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REVIEW OPEN ACCESS

A Scoping Review of 20-100NM Gold Nanomaterials for Cancer Diagnosis

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Abstract

Introduction: With 90% of current chemotherapeutic drugs failing during the metastasis stages of cancer, the early diagnosis and prognosis of tumours is vital for patients. We can now fine-tune nano-sensors to detect trace amounts of biomarkers present in blood to provide a cheaper, faster and less invasive alternative to traditional tissue biopsies. This literature review will focus on the employment of gold nanoparticles (AuNPs) as viable nano-sensors for cancer detection in the bloodstream, given their biocompatibility, NIR/visible light optical properties and functionalization.

Methods: To carry out the research for this review we used published, peer-reviewed articles from a variety of online reputable databases; mainly using the search terms 'AuNP', 'SPR' and 'nano-sensors'; whilst specific effects mentioned within articles were independently searched for.

Results and Discussion: Circulating tumour DNA (ctDNA), exosomes and tumour miRNA (micro-RNA), obtained through liquid biopsies (LBs), can be used as effective biomarkers of cancer. By attaching complimentary oligonucleotides and optical sensors to the surfaces of AuNPs, usually via Au-thiol links, they can detect these biomarkers despite their low concentrations. There are many imaging techniques we can use to then quantify the formation of AuNP-biomarker formation. When fluorophore dyes are used, florescence will be observed since the binding of biomarkers will cause a conformational change to the AuNPs-aptamer-dye structure thus reduce the quenching properties that AuNP's impose on dyes when in close proximity. Due to the optical properties of Au, such as their strong surface plasmon resonance (SPR) effects, they can be used to observe shifts in the absorbance characteristics to quantify AuNP-biomarker formation.

Conclusion: The tuneable optical properties of AuNP means we can gather real time information, using low energy EM waves. Modifying AuNP sensors to resonate within the NIR (near infrared) wavelengths of light will improve their ability to produce a strong detection signal even when inside patients, as the attenuation coefficients of biological tissues at these wavelengths are extremely low. Thus, decreasing diagnosis time and removing the need for samples to be sent to labs; as well as being safer than UV-X-ray wavelengths.

Keywords: cancer; nanoparticles; gold nanomaterials; bio-imaging

Introduction

Characterised by uncontrollable cell growth, cancer is a disease that poses a challenge to healthcare systems globally as it is difficult and expensive to detect and treat. In the initial phases of cancer, clinical symptoms may be absent, however by the time cancerous tumours are detected, metastatic lesions have already disseminated throughout the body making treatment complicated and reducing the chance of survival.

Metastasis, which refers to the spread of cancer cells from the primary tumour to neighbouring tissues and distant organs, is the main contributor to deaths caused by cancer [1]. Therefore, early detection of cancer in patients is crucial in increasing chances of successful treatment and improving patient outcomes.

Current methods of diagnosing cancer include imaging techniques, tissue biopsies and blood biomarkers [2]. Biomarkers, such as proteins, nucleic acids, and metabolites, serve as indicators of physiological or pathological processes associated with disease [3]. Looking at the communication between cells, the state of the microRNAs in exosomes [4] can act as biomarkers and help define the type of cancer and contribute to the identifying of risk factors associated with that cancer. Detection of these biomarkers is crucial to precision medicine, which is a method of treatment that tailors specifically to the genes in the patient's body, which can spare patients from trying out countless other treatments which may be ineffective and cause financial and emotional burden.

Nanomaterials are an emerging technology in biomedical applications due to their unique properties including high surface area to volume ratio, tuneable absorption and emission properties and high stability and biocompatibility. Gold nanoparticles (AuNPs) range from 1 to 100nm in size and can form various structures [5] based on their production method, each of which have different characteristics and can be used in nanomedicine as they are highly specific, sensitive, and minimally invasive [6]. The properties of gold nanoparticles, specifically their low cytotoxicity in comparison with iron nanoparticles [7], their impressive optical, quenching and functionalization properties make it the better nanoparticle conjugate to use in sensing and imaging [8].

The use of the several defined hallmarks of cancer [9] which encompass the biological steps going on during the development and progression of cancer can help simplify the intricacy of this disease and the challenges associated with its detection and treatment. By associating each hallmark with specific biomarkers, nanomaterial-based sensors can target such biomarkers, enabling early identification of the cancer and personalised therapeutic interventions.

The heterogenous nature of cancer poses the largest challenge when determining the correct prognosis for a patient. Cancer heterogeneity refers to the cell diversity observed within tumours of the same type in different patients (intertumor heterogeneity), or the cell diversity within a single tumour (intratumor heterogeneity) [10]; and is the main reason why personalised treatment is so vital when tackling cancer as a disease. These different populations arise from the specific set of environmental conditions surrounding the individual tumours, this could include the effects of pH, oxygen level or nutrient levels [10]. These extrinsic factors surrounding a tumour serve as a selective pressure to drive tumours to evolve, this mainly involves the promotion of different genes that help to 'actively promote' cancer progression [11] in that specific environment. The development of nanodevices, that possess highly specialised surfaces, to help identify overexpressed receptors or RNA sequences can improve our ability to categorise and identify tumours, thus allowing us to directly combat the heterogenous nature of cancer.

Methods

This review was conducted using publicly available medical journals, primarily PubMed. The broad search terms 'nanoparticles', 'biomarkers' and 'LSPR' were used in conjunction with specific materials or structures such as 'Au', 'AuNP' and 'AuNR' to help yield more precise results for different sections of this review. The majority of data was taken from papers published in the last 20 years, however when discussing different synthesis roots of gold nanoparticles, some methods required sourcing data as far back as the 1950's, to provide a more comprehensive history of these methods.

Results

The Synthesis of Gold Nanoparticles

There are various ways to produce gold nanoparticle structures for use in biomedical applications. The synthesis of AuNPs follows two general approaches: the top-down approach and the bottom-up approach. A top-down synthesis approach of AuNPs refers to the breaking down of bulk gold into nanosized gold particles using physical techniques such as etching, grinding, sputtering, thermal/laser ablation, etc. On the contrary, the bottom-up method involves the building up of AuNP on an atom-by-atom basis through chemical reduction of gold. The methods described below are those relevant for the AuNPs used in the targeting and detection of cancer discussed in this review.

Turkevich-Frens Method

Despite newer methods available, the Turkevich-Frens method remains popular due to its simplicity and ease of controlling particle size, however, it is limited to producing spherical AuNPs, and it's not as reproducible for particles above 20nm [12].

In the Turkevich-Frens [12], [13] method, AuNPs are synthesised from an aqueous solution of chloroauric acid ($HAuCl_4$) which is heated until boiling. Trisodium citrate ($Na_3C_6H_5O_7$) solution is then added where it acts as both a reducing agent, reducing Au^{3+} to Au^0 atoms, and a stabilising agent, prohibiting the AuNPs from clustering together and forming a larger aggregate. The citrate adsorbs onto the AuNP surfaces ensuring they remain stable and dispersed while retaining desirable properties such as high surface area and low dispersity.

To control the size of the AuNPs, the concentration of citrate is altered, effectively changing the gold to citrate ratio in the reaction. Stable, spherical AuNPs with diameters of 10-20nm can be achieved [12]. As the concentration of citrate increases, more gold ions are reduced, creating more nucleation sites but leaving fewer gold ions available to be deposited upon them hence creating smaller AuNPs. Conversely, lower citrate concentrations result in fewer nucleation sites with more gold ions per nucleus, forming larger AuNPs.

Seed-Mediated Growth

For precise control over the size and shape of AuNPs, a seed-mediated growth method is employed where pre-synthesised small nanoparticle seeds are added to a growth solution and act as nucleation sites that facilitate further growth of the nanoparticle in the longitudinal direction, resulting in a rod structure.

AuNP spheres are synthesized as 'seeds' using a strong reducing agent such as sodium borohydride ($NaBH_4$) on Au^{3+} ions in the presence of sodium citrate [13]. These seeds are added to a growth solution containing a gold precursor (HAuCl4), a weaker reducing agent such as ascorbic acid (H_2NOH), and a surfactant like cetyltrimethylammonium bromide (CTAB)[14] [15]. The H_2NOH is a mild reducing

agent that selectively reduces the gold precursor ions adsorbed onto the existing 'seed' particle's surface, whilst the surfactant, CTAB, helps stabilise the bilayer around the AuNPs, influencing directional growth and preventing aggregation, which could disrupt the uniformity of the AuNP suspension. In this method, the size of the AuNRs is controlled by adjusting the molar ratio of seeds to gold precursor in the growth solution. As the concentration of gold precursor ions in the growth solution is increased, more gold is deposited on the seed particles, resulting in larger or more elongated AuNPs [16].

The seed-mediated growth method developed by Niko et al. Sayed is a popular method for synthesising AuNRs as it increases the yield of AuNRs made. Silver nitrate (AgNO3) as an additive in the growth solution led to further control over the growth process and aspect (length/width of the particle) ratios of the AuNRs produced because the silver ions selectively adsorbed on certain facets of the growing AuNRs, affecting their anisotropic growth [17]. In addition to increasing the concentration of CTAB in the growth solution, the $Na_3C_6H_5O_7$ in the seed preparation was replaced with CTAB, which meant better stabilisation of the AuNRs and provided electrostatic charge that guided their directional growth [17].

Adjustments for Biomedical Use

The seed-mediated growth method allows researchers to fine-tune the aspect ratio of the AuNRs, which is essential for applications in sensing and imaging. However, the use of CTAB as a surfactant in AuNRs poses a threat to cells and tissues [18], therefore AuNRs must be further modified to ensure safety for biomedical applications.

One way to make it more biocompatible is by lowering the presence of CTAB on the AuNRs' surface by using a binary surfactant system during synthesis [19]. A combination of CTAB and sodium oleate (NaOL) minimises potential cytotoxic effects [20]. However, decreasing the amount of CTAB also affects the size, shape and stability of the AuNPs. Another strategy is ligand exchange, where the original ligand, CTAB, is swapped out for another more biocompatible ligand such as thiol-terminated polyethylene glycol (PEG-SH). This change not only improves the stability of the AuNPs in biological environments but also enables further functionalisation for targeted drug delivery, detection, and imaging.

In the hyperthermia therapy uses looked at later, AuNRs, prepared via seed-mediated growth, are subjected to centrifugation to further purify and separate them from the supernatant containing excess CTAB and residual reactants. They are then redispersed in water, centrifuged again, and redispersed in water once more. The AuNR solution is then treated with a 7% (wt%) solution of methyl(PEG)thiol (mPEG-SH) to enhance biocompatibility and functionalisation [21].

Characterisation of AuNPs

Precise characterisation of AuNPs allows us to categorise their physical and chemical properties, such as size, shape, surface chemistry, and with this information ensures that the nanoparticles behave predictably in technological and biomedical uses. Not to mention it also helps verify the reproducibility of each synthesis method and ensure that they each comply with safety standards.

Table 1. Discussing Characterisation Techniques Used in Gold Nanostructure Production

Technique	Properties Determined From Analysis	Limitations	Ref
Transmission electron microscopy (TEM)	Shape and size of AuNP at high resolution. Size distribution.	Preparation of samples for TEM analysis is complex and might cause damage to AuNPs or result in aggregation. Not representative of the whole population of nanoparticles. Can provide inaccuracy if not used in conjunction with high resolution TEM Only looks at dry states.	[22]
Dynamic light scattering (DLS)	Size distribution of nanoparticles in a suspension.	The nanoparticles measured must be in a dispersed state and undergo Brownian motion. DLS is best used for monodisperse systems and due to uneven scattering of light of different sized particles, it has a low resolution for polydisperse systems.	[23]
Ultraviolet visible (UV-Vis) Spectroscopy	Optical properties and concentrations of AuNPs, functionalisation of AuNPs.	Limited to optical properties and requires proper dilution and dispersal to avoid inaccuracies in concentration and size estimations due to aggregation.	[24]

Technique	Properties Determined From Analysis	Limitations	Ref
X-ray Diffraction (XRD) Analysis	Crystalline structure of the AuNP, crystalline grain size, lattice parameter, nature of the phase.	Not suitable for amorphous materials because they don't produce sharp diffraction peaks due to not having a well-defined crystal lattice. Also, not good for NPs that have a diameter size of 5nm or below, as their XRD broadening peaks.	[25] [26]
Thermogravimetric Analysis (TGA)	Thermal stability of the AuNP, purity of sample, efficiency of functionalisation of AuNP surface with ligands or coatings.	It is not sufficient to provide specific details about the composition of AuNPs without being coupled with other analysis techniques such as mass spectrometry or infrared spectroscopy. Temperature and atmosphere control are crucial for accurate results.	[27]
Nuclear Magnetic Resonance (NMR) Spectroscopy	Ligand identification, confirmation, distribution.	NMR cannot provide information about the size, shape, or crystal structure of the metal core of the AuNP- an important part in applications of AuNPs. Samples must be soluble.	[28]

Biomarker Sensors

Biomarkers are biological molecules that are found within blood, tissue, or body fluids, and can be used to identify the presence of, and type of, tumour in a patient [29]. Types of biomarkers include exosomes [4], Circulating Tumour Cells (CTCs) [30] and micro-RNA (miRNA) [8]; all of which offer key information about the nature of the tumour that produced them. It has been hard to fully utilise these molecules given their low concentrations in blood and small sizes (with most miRNAs being 19 – 24 nucleotides long) [31], this not only causing issues with detection but with our ability to differentiate between similarly sized markers. However, with the recent surge in the development of NP functionalization, we have been able to develop many sensing systems for in vivo and in vitro detection of these biomarkers.

A popular method for the sensing of biomarkers employs The use of these in bioimaging and clinical settings, however, have been limited due to poor stability [32], as well as challenges with interference from environmental factors, such as other chemicals present in a sample affecting the fluorophores optical abilities or producing an optical response themselves [33]. We can obtain a characteristic 'fluorescence spectra' [31] for each fluorophore when they are incident with a specific window of electromagnetic (EM) waves. This fluorescent-response is due to the nature of fluorophore molecules and represents the optical properties in the 'turned-on' state of a dye. Certain molecules called 'chemical quenchers' can be used to reduce this EM re-emission just by being close to, or physically bonded to a fluorescent dye, this causing the fluorophore to be in its 'turned-off' state. This meaning that by changing the distance between quenching-molecules and fluorophores, we can change the florescent properties of these dyes within the same environment.

AuNP can act as quenchers for fluorophores, this ability arises from the optical properties of gold, mainly LSPR. This is when the conductive band of electrons on a AuNP's surface oscillate and resonate with the wavelengths of incident light [34], thus reducing the fluorescent-response of the attached dye. These properties allow AuNPs to provide a quenching effect of up to 100% of fluorescence when in close proximity (<10nm) with a fluorophore [35].

Generally, the specific structure used to create these 'molecular beacons' include a AuNP sphere, a fluorophore and an oligonucleotide (short single stranded DNA/RNA molecule) (Fig.1). The sequence of the oligonucleotide in these structures is complementary to a target mRNA/ miRNA the sensor is being used to target, and when it is not associated with its target sequence, forms a 'hairpin-like' structure. The AuNP and fluorophore are bound to the free ends of the oligonucleotide, therefore in this 'hairpin' configuration are brought close together, therefore causing quenching of any fluorescent responses [31]. When the target sequence is present, the oligonucleotide binds complimentarily to it, this causing the hairpin structure to straighten out, separating the fluorophore from the AuNP's surface, thus de-quenching the fluorophore and allowing increased fluorescent emissions [35]. This florescence can be detected in a fluorimeter or observed by florescence microscopy [7] and can be directly related to the concentration of the biomarker present.

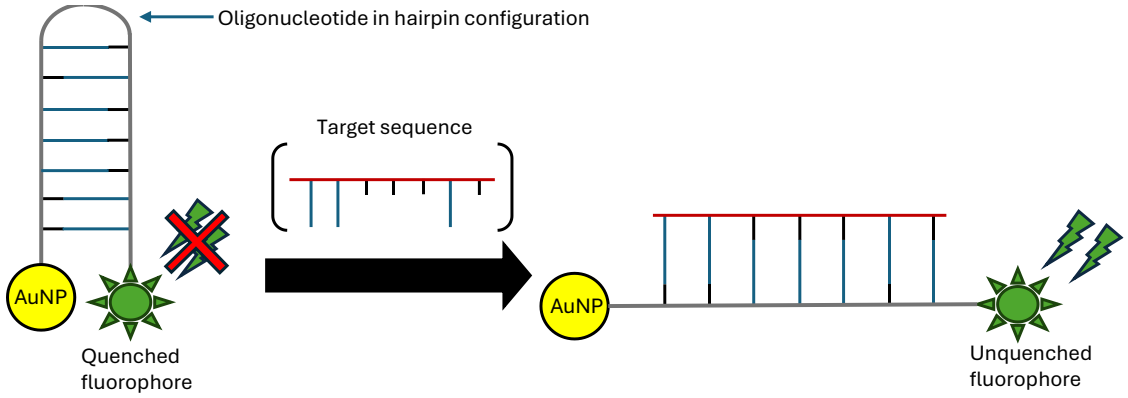

Figure 1. Summary of the conformational change in structure of a AuNP and fluorophore, connected by a single stranded oligonucleotide, when a complementary target sequence is present. The proximity of the AuNP with the fluorophore will prevent florescence when the oligonucleotide connecting them is in a 'hairpin-like' structure, however when a target sequence is present it will bind complementary to the oligonucleotide. This flattening the 'hairpin' structure, separating the fluorophore from the AuNP, allowing it to now fluoresce. Created with Microsoft PowerPoint.

Experiments comparing 1.4nm AuNPs and 4-((4′-(dimethyl-amino)-phenyl)azo)benzoic acid (DABCYL), a widely adopted organic quencher [36], showed that AuNPs provided up to a hundred times more quenching efficiency compared to DABCYL [35]. Moreover, this increased efficiency was observed in NIR wavelengths of light [37], this window of EM radiation coincides with the 'NIR biological window', a span of wavelengths where there is lower attenuation and increased penetration of photons into the body [38]. Many papers described the ability of these sensors to differentiate between analogue (complementary) sequences and sequences with a single mismatched base due to the selectivity of complimentary oligonucleotide to their target sequences. One paper found that when using miR-30a (an overexpressed miRNA in tumorous cells) [39] as a target sequence, a AuNP-fluorophore system successfully distinguished between the target sequence and sequences containing a single mismatch, insertion, or deletion at 2.4 pM concentration [7]. This justifying the viability of using AuNPs as sensors, given they increase the sensitivity and accuracy of fluorophore-quencher systems when detecting biomarkers, as well as utilising low energy radiation (NIR wavelengths) [40].

Hyperthermia Techniques

Photothermal techniques utilise the excitation of gold nanostructures with light to produce localised increases in temperature within cells. These increases in temperature can be utilised for imaging, via photoacoustic (PA) techniques. When AuNPs are exposed with EM waves, the free electrons present on the surfaces of these nanostructure will oscillate together. This causing a localised SPR (LSPR) effect where this energy can be scattered or absorbed depending on the size and shape of the AuNP [38]. The oscillations generated by LSPR can decay and be converted into heat energy [41], this result in the heating, by tens of degrees, of tissues and cells surrounding the nanoparticle [21].

Photoacoustic imaging utilises the thermoelastic expansion from a molecule, that can produce heat when light is shone upon it [42], as a signal to build an image of a biological structure. In short, a sudden increase in local temperature can causes thermal expansions in a tissue that can produce a detectible acoustic wave upon its collapse. We can guide this molecule to tumour sites by functionalising their surfaces with aptamers or peptides that have high affinity to overexpressed receptors on tumorous cells. The acoustic waves can be detected by an ultrasound transducer that reconstruct these signals into a 2D or 3D image [43], similar to ultrasounds taken during pregnancy. 'Pulse lasers' are used to generate theses expansions by radiating short burst of EM waves (usually a few nanoseconds in duration), at specific frequencies, upon photo-sensitive molecules [44].

The most common gold nanostructure used for photoacoustic imaging are gold nanorods (AuNRs). These are cylindrical structures that exhibit extremely high absorption coefficients upon exposure to specific wavelengths of EM waves due to their small cross sections, and small aspect ratios; both of these dimensional factors contributing towards strong production of photoacoustic signals [45]. AuNRs have both a longitudinal and transverse resonance spike, one spike occurring due to 'lengthways' oscillations and the other from 'widthway' oscillations [46]. These 'lengthway' oscillations can be precisely fine-tuned to resonate within NIR wavelengths of light by altering the concentration of the 'shaping-chemicals' used in seed-mediated growth methods of AuNRs [47]. In combination with a highly specific pulse of light from a laser, we can produce high resolution imaging, due to strong photoacoustic signals being returned, with minimal noise, as acoustic waves experience lower attenuation in biological tissue compared to EM waves [48], with approximately 1000 times less

scattering than optical techniques [49]. Moreover, using acoustic waves as the source for image information, we can reduce unintended tissue damage unlike imaging that uses radioactive-ladled species, such as PET, as well as highly ionising radiation, such as gamma camera or x-rays.

One paper discussed AuNRs that were functionalised with cyclic CphgisoDGRG peptide (Iso4), a peptide complementary to the integrin α5β1 receptor that is overexpressed in bladder cancer cells [50], in the photoacoustic in vivo imaging of tumours in mice. This AuNR-peptide system was successful in producing images, via photoacoustic methods @820nm [51], that helped to successfully distinguish between mice with healthy or tumour containing bladders. Thus proving the in vivo potential this type of imaging has. Furthermore, there was observed to be no binding of the AuNRs to the bladders of healthy mice [51], thus further solidifying the highly selective nature of these systems.

Discussion

AuNP-fluorophore biomarker sensors allow for the 1 to 1 detection of target molecules in real time. Traditional detection techniques that are comparable to this, such as real-time PCR, often suffer from false-positive signals, due to errors made in amplification steps, as well as being much more resource heavy and time consuming [31]. These false-positive results often stem from the fact that most miRNAs are extremely small (19-24 nucleotides in length), therefore during the genetic amplification and elongation steps of PCR, miRNA's may be misrecognised and inadvertently cause a signal. Hence reiterating the superiority that 1 to 1 binding of a target sequence to a sensor has over other PCR-based analytical techniques.

The vast amount of research into the utilisation of AuNRs in PA imaging shows their promising application in the field of bioimaging. By utilising low energy EM lasers (NIR wavelengths), PA imaging is much less damaging to tissues than other imaging techniques such as CT, that uses high energy X-rays, and PET, that use radionuclides. The ability to tightly control the resonating frequency of gold nanomaterials, specifically AuNRs, so that they overlap with a window of EM frequencies with low scattering in biological tissues, this allowing us to image at up to 6cm in depth [38]. Although the controlled synthesis of AuNRs is well studied and understood [38], the production of other gold nanostructures such as gold nanospheres (AuNS) pose difficulties in both size and shape control [52]. With further research into the precise reproducibility of other AuNP structures, different shapes can be possibly identified that help overcome the limitations of AuNR. One of these limitations is the photostability of these structures, which causes a transition from the rod-like shape to a more spherical one upon repeated resonance with EM waves [38], this obviously causing issues in imaging as when the gold nanostructure changes its dimensions, its optical properties (mainly the wavelengths at which it resonates at) will change, thus effecting the perceived signal. This photostability can be improved using an array of different coatings on the surfaces of AuNRs, for example one research paper found that by using 20nm coatings of silica, no deformation of AuNR into spherical/elliptical shapes was observed [53]. Additionally, a 6nm coating resulted in small 1-4nm changes in the AuNRs structure, these not being large enough to significantly alter its spectra. Thus showing that surface enhancements can be made to AuNRs to ensure their structure remains constant.

Conclusions

Whilst most of the applications of these diagnosis and imaging techniques discussed in this review occurred in mice or in vitro, these experiments suggest that gold nanomaterials can revolutionise the early detection and diagnosis of cancer in human patients. AuNP were found to be an effective quencher of florescent signalling molecules, these could be used in tandem with an oligonucleotide to allow for the 1 to 1 detection of biomarkers. This offering rapid and highly precise detection of specific biomarkers, that can serve as vital information in the early detection and characterisation of tumours. Additionally, the role of AuNRs in PA imaging promises non-invasive imaging of tumours without the use of radiative molecules or harmful EM waves. As advancements continue in the control and accuracy of gold nanostructure production, as well as in the reproducibility of complex AuNP systems, it is only a matter of time before gold nanomaterials are fully adopted into cancer treatment.

List of Abbreviations

AuNP: gold nanoparticle
AuNR: gold nanorod
CT: computer tomography
EM: electromagnetic
LSPR: localised surface plasmon resonance
NIR: near infrared
PA: photoacoustic
PCR: polymerase chain reaction
PEG: polyethylene glycol
PET: positron emission tomography
SPR: surface plasmon resonance

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

As this is a literary review, there was no need for participant consent or screening by an ethics board.

Authors' Contributions

ANS: Made contributions to the design of the study, collected and screened data, analyzed studies, drafted the manuscript, and gave final approval of the version to be published.

WVF: Made contributions to the design of the study, collected and screened data, analyzed studies, drafted the manuscript, and gave final approval of the version to be published.

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