the amount of PR used. For example, the addition of PR to ZnO nanoparticles resulted in an increase in size from 66.1 to 161.9 nm [35]. The thickness of the PR layer can also affected the physicochemical properties of the hybrids, as demonstrated by Zachanowicz et al. in their study of PR/$MnFe_2O_4$ [23]. They found that the size of the particles increased as the monomer ratio increased, with sizes 20 ± 2.6 nm, 62 ± 20 nm, and 110 ± 50 nm for ratios of 10 %:90 %, 37 %:63 %, and 45 %:55 %, respectively. Additionally, the preservation of the particle diameters was confirmed by the hydrodynamic size measurements. The reduction in the surface energy of nanoparticles was triggered effectively by the polymer coating, delivering adequate stability of the PR/$MnFe_2O_4$ composites in a suspending medium [23].

The product structural characteristics are confirmed using TEM, and selected area electron diffraction (SAED) offers a more precise measurement of particle size, distribution, and shape. The results show that each particle size was single with separate crystallite, relatively narrow particle distribution and irregular morphology on the product [23]. Similar results were observed for PR/$CoFe_2O_4$ [3] and PR/$NiFe_2O_4$ [15]. However, it was noticed that $NiFe_2O_4$ nanoparticles and PR/$NiFe_2O_4$ had similarities in terms of polygon structure. PR/$NiFe_2O_4$ had a smaller and more uniform particle size ranging between 10 and 20 nm, as opposed to the broader size distribution observed in $NiFe_2O_4$ nanoparticles, which ranged from 30 to 100 nm. Moreover, the PR shell protected $NiFe_2O_4$ particles from agglomeration while a high surface area to volume ratio was attributed to the polygon structure, which was a vital factor in various biological applications [15].

3.3. X-ray diffraction analysis

X-ray diffraction analysis (XRD) is a non-destructive approach providing in-depth about the chemical composition, crystallographic structure, and physical properties of a material. To investigate the structural properties of the organic-inorganic hybrid materials, XRD analysis is conducted. The results are usually compared with those of the control sample, which consisted of pure inorganic nanoparticles. For example, the diffraction pattern of PR/$CoFe_2O_4$ was found to be the same as that of the pure $CoFe_2O_4$ nanoparticles, indicating that the modified inorganic material with the PR shell did not cause any crystalline configuration changes for the magnetic $CoFe_2O_4$. Furthermore, the absence of other diffraction peaks indicates that there were no impurities in the hybrid structure. Thus, as suggested by Zachanowicz et al. , the inorganic nanoparticles with the polymeric layer are unaltered with the chemical natures of the nanoparticles [23].

Debye Scherrer's equation is applied to estimate the size of PR nanocomposites.

$$d = \frac{K\lambda}{\beta \,\mathbf{Cos}\, \theta}$$

Where d is the mean diameter of crystalline nanoparticles (angstrom), K is a geometrical factor which links to lattice direction and crystallite morphology (K = 0.89), λ is the X-ray wavelength (nm) (λ = 0.154056), β is the line broadening at half maximum (FWHM) of the diffraction lines, and θ is half of the diffraction angle θ.

3.4. Thermal gravimetric analysis

To assess the thermal stability of PR hybrids and investigate the processes involved in soft material decomposition and shell coating, thermal gravimetric analysis (TGA) is conducted. TGA is performed under air or an inert nitrogen atmosphere at temperatures ranging from 25 to 260 °C. As reported in the TGA analysis, an initial weight loss was found in the PR hybrid materials at temperatures up to 110 °C, which could be caused by moisture loss. Followed by a second step between 110 and 290 °C (52 %), the thermal degradation of the main PR chain and depolymerisation was indicated. The core-shell structure with PR showed improved thermal stability, as observed in the TiO_2/PR core/shell hybrid nanostructure. The interaction between the PR and TiO_2 nanoparticles' surface was involved and the segmental motion of polymer chains was limited by the homogeneous distribution of PR chains on the surface of

Table 3
Summary of the biological applications of PR.

Modification	Application	Method	Results	Ref.
Needle-like-TiO_2/PR	Antibacterial (*S. aureus*, *K. pneumoniae*, and *E. coli*)	Well diffusion method, bacterial colony-counting method, modified Kirby-Bauer disk diffusion method	According to the colony-counting method, the needle-like TiO_2/PR hybrid showed the highest effectiveness in killing *E. coli* bacteria.	[37]
Silica/PR	Antibacterial (*S. aureus* and *E. coli*)	Bacterial colony-counting method the minimum inhibitory concentration (MIC) test	The antimicrobial activity against both *E. coli* and *S. aureus* was found to be excellent.	[41]
Silver/PR	Antibacterial (*S. aureus* and *E. coli*) and cytotoxicity	Bacterial colony-counting and MIC test	The antimicrobial activity against both *E. coli* and *S. aureus* was found to be excellent.	[40]
Silver/PR	Antibacterial (*S. aureus, E. coli*)	Modified Kirby-Bauer Test	Superior antibacterial effect on all bacteria	[39]
CNCs/PR	Antibacterial (*B. subtilis, E. coli*) and cytotoxicity	Bacterial colony-counting and MIC test	Rod-like CNC@PR nanoparticles showed noteworthy antibacterial potential towards *E. coli* and *B. subtilis*	[19]
CNCs/PR	Optical pH indicator	UV–Vis	Reversibly responded to changes in the pH	[18]
PR/Fe_3O_4/GO	Antibacterial (*Pseudomonas aeruginosa, E. coli, E. faecalis, S. aureus, and C. albicans*). Anticancer	Minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), and minimum fungicidal concentration (MFC). *In vitro* cell toxicity assay against hepatocarcinoma (Hep-G2) cells	The most significant impact against *E. coli* was observed with the use of PR/Fe at a concentration of 7.8 μg/mL. On the other hand, *P. aeruginosa* exhibited approximately a 50 % increase in growth when treated with PR/Fe/GO at 7.8 μg/mL.	[4]
PR@$CoFe_2O_4$	Cytotoxicity towards mouse macrophage and human osteosarcoma cell line. Antibacterial activity (*E. coli, S. aureus*)	MTT assay Kirby-Bauer disc method.	It indicated an interesting bactericidal property towards both gram-positive and gram-negative bacteria with minimal cytotoxicity	[3]
PR@$MnFe_2O_4$	Cytotoxicity against macrophages (RAW 264.7), osteosarcoma cells line (UMR-106), and stromal progenitor cells of adipose tissue (ASCs) Antibacterial activity (*E. coli, S. aureus*)	*In vitro* cell toxicity effect. Agar diffusion method.	The hybrids could control the physiological activity of cells in a manner that is proportional to their concentration. Additionally, the number of viable bacteria in the tested materials decreased significantly with increasing amounts of PR.	[23].
PR/$NiFe_2O_4$	Antibacterial activity (*E. coli, S. aureus*)	Disc diffusion method, MIC and MBC test	The antibacterial activity against both *E. coli* and *S. aureus* was found to be excellent.	[15]
PR	Antivirus and toxicity	*In ovo* assay Blood serum biochemical parameters and tissue harvesting	Antiviral activity for PR and no toxicity	[16]
Sulfonated-polyethersulfone/PR	Antifouling (*E. coli, S. aureus*)	Liquid culture test, linear cultivation tests, disk diffusion method, and Colony Forming Unit Counting Method	Excellent antibacterial activity and high membrane water flux	[36]
ZnO/PR	Antibacterial membrane	Colony counting and disk diffusion methods.	Enhanced the membrane properties	[22]
PR/Fe_3O_4/GO	DOX detection in biological fluids	Electrochemical assessment of the fabricated biosensor	Superior sensitivity of the biosensor	[5]
PR@$MnFe_2O_4$	Osteoporosis treatment	Cell line culture, cell viability assay, analysis of mRNA expression profile	The hybrid compound at a ratio of 10/90 enhances the viability of the pre-osteoblasts	[30]

TiO_2 particles. As a result, the TiO_2/PR core/shell nanocomposite structure was improved in the decomposition temperature [37].

4. Biological application of PR

PR possesses distinctive properties, which are favourable in various applications, such as corrosion inhibition [42], lithium batteries [43], and heavy metals adsorption [44]. This review focus on PR's applications in different biological and medical fields, including antibacterial, antiviral, antiparasitic, and anticancer activities. Table 3 summarises the previously published papers on this topic, along with the latest updates. Furthermore, Fig. 2 provides a schematic diagram that illustrates some of the fundamental discussions on PR's biological application.

4.1. Antimicrobial activity of PR

Antimicrobial resistance refers to changes that occur in bacteria, viruses, fungi, and parasites over time, making them unresponsive to medicines and rendering the infection more arduous or impracticable to cure. Treatment resistance increases the risk of disease dissemination, serious illness, and fatality. Researchers estimated that in 2019, antimicrobial resistance in bacteria caused around 1.27 million deaths. The six most significant pathogens for deaths related to resistance are *Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, and Streptococcus pneumoniae*, responsible for 929,000 deaths attributable to antimicrobial resistance in 2019 [10]. Furthermore, the tolerance of the bacterial cells increases when the resistant bacteria are treated with antibiotics. As an example, methicillin resistance (MRSA, methicillin-resistant *S. aureus*) is observed in 40–60 % of *Staphylococcus aureus* strains isolated from US hospitals. In some instances, resistance extends to last-resort antibiotics, such as carbapenems and vancomycin [45]. Due to the rising health risk, there is an urge to seek new strategies to overcome this problem. Many promising therapeutic strategies have been explored, such as antimicrobial peptides and nanomaterial-based treatments.

Nanomaterials have diverse physio-chemical properties that make them suitable to effectively treat bacteria-resistant infections. They are used as a carrier for natural antimicrobials and antibiotics, as well as to attack bacteria themselves [46]. The efficacy of nanomaterial-based antimicrobials depends on the modification of core material, shape, size, and surface chemistry of the nanomaterial composite [47]. These characteristics enable nanomaterial-based treatments to overcome antibiotic resistance through several bactericidal pathways. Some of these pathways include binding and disrupting the bacteria's membrane, which causes a leakage of cytoplasmic components. Nanomaterials can also attach to intracellular components within the bacteria, such as DNA, enzymes, and ribosomes, interfering with the normal cellular machinery and leading to enzyme inhibition, electrolyte imbalance, oxidative stress, and ultimately causing cell death [46,48].

4.1.1. Core-shell antibacterial nanostructure

Recently, many studies have been conducted on nanomaterial-based antimicrobials. Scientists have used several types of materials and modifications of the core material for different treatment mechanisms. One of these materials is rhodanine and its polymer, which have garnered significant attention because they can be structurally fabricated into various biotic composites. PR is a conducting polymer that is used in many applications, including the medical field. Functional groups such as amide, carbonyl, dithiocarbamate, and sulphide, in conjunction with free electron pairs, facilitate the modification of PR for usage in antibacterial activity [23,49]. To achieve the best properties of the PR, various fabrication methods have been employed, such as forming a core-shell structure by coating with PR, dispersing in a polymer matrix or creating a nanostructure that is bonded covalently.

A needle-like TiO_2/PR core/shell nanocomposite by electrostatic interactions was prepared through a cost-effective and simple

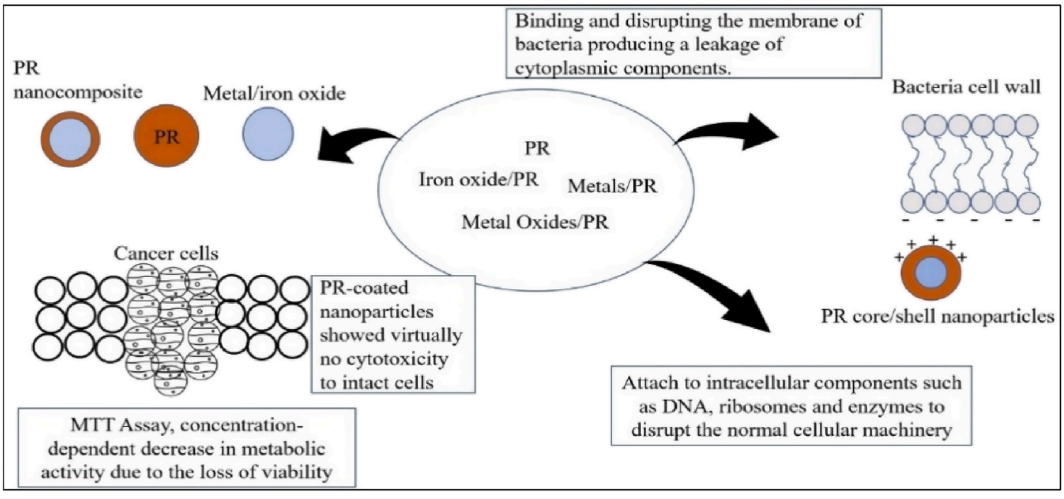

Fig. 2. Scheme of the fundamentals of PR biological activity.

chemical procedure [37]. TiO_2, one of the metal oxides recently investigated for its diverse properties, including antimicrobial properties, is being used in the medical field. Three different methods, including the good diffusion method, bacteria colony-counting method, and modified Kirby-Bauer disk diffusion method, were utilised to determine the antimicrobial activity of TiO_2/PR. Ozkan et al. investigated the zone of inhibition of needle-like TiO_2, rhodanine, and TiO_2/PR by using a modified Kirby-Bauer disk. After 24 h of incubation, needle-like TiO_2 did not exhibit any antimicrobial activity towards *S. aureus*. However, TiO_2/PR nanocomposite particles and rhodanine showed a clear visible zone of inhibition towards *S. aureus*, with average zone diameters of 12 mm and 18 mm, respectively [37]. This study exhibited that the average thickness of the needle-like TiO_2 nanoparticles, after being coated with PR shells, was 4.8–6.5 nm, which gained after antibacterial activity towards *S. aureus*. This was likely due to the partial protonation process in tertiary amide groups from PR shells involved in aqueous media, which can promote positive charges on PR chains. These charges can then attract the negatively charged cell walls of bacteria, causing their death. Rhodanine demonstrated superior antibacterial action against *S. aureus* than needle-like TiO_2/PR nanocomposite based on the variations in zone diameters. However, there was no such antibacterial activity found in *K. pneumoniae* in the same approach, which was probably due to the bacteria capsule layer [37].

In summary, the TiO_2/PR hybrid demonstrated promising potential as a long-term antibacterial material against three bacterial strains (*S. aureus, E. coli,* and *K. pneumoniae*), as confirmed by the colony count method. Additional in vivo testing may further support this claim. Furthermore, the electrokinetic properties of the TiO_2/PR hybrid indicated the formation of stable aqueous dispersions, effectively addressing the agglomeration issue that is commonly observed in such systems [37].

Obviously, the core/shell type nanocomposites, that use the solid inorganic nanoparticles as a core material and the polymer as a coating shell, demonstrate a potential solution for the agglomeration of these nanocomposites [21]. Furthermore, the core/shell nanocomposite provides an additional antibacterial characteristic to the nanocomposites. Among the nanoparticles, that are used as a core in the nanocomposites, are silica nanoparticles. Silica has been used recently due to its low toxicity, controllable particle size, and tunable surface structure [40,50]. Silica/PR core/shell nanoparticles were formed by chemical oxidation polymerisation. Fe(III) ions acted as catalysts, initiating the polymerisation on the surface of the silica nanoparticles where the process continued. The nanocomposite silica/PR showed excellent biocidal activity towards Gram-negative *E. coli* and Gram-positive *S. aureus* [41]. After treatment with silica/PR nanoparticles on this microbial activity, FE-SEM and TEM were used to observe the morphological variations in *E. coli* and *S. aureus*. The contact between silica/PR and bacteria resulted in a severe disruption in the outer membrane, therefore compromising cell structure. Interestingly, by varying the diameter of the silica core, the size of the core-shell nanoparticles could be

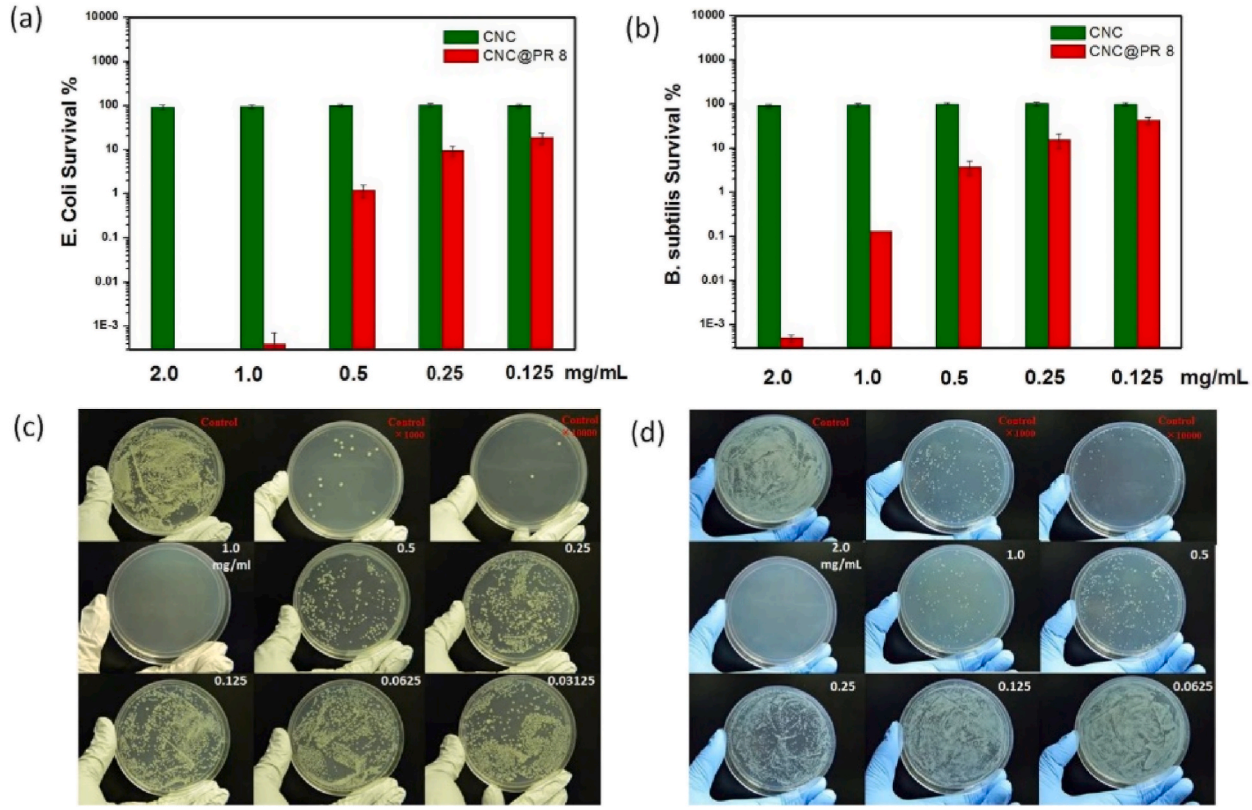

Fig. 3. Antimicrobial testing of pristine CNC and CNC@PR 8 suspensions against (a) *E. coli* and (b) B. subtilis; Photo images of (c) *E. coli* and (d) *B. subtilis* colonies grown on LB agar plates after incubation with CNC@PR. Reprinted with permission from Tang J et al. [19] Copyright 2015 American Chemical Society.

manipulated. The antibacterial activity of the nanoparticles was improved by decreasing the size of the nanoparticles.

For instance, silica was used in an antibacterial nanocomposite, as seen in the case of the silica-decorated silver/PR composite [40]. Silica nanoparticles served as the surface where PR polymerisation took place, and the reduction of Ag^{+} ions led to the development of metallic Ag nanoparticles on the surface of the silica nanoparticles, forming a diameter of approximately 7 nm with silver/PR-composite nanoparticles. Silver nanoparticles were notable for their excellent therapeutic properties, powerful antimicrobial agent, and low microbial resistance, making them highly useful in several medical research fields [38]. The bacterial colony-counting method and minimum inhibitory concentration (MIC) test were utilised for the effectiveness of the antibacterial activity of these nanoparticles. FE-SEM images investigated morphological changes in the bacteria. As a result of the antibacterial properties exhibited by the silver nanoparticles and the PR, Song et al. showed that the silver/PR-nanocomposite-decorated silica nanoparticles displayed strong antimicrobial efficacy against *E. coli* and *S. aureus* [40]. There was no growth of bacterial colonies Luria Broth (LB) agar with SiO_2–Ag/PR nanoparticles. The MIC of the nanoparticles towards *E. coli* and *S. aureus* were 1.5 mg mL^{-1} and 2.5 mg mL^{-1}, respectively. Furthermore, Kong & Jang confirmed the superior effect of the silver/PR complex on bacteria using the modified Kirby-Bauer test against both Gram-positive bacteria (*S. aureus*) and Gram-negative bacteria (*E. coli*) [39]. The results showed that silver/PR nanotubes had a stronger effect on bacteria compared to silver sulfadiazine. This effect can be triggered by the synergistic effect of both silver and rhodanine. Moreover, the antibacterial behaviour was intensified when the tubular structure of the silver/PR complex ruptured the cell wall, creating a synthetic pore. This resulted in cell damage and the release of the cellular components [51].

Owing to the increasing focus on environmental concern and sustainability, there is a need to use renewable, sustainable, and non-toxic resources for antimicrobial applications. Cellulose is the most ubiquitous biopolymer, with a yield rate of around 1.5×10^{12} tonnes per year. The acid hydrolysis process of pulp cellulose fibres can produce cellulose nanocrystals (CNCs) by degrading the amorphous domains of the fibre and cleaving the hydrogen bonds to form crystalline rods [52]. CNCs exhibit numerous attractive properties, making them well-suited for diverse applications. These include their substantial surface area, tensile strength, stiffness, and high quantity of surface hydroxyl groups. The hydroxyl groups offer the potential for chemical modification, including the conversion to aldehyde, amine, carboxylic acid, or thiol groups, which can be used for further modifications [53,54]. Many molecules and nanoparticles have been used to modify the surface of CNCs, enabling their functionality antibacterial and antiviral agents [55], biomarkers or sensors [56], tissue engineering scaffolds [57], gene vectors, and drug delivery vehicles [58].

PR is one of the nanoparticles that were coated onto the surface of CNC, an eco-friendly technique by Tang et al. was adopted to modify the surface of CNC to fabricate CNC@PR core-sheath nanoparticles. Using ferric chloride as the initiator and oxidant, the rhodanine monomer was polymerised on the surface of negatively charged CNC [19]. The coated composite had outstanding colloidal stability, preventing aggregation or flocculation for several months. Fig. 3a and b demonstrates the antimicrobial testing of CNC and CNC@PR from 8 sample suspensions toward *E. coli* (Gram-negative) and *B. subtilis* (Gram-positive), respectively. The results showed that CNC dispersion did not have antimicrobial activity on both *B. subtilis* and *E. coli*. Fig. 3c shows that the density of the bacterial colonies reduced when CNC@PR concentration increased, leading to the removal of *E. coli* entirely once the concentration was nearly 1 mg/ml. Likewise, Fig. 3d illustrates the same trend of removal of *B. subtilis* colonies as the concentration of solution increased.

Compared to spherical nano-composite particles, it can be confirmed that a potential antibacterial property against *E. coli* (Gram-negative) and *B. subtilis* (Gram-positive) was rod-like CNC@PR nanoparticles. Therefore, the core-sheath nanomaterial held promise for applications in antimicrobial settings, encompassing the incorporation as antimicrobial additives, surfaces or coatings, and within the domain of food packaging.

Furthermore, CNCs@PR nanoparticles were fabricated in an aqueous solution through in-situ polymerisation for use as an optical pH indicator [18]. These nanoparticles had good colloid stability, good mechanical strength, and a high surface area. In several fields such as food, clinical diagnostics, bioprocessing, and wastewater treatment, pH is typically adopted to manipulate solution conditions. Utilising changes in spectroscopic properties in response to pH for optical sensing offers a convenient method to streamline analysis. Tang et al. demonstrated that the CNCs@PR core-shell nanoparticles had reversible feedback in pH variations, with the colour shifting progressively from a pale to bluish-violet as the pH was manipulated from 2.04 to 12.04 [18].

4.1.2. Superparamagnetic hybrid nanostructure

Owing to their superparamagnetism under biological compatibility, high stability and magnetic fields, the superparamagnetic iron oxide nanoparticles have garnered the interest of many researchers among all the superparamagnetic nanoparticles. The superparamagnetic nanoparticles, including maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4), are commonly utilised for biomedical applications, such as catalysis, cancer therapy, contrast agents, and magnetic fluids [59–63]. To be used for biomedical applications, minimal cytotoxicity is a vital requirement. Although iron oxide nanoparticles have been endorsed for clinical use, their cytotoxicity is still under discussion, especially as it differs after different modifications. Thus, iron oxide is frequently coated with biocompatible polymers, such as PR, to prevent surface oxidation, magnetic clumping, and the lack of functional groups [4]. Another high-value material used in the modification of iron oxide in clinical studies is graphene oxide (GO). The combinational structure of GO, which includes oxygen-based functional groups, makes it an excellent candidate for the modification process [24]. While GO in its hybrid structure can offer minimal toxicity, GO/inorganic nanocomposites offer cytotoxic control. As a result, PR/Fe_3O_4 modified by GO showed improvement in the structure configuration stability, morphology, functional groups, and catalytic activity of both PR and Fe_3O_4 [4]. The nanocomposite PR/Fe_3O_4/GO showed antibacterial activity against *P. aeruginosa, E. faecalis, C. albicans, E. coli,* and, *S. aureus*, and its activity was increased under the effect of a media composed of kombucha supernatant. The nano-structural materials that combine magnetic cores and polymeric shells are important for developing the functional properties of both materials simultaneously.

It was recommended that the formation of ternary metal oxide structures through the synergistic effect of ferrite with metals like

cobalt, copper, nickel, and zinc. These structures exhibit interesting biomedical behaviour due to their strong coercivity, elevated curie temperature, medium magnetization and high magneto crystalline anisotropy [64]. Furthermore, coating the iron oxide composite with a polymer shell can be performed to prevent it from aggregation and the undesirable impacts of direct contact with the biological media. Two hybrid nanomaterials were synthesised by Zachanowicz et al., which are PR@$CoFe_2O_4$ and PR@$MnFe_2O_4$. Zachanowicz et al. reported the synergistic effect of PR/cobalt ferrite hybrid nanomaterial that was successfully synthesised by using a two-step process. It was started with the dispersion of the purified stock nanoparticles and followed by the oxidative polymerisation of rhodamine monomer in the presence of $CoFe_2O_4$ [3]. The hybrid composite PR@$CoFe_2O_4$ showed an interesting bactericidal property towards both gram-negative and gram-positive bacteria. This effect was achieved through the collaborative action of the PR coating, known for its antimicrobial properties and high biocompatibility to mammalian cells, and the magnetic behaviour of the spinel nanoparticles. Interestingly, the increase in the polymeric shell thickness showed an influence on the antimicrobial activity but stopped at a certain amount of polymer. This suggested the potential use of the hybrid material as an antimicrobial agent, adopted for magnetic carrier or magnetic hyperthermia. The same results were reported for PR@$MnFe_2O_4$ revealing the efficacy of the antimicrobial activity using the agar diffusion assay testing and Kirby-Bauer disk technique. In fact, PR showed distinct antimicrobial properties towards *S. aureus* and *E. coli*. A significant decrease in viable bacteria number was observed in all investigated samples while the amount of polymer influences hybrid activity. This effect was comparable to PR action at a ratio of 1:1 [23].

A different combination of ferrite with metals is $NiFe_2O_4$. This material exhibits various types of magnetic characteristics, including ferromagnetic, paramagnetic, or superparamagnetic characteristics depending on the particle morphology, such as the size and the shape of the particles [31,65,66]. As a result of these properties, Soleimani Lashkenari et al. investigated the formation of the nanocomposites PR/$NiFe_2O_4$ and its antibacterial activity against Gram-positive *S. aureus* and Gram-negative *E. coli* using disc diffusion method, MIC and MBC test [15]. The radiuses of inhibition growth for *S. aureus* and *E. coli* were 16 mm and 11 mm, respectively. The hybrid compound showed a better result for the inhibition zones than for $NiFe_2O_4$, which was 13 mm for *S. aureus*. However, no specific inhibition region for *E. coli* was observed. It can be indicated that the PR structure contains functional groups that interfere with the cell walls and membranes within microorganisms [67]. The electrostatic contact between cationic and the negative-charged cell wall components led to cell membrane damage and, therefore cell death [68]. Moreover, as a comparison between PR/$NiFe_2O_4$ nanocomposites with two commonly used antibiotics (Streptomycin and Chloramphenicol) referring to the research results of Kheshtzar et al. [69], the inhibition growth radius for Streptomycin was 6.3 and 6 mm against S. *aureus* and *E. coli*, respectively. In contrast, Chloramphenicol resulted the inhibition growth radii of 10 and 18 mm for *E. coli* and *S. aureus*, respectively. PR/$NiFe_2O_4$ nanocomposites showed better antimicrobial activity towards *E. coli* and *S. aureus* bacteria compared to conventional Streptomycin and Chloramphenicol antibiotics. However, the commercial antibiotic Chloramphenicol caused slightly better antibacterial effectiveness against *S. aureus* bacteria with a radius difference of 2 mm. Remarkably, $NiFe_2O_4$ nanoparticles had no cytotoxicity at low concentrations [70]. Thus, the resulting toxicity of the encapsulated $NiFe_2O_4$ by PR was mainly dependent on the toxic properties of the PR, which will be discussed in another section.

4.1.3. Antivirus, antifouling, and antiparasitic activity of PR

Newcastle disease virus (NDV) is a highly fatal disease in the poultry industry. To combat the spread of this virus, researchers have proposed studying the use of PR with a chicken embryo (in *ovo*) model [16]. The chicken embryo model is a suitable alternative to mammalian cells because it can grow independently of many environmental and maternal factors, and it has different types of growing cells. Additionally, its fast development and organisation make it an ideal candidate for research [71,72]. During an outbreak of Newcastle disease, the antiviral activity of PR was tested in *ovo* to assess its potential for reducing the EID50 index of a pigeon-isolated NDV strain. The results showed that embryos treated with 100 ppm/0.1 ml PR had no positive hemagglutination reaction, indicating a reduction in NDV replication. The absence of embryo death was attributed to the antiviral activity of PR [16]. PR has many characteristics that make it an effective disinfectant. As a polymeric nanocomposite, it has a small particle size, high surface area, resistance to volatility, and chemical changes. It is sparingly soluble in common solvents including water [73–75]. Viruses such as influenza and paramyxoviruses, which are found on porous surfaces, are highly resistant to disinfectants. Therefore, a high-penetration disinfectant is crucial in various disinfecting applications [74]. Most molecules in the PR nanostructure are located on the surface, enhancing the interaction between target molecules and PR functional groups. This interaction contribute to the disinfectant effectiveness of the PR nanostructure [76].

Biofouling means the microorganisms adhering and growing on the surface of a membrane or within its pores [77,78]. This issue is a serious concern as it increases operational costs, reduces membrane performance and poses a threat to human health [79,80]. Various methods have been employed to address biofouling, including the establishment of fouling-resistant membranes with anti-bacterial and anti-adhesive behaviours. Increasing the hydrophilicity of the membrane surface can improve its anti-adhesive behaviours, while the incorporation of anti-bacterial composites can limit microorganism growth [81–83]. Recent studies have focused on modifying the membrane surface, such as the fabrication of sulfonated-polyethersulfone/PR (SPES/PR) polymer and membrane by in situ polymerisation [36]. SPES/PR membrane exhibited significantly higher flux loss of 24 % and 36 % for SPES/PR and SPES, respectively. Furthermore, SPES/PR demonstrated effective antimicrobial activity towards *S. aureus* and *E. coli* using a Colony-forming Unit, disk diffusion technique, linear cultivation tests, and liquid culture tests (spectrophotometric method). Compared to the pristine SPES membrane, the SPES/PR membrane demonstrated higher hydrophilicity, better fouling resistance, and exceptionally high water flux.

In addition, PR nanoparticles have provided a solution to the challenges associated with thin film composite (TFC) membranes and forward osmosis (FO), such as biological fouling and membrane degradation when exposed to chlorine or its derivatives-based disinfectants and oxidants [84,85]. Rahimpour et al. fabricated FO/TFC-PR membranes that enhanced antimicrobial, antifouling, and

transport characteristics [8]. Owing to the strong compatibility and small size of PR nanoparticles with polyamide chains, the existence of PR on the surface of the TFC-PR-0.01 (with 0.01 wt% PR) active layer displayed enhanced permeability and selectivity. For instance, the water flux of TFC-PRh-0.01 membranes, which was 41 l/(m^2.h), showed higher than that of pristine TFC membranes, which measured 34 l/(m^2.h) during FO when a draw solution, which is 1.5 M NaCl, was utilised in the active-layer feed-solution mode. Further, the surfaces of pristine TFC membranes showed rougher and more hydrophobic properties than the TFC-PR membranes. Hence, antifouling properties were enhanced, as evidenced by the fact that when examined with a sodium alginate solution, pristine TFC membranes exhibited a 50 % reduction in flux, while TFC-PR-0.01 membranes showed a slightly lower reduction of 38 %. Finally, the antimicrobial properties of the TFC-PR-0.01 membranes were analysed using fluorescence microscopy and colony-forming units. Compared to the pristine TFC membranes in Fig. 4 (A &B), the surface of TFC-PR-0.01 membranes demonstrated a substantial reduction in the number of attached viable cells. The deactivation of bacteria exceeded 89 % for *E. coli* and 92 % for *S. aureus* bacteria, respectively, as shown in Fig. 4C. Compared to the TFC membranes in terms of the quantity of live bacteria, the TFC-PR-0.01 membrane surface had significantly fewer live bacteria. The live/dead cell ratio was 24 % for TFC-PR-0.01 and 86 % for TFC membranes, which implied the antimicrobial result where the green (live) and red (dead) staining on both surfaces, as indicated in Fluorescence microscopy images (Fig. 4D). As confirmed by the SEM results, the remarkable antimicrobial activity for TFC-PR membranes at an extremely dilute concentration of PR nanoparticles (0.01 wt%) can be attributed by the minimal aggregation and even dispersion of PR nanoparticles within the active layer of polyamide membranes. PR nanoparticles provided the TFC-PR membranes with antimicrobial properties because of the existence of tertiary amide groups capable of undergoing partial protonation in aqueous solutions, resulting in the formation of positive charges. Further, there was an interaction of these cationic charges to the lipid bilayer structure of the bacteria, causing to the release of cytoplasm and ultimately the bacterial demise.

Zinc oxide (ZnO) is one of the inorganic biocides that affects many types of microorganisms through several mechanisms, such as disruption of membrane bacteria through exposure to ZnO, the liberation of zinc ions (Zn^{2+}), interaction of intracellular content with Zn^{2+}, and formation of reactive oxygen species (H_2O_2) [34]. In an interesting study, Soleymani Lashkenari et al. improved the antibacterial ability and the membrane surface hydrophilicity through the combination of PR and ZnO on a polysulfone (PSf) membrane [22]. A contact-active mechanism revealed PR has antibacterial activity. The cell damage was induced when there was interaction between the anionic charge of the bacteria cell and the protonated tertiary amide groups of PR in an aqueous medium [40]. As a result, the researchers prepared a membrane consisting of glutaraldehyde (GA, as crosslinker of PVA), polyvinyl alcohol (PVA, as a binding agent of the ZnO-PR couple nanoparticle), and ZnO-PR coupled nanoparticles (as an antibacterial agent), which was deposited on a polysulfone (PSf) support. The combination of 5 % of GA and 0.75 % of nanoparticles on the treated membrane demonstrated the highest flux. Moreover, the addition of ZnO-PR/PVA to the membrane increased all of the following; permeate flux (from 24.458 to

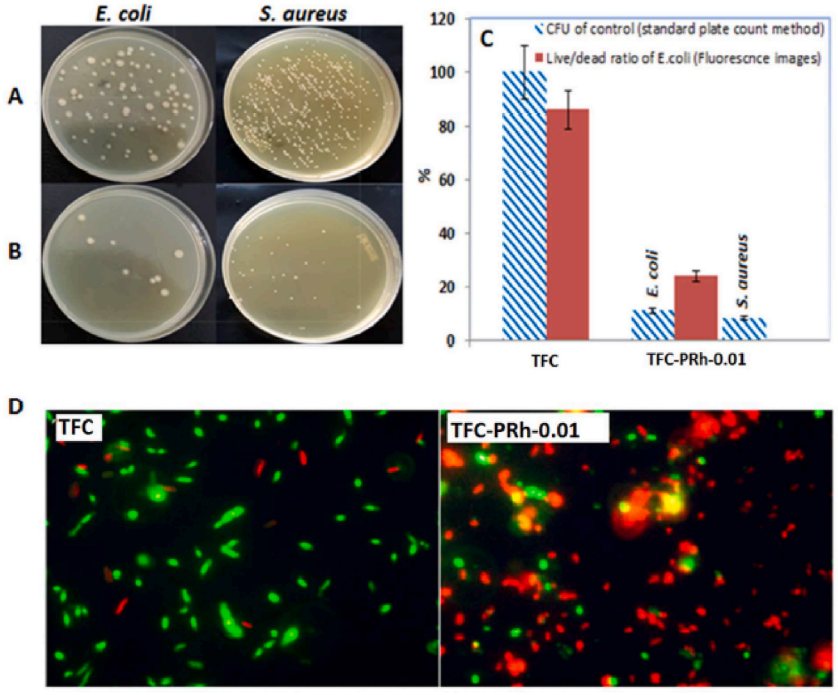

Fig. 4. Antimicrobial behaviours of the TFC (top) and TFC-PR-0.01 (bottom) membranes towards *E. coli* and *S. aureus* bacterial cells for 1 h (A & B). Percentage of colony forming units (CFU) of *E. coli* and *S. aureus* cells in comparison to that on the pristine TFC membrane (control membrane) and quantitative analysis of live (green)/dead (red) *E. coli* ratios (percent) on the TFC and TFC-PR-0.01 membranes calculated from fluorescence images (C). Fluorescence microscopy images of *E.coli* on the TFC and TFC-PRh-0.01 membranes (D). Reprinted with permission from Rahimpour A et al. [8] Copyright 2018 American Chemical Society.

46.653 kg $m^{-2}.h^{-1}$ for the PVA and ZnO-PR/PVA membranes, respectively), the rejection (from 81.521 to 97.52 % and 83.77–98.97 % for citrate and total phosphate samples), surface hydrophilicity (from 111.8 to 59.0° of water contact angle), fouling resistance, and antibacterial property [22].

On the other hand, PR-coated ZnO nanoparticles were utilised for disabling Trichomonas gallinae, which is one of the most common parasites that lead to trichomoniasis in birds and humans around the world [35]. The pure ZnO and PR-coated ZnO nanoparticles demonstrated the ability to minimise the viability of Trichomonasgallinae trophozoites. Moreover, the findings showed that the viability rate of Trichomonas gallinae trophozoites decreased when the exposure time was prolonged and the concentration of the nanoparticles was increased. Comparing the effectiveness of pure ZnO and PR-coated ZnO with that of metronidazole in the same duration, the prepared nanoparticles showed a significant impact on the growth of Trichomonas gallinae trophozoites. The parasite inactivation occurred due to the attachment of nanoparticles on the membrane, restraint of the role of the hydrogenase enzyme, reduction of ATP level, and disturbance on the binding of t-RNA to the ribosome, which results in DNA damage and cell demise [86]. PR-coated ZnO nanoparticles had a crucial role in treating trichomoniasis, and more investigations are needed to explore this issue.

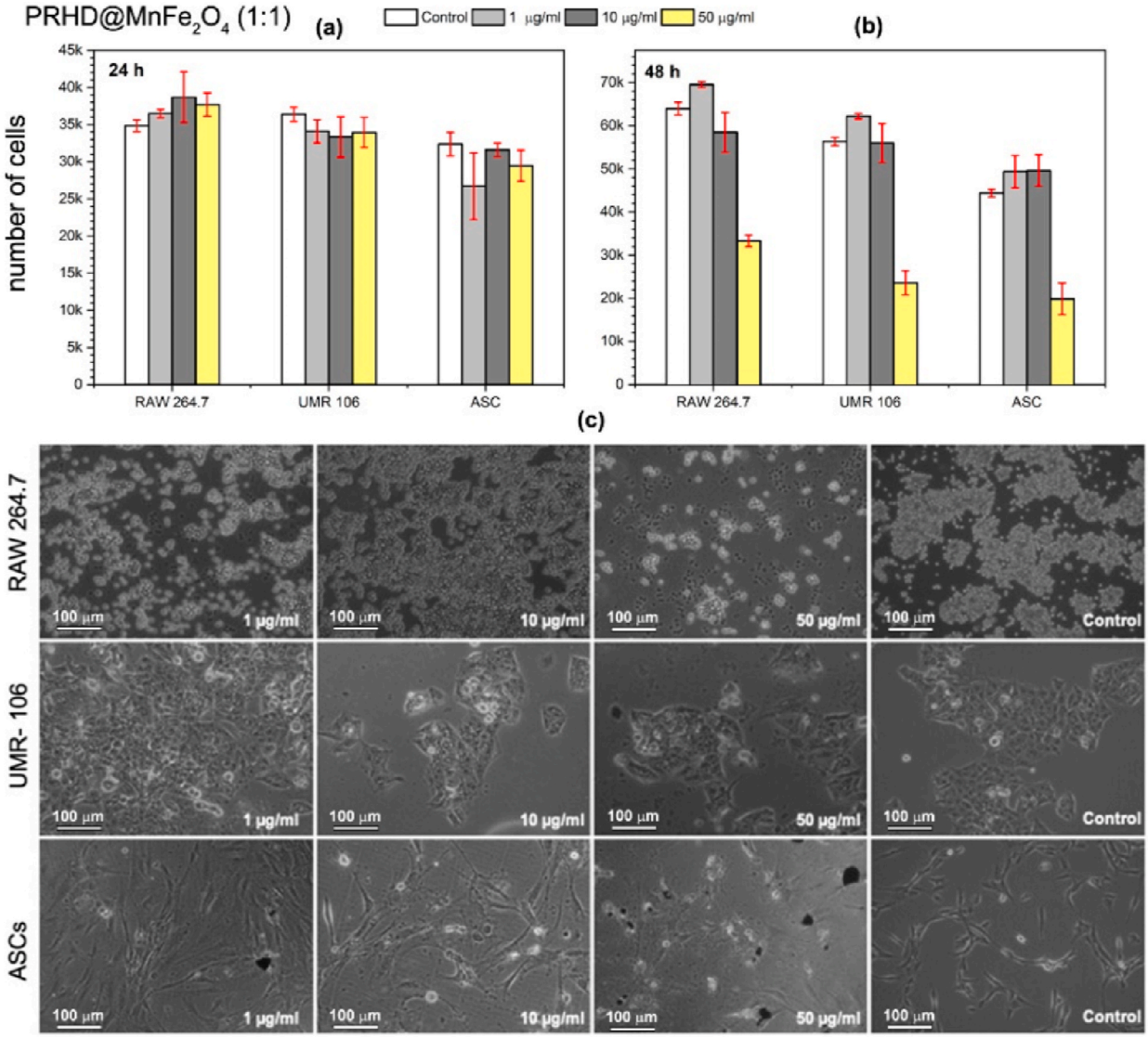

Fig. 5. Impact of in vitro PR@$MnFe_2O_4$ (1:1) activation of macrophages (RAW 264.7), osteosarcoma (UMR-106), and stem-cells (ASCs) proliferation depending on concentration (a) after 1 day and (b) after 2 days of exposure. Panel (c) demonstrates morphology variations of macrophages (RAW 264.7), osteosarcoma-derived cells (UMR-106), and stem cells (ASCs) after 2 days of exposure to PR nanoparticles in a controlled in vitro environment [23].

4.2. Anticancer activity of PR

Cancer has significant societal implications, causing nearly 10 million deaths in 2020 and being a major contributor to global mortality. The most common cancers are breast, colon, lung rectum, and prostate cancers, which are also the most common factors of cancer death in 2020 [12]. Cancer death can be minimised when cases are detected early and treated effectively. For instance, breast cancer and cervical cancer are the most successfully treatable kinds of cancer if they are detected early. Even when they are diagnosed in late stages, they can also be controlled with appropriate treatment [87]. The conventional treatments for cancer in general are surgery, chemotherapy, and radiation. Although these approaches are designed to eradicate the tumour, they are faced with many challenges. For example, surgery is used to remove cancerous tumours or growth, especially when it is confined to a particular region of the body. This form of therapy is frequently regarded as the initial treatment. But in case of recurrence or metastases to different organs, such as bones, lungs, and liver, it is not effective [88,89]. Other treatments are used with the surgery or as an independent approach, such as chemotherapy and radiotherapy. These treatments play a primary role in cancer therapy, as they cause the cytostatic of the cancerous cells, therefore, increasing the survival rate. However, they have many downsides, including the complication in choosing the appropriate dosage, an absence of specificity that generates cytotoxicity to normal cells, rapid drug metabolism, and the development of drug resistance. Moreover, acute side effects are caused by these treatments, such as fatigue, gastrointestinal, skin

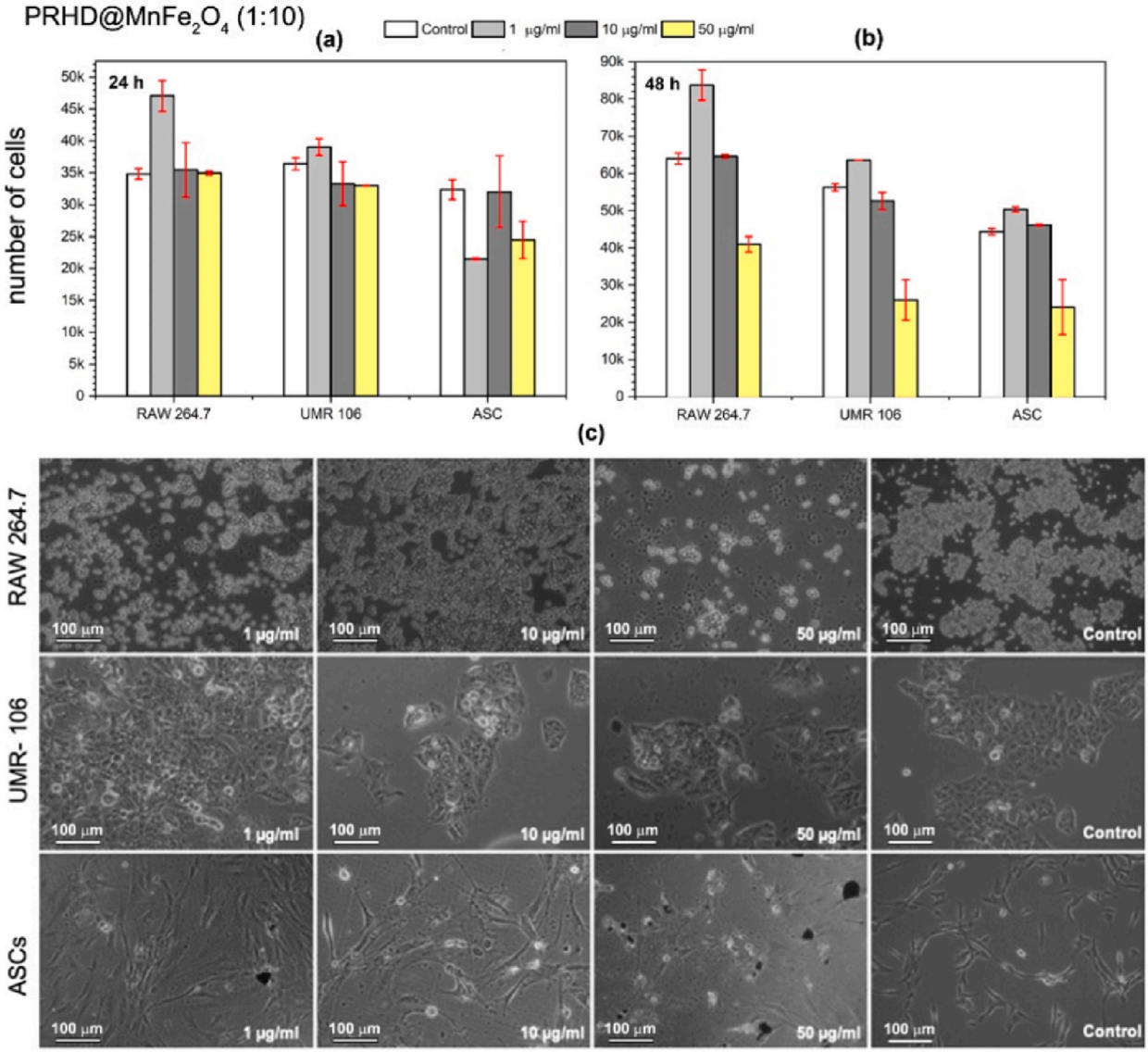

Fig. 6. Impact of in vitro PR@$MnFe_2O_4$ (1:10) activation of macrophages (RAW 264.7), osteosarcoma (UMR-106), and stem (ASCs) cells proliferation depending on concentration (a) after 1 day and (b) after 2 days of exposure. Panel (c) demonstrates morphology variations of macrophages (RAW 264.7), osteosarcoma-derived cells (UMR-106), and stem cells (ASCs) after 2 days in a controlled in vitro environment [23].

disorders, hair loss, and suppression of bone marrow [90,91].

To avoid these risks, it is crucial to seek new molecules with beneficial medical properties for targeting cancer cells. In 2021, nearly one-third of all drugs adopted for healthcare interventions were new anti-tumour agents, which were affirmed by the U.S. Food and Drug Administration [92]. In this context, thiazolidinone (heterocyclic compound) and its derivatives have been the centre of attention for many years. Rhodanine consists of a five-membered heterocycle with amino and thioether groups at positions 3 and 1, respectively. It is one of the subtypes of thiazolidinone that is widely used to synthesise the new compounds with different biological applications. A variety of thiazolidinone compounds have been used in drugs as antibacterial [93], antiviral [94], anti-inflammatory [95], and antifungal [96]. Thus, rhodanine has attracted many scientists to study its biological applications. PR is synthesised from its monomer rhodanine through the oxidative polymerisation process. The structural properties of rhodanine and its polymer make them the centre of attention due to their active sites and the free electron pairs that facilitate the formation and modification of high-value new materials [6].

Rhodanine and its derivatives have been widely studied as a potential anti-tumour agent due to its medical properties [97–99], however, PR has participated in a limited number of cancer-related research. A series of neocryptolepine–rhodanine hybrids was formed and tested as an anticancer drug [100]. The MTT assay showed that most of the formed hybrids had effective cytotoxicity on the tumour cell line hepatocellular carcinoma (HepG-2), similar to the standard drug 5-fluorouracil (5-FU). Furthermore, the molecular docking studies indicated that the enhancement of DNA intercalation and the inhibition of DNA topoisomerase activity were triggered by the combination of planar indoloquinoline, which combines four rings and flexible side chain groups.

Among many, superparamagnetic iron oxide nanoparticles (MNPs) have recently accentuated in magnetically induced hyperthermia, photothermal therapies, or the integration of both near-infrared light radiation (NIR) and magnetic field [101,102]. MNPs provide direction to drugs towards specific locations through the circulatory system in tumour-targeting therapy [28], and targeted drug delivery [103]. While NIR is for heat induction in the tumour sites [104], it is particularly appealing for shallow and non-invasive treatments that are harmless to the skin. Moreover, NIR light penetrates biological systems much deeper and has negligible damage compared to UV light. Thus, materials with intense absorbance between 650 and 1350 nm have higher photothermal efficiency, such as metallic nanoparticles. $MnFe_2O_4$ have effective heating capability when exposed to NIR. However, adequate biocompatibility is required on the surface of the nanoparticles for inhibition of particle agglomeration in a biological environment, reduction of cytotoxicity, and reduction of MNPs premature elimination. Therefore, Zachanowicz et al. showed that coating the ferrites with rhodanine oxidative polymerisation can substantially decrease the cytotoxicity of MNPs [3]. In this context, PR@$MnFe_2O_4$ hybrids were synthesised and tested to analyse their impact on cells regulating inflammatory response (macrophages), bone cancer (osteosarcoma), and progenitor stem cells (ASCs) [23]. The findings demonstrated that the regulation of the cytophysiological activity of cells can be modulated by PR and PR@$MnFe_2O_4$ hybrids in a dose-dependent manner. PR diminishes the viability and typical morphology of macrophages, osteosarcoma-derived cells, and ASCs when utilised at elevated concentrations within the range of 10 and 50 μg/mL. Moreover, PR@$MnFe_2O_4$ hybrids in a ratio of 1:1 (45 %@55 %) and 1:10 (10 %@90 %) increased cellular proliferation on the first day, as shown in Figs. 5a and 6a. While macrophages and tumour cells preserved their common cellular structure, ASCs lost the number of progeny that they generated and demonstrated apoptotic phenotype even when exposed to the lowest concentration of PR@$MnFe_2O_4$. Their cellular proliferation with their morphologies changed after 2 days of in vitro exposure to PR nanoparticles in a controlled environment are depicted in Fig. 5b, 5c, Fig. 6b and 6c. Another goal of this study was to assess the heat generation ability of the PR@$MnFe_2O_4$ hybrids upon exposure to NIR laser. The results illustrated that the specific heat capacity of PR within the temperature range 20–50 °C was 1.4–2.15 J/g°C and can convert energy into heat because of its capacity to absorb within the NIR spectral region. Furthermore, the inclusion of MNPs enhanced the overall heating efficiency drastically. However, further research is needed to identify the mechanisms underlying cellular response associated with the hybrids.

As mentioned before, magnetic nanoparticles are used in biological applications due to their excellent characteristics, such as low toxicity, affordable and eco-friendly performance, and biocompatibility [105]. However, the usage of polymer coating is essential to overcome surface oxidation, and magnetic clumping, and to increase the functional groups for the magnetic nanoparticles. Mousavi et al. synthesised a PR/Fe_3O_4 modified by graphene oxide (GO) to improve the morphology, structural stability, functional groups, and catalytic activity of PR and Fe_3O_4 [4]. Moreover, they boosted the activity, biocompatibility, sensitivity, relative active functional groups, and morphology of PR by adding kombucha (Ko) solvent to the hybrid platform. MTT assay facilitated the study of the cytotoxicity of PR/Fe_3O_4/GO/Ko on a human liver cell line (Hep-G2). As a result, the metabolic activity of cells can be eliminated by PR in PR/Fe_3O_4/GO at maximum concentrations, mostly more than 50 μg/mL, when compared to Fe_3O_4/GO. Furthermore, certain promotive effects on cell growth were induced by PR/Fe_3O_4/Ko, which improved the percentage of viability significantly. Likewise, PR/Fe_3O_4/GO/Ko showed a much higher cell viability percentage than PR/Fe_3O_4/GO, which can be ascribed to the addition of Ko in the compound. As a result, it has been claimed that the PR-based nano compound can be used as a drug carrier due to its low toxicity effect and efficiency against cancerous cell lines [4].

4.3. Other biological applications of PR

Doxorubicin hydrochloride (DOX) is an anthracycline group of chemotherapeutic agents in cancer treatment [106]. The accumulation of reactive oxygen species (ROS) is a challenge in the treatment using DOX. This accumulation is induced by scavenger enzymes after long-term therapeutic application. The cytotoxicity that affects normal cells causes severe cardiotoxicity, which triggers heart failure [107,108]. During chemotherapy, it is crucial to monitor DOX levels in the blood to prevent excessively high serum concentrations. Therefore, there is a need to regulate the levels of DOX in biological fluids [109]. The electrochemical approach has been recognised as an excellent detection method because it is inexpensive, highly selective, and sensitive. Moreover, the chemical

reactive groups in the chemical configuration of DOX make the electrochemical approach as the preferred analytical method for DOX level detection in blood [110].

In this communication, PR is a promising polymer-based platform due to its medical properties, including the presence of active functional groups and high electrical conductivity. Hashemi et al. reinforced the PR structure with Fe_3O_4 nanoparticles and GO to enhance its catalytic activity, functional groups, morphology, and structural stability [5]. The performance of the hybrid PR-GO-Fe_3O_4 platform in detecting DOX in biological fluids was investigated using electrochemical assessment of the fabricated biosensor. The findings for this developed biosensor demonstrated superior sensitivity (167.62 μA μM^{-1} cm^{-2}), low detection limit (DL, 0.008 μM), and quantification limit (QL, 0.056 μM). Optimal accuracy (>99 %) in detecting DOX in biological fluids can be achieved using the biosensor, highlighting the efficiency of the developed polymeric biosensor.

PR and its derivatives have been studied for their biological activity, and PR manganese ferrite binary nanohybrids (PR@$MnFe_2O_4$) have been investigated for their feasible application in osteoporosis treatment [30]. Osteoporosis is defined by the decline in bone mineral density and the attenuation of skeletal strength, which can lead to bone fragility and an increased risk of fractures [111]. The study showed that PR and its modifications improve pre-osteoblast proliferative abilities while diminishing the activity of osteoclast specifically at a ratio of 10/90. Moreover, at the same ratio, the gene expression profiling indicated improved apoptosis of osteoclasts and potent anti-inflammatory characteristics, as evidenced by reduced expression of Interleukin-1 beta (Il1b), transforming growth factor beta (Tgfb), and transforming growth factor alpha (Tnfa) in preosteoclasts and osteoblasts. PR@$MnFe_2O_4$ promoted pre-osteoblast differentiation via the ALP-OPN-OCL axis, as evidenced by the increased expression of markers linked with bone remodelling. For instance, alkaline phosphatase (ALP), osteocalcin (OCL) and osteopontin (OPN) [30].

5. Properties of PR

PR is a conductive polymer that has several interesting properties. It serves as a stable and conductive matrix that has more than one active functional group to act as a corrosion inhibition barrier that blocks the aggressive anions from the surface [7]. Moreover, its compatibility provides a distinctive combination of high thermal conductivity and high mechanical properties for the formation of elastomers [112]. Additionally, the metal-binding functional groups are potent additive for detecting or adsorbing metal ions. PR could be used as a recyclable and easy-harvested material for the elimination of heavy metals from contaminated water, owing to its magnetic and regeneration characteristics [44]. Furthermore, PR is a biocompatible polymer that has been used with various cell types including the cancer cell line, pre-osteoblasts, macrophages, and adipose stromal/stem cells [23,30]. As mentioned, PR is an electrically conductive polymer, which makes it a suitable material for biosensing applications. The electrical properties can be used to detect changes in the biological environment, such as the presence of certain molecules or changes in pH [5,18]. Many surface modifications were performed for PR to tailor its properties for specific applications. For example, the polymer can be modified to form a core-shell nanocomposite, such as γ-Fe_2O_3/PR to reduce the magnetically-induced aggregation and surface oxidation of iron oxide [105]. The configuration of PR not only serves as a function in the fabrication of new nanocomposites but also plays a role in antibacterial activity. It can be proposed that electron pairs not shared between sulphur and oxygen groups in PR strengthen the antibacterial activity of the nanoparticles. Moreover, the establishment of a positive charge could be triggered by the partial protonation of the tertiary amide groups in the core-shell nanoparticles in aqueous conditions. The positively charged parts of the PR shell interact with the lipid bilayer structure of the bacteria membrane causing cell death [37]. It is widely accepted that the PR hybrid compounds, exhibiting synergistic effects with different antibacterial behaviours, can overcome some of the drawbacks of antibacterial materials when used separately. For example, in the silver/PR hybrid compound, the silver compound has a time-limited effect on bacteria destruction because the mechanism depends on the release of Ag^+ ions to disrupt bacteria [113]. Therefore, the nanocomposite can sustain the antibacterial behaviour because of the PR existence after silver depletion. Song et al. observed the antibacterial behaviour of PR in SiO_2–Ag/PR nanoparticles by creating two experiments [40]. First, the silver ions are eliminated using a silver-ion scavenger in the antimicrobial test, such as a neutralizer solution, limiting the antibacterial effect of silver nanoparticles. The second study was observing the effectiveness of antibacterial activity on the pristine silica nanoparticles. Regardless of the presence of the silver-ion scavenger, silica nanoparticles did not perform antimicrobial activity. The results illustrated that PR contributed to the antimicrobial effectiveness of SiO_2–Ag/PR nanoparticles. Furthermore, the antibacterial activity against *E. coli* and *S. aureus* was maintained at 81 % and 63 %, respectively, once the silver-ion scavenger was applied.

The utilisation of nanomaterials in biomedical applications, such as antimicrobials, biosensors, drug delivery systems, and imaging contrast agents, should have a group of important properties. High biodegradability and less cytotoxicity to intact cells are among the most crucial characteristics of therapeutic nanomaterials. For example, silver nanoparticles have attracted attention for several medical applications. However, their use is still limited due to the possible cytotoxic effects. Many researchers are using a coating technique to attenuate the toxicity impact of the uncoated silver nanoparticles [114]. Some of the effects of silver nanoparticles cause the impairment of the cell membrane, the change in the gene expression, and the oxidation of the biological cell components by the reactive oxygen species production [115]. Moreover, inorganic nanomaterials such as carbon-based nanomaterials, quantum dots (QDs), and silica-based nanomaterials, have been utilised for diagnosis and treatment. However, they frequently accumulate in the reticuloendothelial system (RES), which makes them have long-term toxicity and low passive targeting specificity. As a result, the advancements of such nanomaterials in clinical trials would be hindered [116,117]. The full clearance of administrated contrast agents from the body in a relatively short span of time is mandated by the US Food and Drug Administration (FDA). Therefore, assessing the toxicity and metabolic activity of nanomaterials in the body is an essential step to extend their application into clinical trials [118]. Likewise, studying the cytotoxicity of PR is equally important to the investigation of its biological activity. Assessment of the possible cytotoxicity of PR nanoparticles is a critical consideration in biological applications. Eggers et al. studied the toxicity of rhodanine on

kidney cells of monkeys, his results demonstrated that rhodanine had no toxic effect at a concentration of 150 μg/ml, but caused granulation of cells at a concentration of 200 μg/ml after a 4-day or longer exposure [119]. El-Bahnsawye et al. evaluated a series of neocryptolepine (a natural plant extract) and rhodanine hybrids towards human breast (MDA-MB-231) and hepatocellular carcinoma (HepG-2) cancer cell lines [100]. In this research, they revealed that the tested hybrids showed strong selectivity for cancer cells over normal skin cell lines (BJ-1) at the maximum concentration.

A study was conducted to investigate the influence of PR on the treatment of Newcastle disease virus (NDV), as well as its cytotoxicity on chicken embryos. The results showed that PR did not cause any gross abnormalities in chicken embryos when injected in *ovo* at concentrations of 0.1 ppm, 1 ppm, 10 ppm and 100 ppm. Blood serum biochemical indicators were also not affected. Additionally, histological assessments of various tissues, including the heart, kidney, bursa of Fabricius, spleen, and central nervous system, showed no pathological variations [16]. It is worth noting that increased activity of liver enzymes is an indicator of hepatotoxicity [120], but PR did not affect these indicators.

In another research study by Soleimani Lashkenari et al., it was suggested that the toxicity of encapsulated $NiFe_2O_4$ nanoparticles with PR is highly dependent on the poisonous properties of PR [15]. This claim was supported by Al-Qasmi et al. who demonstrated that $NiFe_2O_4$ nanoparticles are not harmful to organ cells at optimal concentrations [121]. Therefore, it was hypothesised that a lower concentrations of PR/$NiFe_2O_4$ nanocomposite would pose no harm to living cells, based on the research of Nazaktabar et al. This research indicated that PR is not harmful to tissues [16].

Zachanowicz et al. studied a comparison of cytotoxicity between PR, non-covered $CoFe_2O_4$, and PR@$CoFe_2O_4$ hybrid in two different cell lines. In J774.E macrophages, the metabolic activity, which is indicative of loss of viability, was reduced in a concentration-dependent manner by $CoFe_2O_4$. PR also showed a concentration-dependent reduction in viability, but it was less pronounced. In U2OS cells, both PR and $CoFe_2O_4$ caused a slight reduction in viability [3]. This issue may be related to the phagocytal action of J774.E cells, expanding the cells loading with particles and heightened toxicity risk [122]. However, the PR@$CoFe_2O_4$ nanoparticles do not show any cytotoxicity in either cell line. This may be due to the unique interface between the cell-particle formed on the coated particles, differing from interfaces observed in the two previous types, which could prevent eliciting a cytotoxic activity. This could also result from a reduction in particle accessibility due to increased agglomeration within these particles [3].

Due to the safety considerations, CNCs have been proposed for utilisation in biomedical applications but it is important to investigate their composites [123]. In this regard, the antimicrobial activity of CNCs@PR was assessed. Since the antimicrobial mechanism of nanoparticles towards bacterial cells involved disrupting the cell membrane, it was crucial to evaluate their effect on human cells. To this end, Tang et al. (2015) studied the cytotoxicity between CNC and CNC@PR on HeLa cells. Below 0.5 mg/mL, both nanoparticles showed no significant toxicity against HeLa cells at concentrations. At higher concentrations that demonstrated strong antibacterial potential (1 mg/mL), CNC caused only a 6–7% reduction in HeLa cell viability. In contrast, CNC@PR triggered some toxicity, resulting in up to a 50 % reduction in viability. However, this toxicity can be lowered to approximately 10 % by reducing the concentration of CNC@PR to a level at which the nanoparticles maintain their antimicrobial behaviour (0.5 mg/mL and 0.25 mg/mL).

6. Conclusion and future perspective

With the growing global burden of human health issues, there is an urgent need for more effective approaches to treat microbial infections and cancerous tumours. Nanotechnology is at the forefront of these efforts, with rhodanine developed as a potential polymer for use as an antimicrobial and anticancer agent in various studies. PR has also gained attention in biological applications due to its unique properties, which can enhance the performance of nanocomposites used in these fields. Additionally, PR's surface can be easily modified, making it a valuable candidate for nanocomposite formation. One approach that has been successful in overcoming challenges associated with hybrid compounds is the use of PR as a shell in core-shell structures. PR has demonstrated efficacy in many biological fields, including antibacterial, antiviral, antifouling, antiparasitic, anticancer, and biosensing applications. Furthermore, research has shown that the cytotoxicity of PR is negligible in biological applications. In conclusion, PR has significant potential for a diverse array of treatments due to its distinctive properties and flexible structure. However, further investigation is needed for a better understanding of the interactive effects of specific nanocomposite platforms on treatment outcomes. It is also essential to explore the use of additional inorganic nanomaterials in hybrid nanostructures with PR. Finally, PR's properties should be explored further for potential use as an anticancer agent and drug carrier, as there is a lack of research in these areas in the current literature.

Data availability statement

No data associated with this study have been deposited into a publicly available repository. Data included in article/referenced in article.

CRediT authorship contribution statement

Ibrahim Huzyan Hiba: Writing – original draft, Resources, Conceptualization. **Jin Kwei Koh:** Writing – review & editing. **Chin Wei Lai:** Writing – review & editing. **Seyyed Mojtaba Mousavi:** Writing – review & editing. **Irfan Anjum Badruddin:** Supervision. **Mohamed Hussien:** Supervision. **Jest Phia Wong:** Writing – review & editing, Visualization, Validation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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