Bimetallic nanoparticles for biomedical applications: a review.

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Abstract

Bimetallic nanoparticles, or BMNPs, are nanosized structures that are of growing interest in biomedical applications. Although their production shares aspects with physicochemical approaches for the synthesis of their monometallic counterparts, they can show a large variety of new properties and applications as a consequence of the synergetic effect between the two components. These applications can be as diverse as antibacterial treatments or anticancer or biological imaging approaches, as well as drug delivery. Nevertheless, the utilization of BMNPs in such fields has received limited attention because of the severe lack of knowledge and concerns regarding the use of other nanomaterials, such as stability and biodegradability over time, tendency to form clusters, chemical reactivity, and biocompatibility. In this review, a close look at bimetallic systems is presented, focusing on their biomedical applications as antibacterial, anticancer, drug delivery and imaging agents, showing significant enhancement of their features compared to their monometallic counterparts and other current used nanomaterials for biomedical applications.

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1. Nanotechnology for biomedical applications.

1.1. Nanotechnology and nanomedicine. The born of a new era.

In 1959, Richard P. Feynman gave his famous after-dinner lecture named "There's Plenty of Room at the Bottom" (Olsman and Goentoro 2018), setting the basis for the future of a field whose name was given fifteen years later. The word *Nanotechnology* was used for the first time by the Japanese investigator Norio Taniguchi in a 1974 paper on production technology invilving the generation of objects and features in the nanometer scale (Taniguchi and N. 1974). Nowadays, nanotechnology is defined as the study and application of materials with sizes less than 100 nm. Since the beginning, it has been beneficial in a variety of fields like chemistry, physics, biology, biochemistry, as well as medicine (Whitesides 2005; Pearce 2012; Salata 2004; Seeman 2003)

Feynman suggested the use of nanotechnology to develop medicine to his colleague Albert R. Hibbs. Consequently, a new field was born from this interaction: Nanomedicine, that impacts the medical applications of nanomaterials and biological devices, nanoelectronic biosensors, and even possible future applications of molecular nanotechnologies, such as biological machines (Andrew and M. 2000).

Nanostructures have been employed in a variety of biomedical applications, i.e., as antibacterial (Webster and Seil 2012), anticancer (Kamal et al. 2012), drug delivery (J. Shi et al. 2010) or imaging (Cormode et al. 2009) agents. Thus, the number of nanotechnology publications has raised over time with an unexpected trend, with hopes that if we can master this technology, we will be able to improve not just medicine, but all aspects of the modern life.

1.2. The use of metallic nanoparticles in nanomedicine.

The use of nanotechnology in the medical field has brought the utilization of different nanostructures to medical applications, such as carbon (Bekyarova et al. 2005) or silica (S. Shi, Chen, and Cai 2013), among others. Nonetheless, metallic nanoparticles (NP) have been gaining popularity due to their large variety of chemical and physical properties, along with their tenability, which is hugely related to their performance, making them perfect materials for biomedical applications (Ramos et al. 2017). From noble metals like gold (Au) to metalloids, such as selenium (Se), or magnetic metals like iron (Fe), this diversity of materials has allowed broad applications in many areas of study such as antibacterial, anticancer, imaging or drug delivery processes (Mody et al. 2010; Raliya et al. 2016; Vernon 2013)

In this way, there are different metallic systems implemented in the nanotechnological field, which can be classified in magnetic, pure metallic, metal oxide nanomaterials without magnetic behavior, and bimetallic nanoparticles.

Magnetic nanoparticles

Magnetic nanoparticles can show different features when subjected to a magnetic field. These configurations are known to present either ferri- or ferromagnetic behavior. These magnetic properties are found in materials such as nickel (Ni), cobalt (Co) or iron (Fe). Among all the configurations, the most common ones are oxides (also known as ferrites). A further classification includes ferrites with a shell, pure metallic magnetic nanoparticles and metallic with a shell (Dutz et al. 2015).

Iron oxide nanomaterials are the most widely used for research along magnetic nanostructures, showing essential features for nanomedicine. For instance, the structures become superparamagnetic -magnetization can arbitrary change the direction under the effects of temperature- preventing aggregation, which is a significant concern in biomedical applications (Dutz et al. 2015). At the nanoscale regime, the surface chemistry of the structures become highly significant. However, the surface of ferrite nanostructures is relatively inert, because of the presence of a coating, mainly a layer of silica, among other materials, producing what is commonly called ferrites with a shell (Kralj et al. 2010). The use of surfactants and polymers and processes such as oxidation can passivate pure metallic magnetic (Dutz et al. 2015).

Notably, iron oxide nanomaterials are the most promising ones, due to their reduced toxicity in biological matrices, and their antibacterial and anticancer features (Cardoso et al. 2018). As an example, Tokajuk et al. described how iron oxide nanoparticles may be utilized as a successful drug delivery agent for chlorhexidine, an active antimicrobial agent, against *Staphylococcus aureus* and *Candida albicans* (Tokajuk et al. 2017).

Pure metallic nanoparticles without magnetic behavior

Pure nanoparticles composed of single metals, for instance, gold (Au), silver (Ag) or platinum (Pt), have important biomedical applications. For instance, gold nanoparticles have been primarily used in hyperthermia treatments towards cancer – inducing apoptosis in cancerous cells – as a consequence of their optical properties (Jain, Hirst, and O'Sullivan 2012). Similarly, silver nanoparticles are known to present a powerful antibacterial activity, and therefore they have been largely used to alter orthopedic implants with the aim to avoid infection (Qing et al. 2018). However, not only noble metals can be used. For instance, bacteria-mediated selenium nanoparticles showed potent antibacterial activity against different bacteria in their antibiotic-resistant phenotypes, such as Methicillin-Resistant *S. aureus* (MRSA) or Multidrug-resistant (MDR) *Escherichia coli* (Medina Cruz, Mi, and Webster 2018).

Metal oxide nanoparticles without magnetic behavior

Metal oxide nanoparticles are composed mainly of transition metals combined with oxygen atoms, producing copper (Cu), zinc (Zn) or titanium (Ti) oxide formulations with relevant biomedical features. For instance, Amiri et. al. described the antibacterial and antifungal effects of CuO nanoparticles (Amiri et al. 2017), while Zhijun Jiao et al. explored a new drug delivery system utilizing titanium dioxide (TiO_2) nanoparticles due to its key function in improving the anticancer properties of doxorubicin as well as diminishing side effects (Chen et al. 2011).

Bimetallic nanoparticles

Bimetallic nanomaterials are composed for a combination of two different metals. There is a significant variety of different compounds that can form bimetallic nanoparticles. Nevertheless, some common combinations include the use of transition metals such as gold and silver. These two metals can be combined either between them or with other metals such as Co or Fe in order to get different features including the enhancement of their biomedical applications (Ding et al. 2017). This review will center its attention on the application of these bimetallic formulations as a powerful tool for the field of biomedicine.

2. Bimetallic nanoparticles (BMNPs). A step further.

Bimetallic nanoparticles have been widely used as biomedical agents for a long time. The reason behind this fact is related to the synergetic interaction created when two different metals are combined, leading to an enhancement of the features of the nanostructure in comparison with its monometallic configurations.

Due to the full range of different possible arrangement of the metals, such as alloy, core-shell, and cluster-in-cluster, new features arise. Therefore, the variations of the atomic structure in bimetallic nanoparticles present a significant advantage in comparison to monometallic nanoparticles, as they only can achieve a change in shape or size, leading to an improved optical or catalysis properties, as well as anticancer and antibacterial contributions. Nevertheless, and in comparison, with single metal formulations, less research has been focused on bimetallic nanoparticles. Despite this, bimetallic structures have risen considerable interest because of their improved catalytic activity and selectivity compared to their monometallic counterparts, which have their origin on the synergetic effect between both components (Jiang and Xu 2011; Y. Sun and Lei 2009; Allaedini, Tasirin, and Aminayi 2016).

For instance, Xu QH. Et al. demonstrated two-photon imaging of bacteria by Au-AgNPs under near-infrared (NIR) femtosecond laser pulses which improved antibacterial activity by the use of the NIR two-photon photothermal effects (Ding et al. 2017). Similarly, Cho et al. have developed a bimetallic hybrid Zn-Au nanomaterial with zinc cores and gold shells, with the aim to show their *in vivo* visibility by using positron emission tomography (PET) once the proton into the zinc core have been activated (Cho et al. 2016). The structures were also able to produce radiosensitization when Au cover was irradiated by different sources and therefore emitted secondary electrons (SE).

Moreover, from the biomedical point of view, BMNPs could induce higher cytotoxicity when they are in contact with the body, as more than one metallic configuration would be reacting at a time, compromising the effectiveness of these systems, due to a more significant production of reactive oxygen species (ROS) and stimulation of metal-ion release (J. L. Li et al. 2018). In an elegant study, T. Li et al. found that bimetallic nanostructures with a composition of 80% Ag and 20% Au had significantly lower toxicity compared to AgNPs, whereas if the composition was changed to 20% Ag and 80% Au the levels of toxicity increased unexpectedly (T. Li et al. 2010). Their results confirmed that AgNPs presented significant higher toxicity than AuNPs and thus

the presence of gold into silver structures potentially decrease their environmental repercussions by reducing the quantity of bioavailable Ag.

2.1. Synthesis of bimetallic nanoparticles.

The production of nanoparticles, including bimetallic ones, can be split into two main divisions that depend on the approaches followed for the production of the structures: the top-down and the bottom-up methods (Anu Mary Ealia and Saravanakumar 2017). The bottom-up method -also known as constructive process-, uses atoms or molecules of the precursors as starting materials, which react to form clusters, followed by the formation of nanoparticles. This method includes the synthesis of nanoparticles by sol-gel, chemical vapor deposition (CVD), molecular self-assembly, atomic layer deposition, nanocluster sources, wet chemical reduction, and other approaches (Thiruvengadathan et al. 2013). On the other hand, the top-down synthesis -also called destructive method-, is characterized by the use of bulk materials as the starting point, which is transformed into a fine powder until nanometric particles are obtained or patterned into nanostructures. Some examples include mechanical milling and different nanolithography techniques, such as e-beam lithography, ultraviolet (UV) lithography, focused ion-beam lithography, and nanoimprint (Merkel et al. 2010).

Recently, an alternative classification for the methods of the generation of metallic NPs has been proposed, based on the biocompatibility of the substances -except the metal precursor- used to produce the nanomaterials: the physicochemical synthesis (involving the top-down and bottom-up methodologies) and the green synthesis (Y.-H. Lee et al. 2017). We will follow this classification, although devoting special attention to the nanocluster sources among the physicochemical methods due to its commercial availability ("Mantis Deposition Systems" 2019; "Nanocluster Deposition Source" 2019).

2.1.1. Physicochemical approaches.

The physicochemical approaches for the synthesis of nanomaterials are characterized for taking knowledge from both physics and chemistry in order to build efficient pathways for formulation. Therefore, there is a wide variety of these approaches to synthesize any nanomaterial, including BMNPs (P.-C. Lin et al. 2014). They rely upon the nature and composition of the targeted nanomaterial and are characterized by different reaction times, physical parameters and chemical intermediates. Some examples of nanoparticles made by these methods appear in Figure 1.

One of the most important methods is laser ablation or pulsed laser deposition (PLD), where a specific spot on the surface is irradiated by a pulsed laser beam to the point of evaporation or sublimation (Barnett et al. 2016). Classified in a single photon process -splitting chemical bonds- and multiphoton excitation -thermal evaporation-, laser ablation is mostly used to produce semiconductor quantum dots (QD), carbon nanotubes (CNT), nanowires (NW), and core-shell NP (Tajdidzadeh et al. 2014). When performed in a high vacuum chamber, the advantage of the laser ablation method is that the resulting products are highly pure, although there is low control in the size distribution, agglomeration, and crystal structures (Sportelli et al. 2018). Another

advantage is that the laser beam can irradiate a target dipped in a solution, which facilitates the functionalization of the obtained nanoparticles (Amendola et al. 2013)

A variety of BMNPs may be synthesized following the physicochemical fashion, as can be seen in Table 1. For instance, Nakamura T. and Sato S. developed a solid-solution of palladium-platinum (Pd-Pt) particles with total variable composition that was synthetized using high-intensity laser irradiation of liquid solution of palladium and platinum ions where no reducing agents or thermal processes were employed (Nakamura and Sato 2015). Similarly, a laser ablation deposition technique was utilized to generate silver–nickel (Ag-Ni) bimetallic nanoparticles (Xiao et al. 2011); while Ag-Pd nanoparticles have been synthetized by colloids of AgNPs using liquid methodology by pulsed laser ablation in aqueous media (Mottaghi et al. 2014).

Oxidation is a type of chemical reaction that involves a substance that gives away electrons, meaning that it is oxidized. This chemical principle can be used for the production of nanomaterials by oxidation of metal ions (Y.-J. Lee et al. 2012). For instance, a facile in situ green approach for the generation of nanoparticles by process was elaborated by J. Liu et al. to prepare Ti^{3+} and N self-doped SrTiOxNy nanoparticles using TiN and H_2O_2 as precursors, with the resultant nanoparticles showing a pronounced absorption in a range between 400 and 800 nm utilizing UV-visible (vis) diffuse reflectance spectroscopy (UV-vis DRS) (J. Liu et al. 2018).

On the other hand, reduction in a chemical reaction involves a substance gaining electrons by one of the atoms implicated in the chemical process. Due to the feasibility of the reaction and the disponibility of reagents, chemical reduction methods are the most widely utilized for the production of BMNPs (Mukha et al. 2017). For the chemical reduction to take place, a metal precursor, a reducing agent and a stabilizing agent are needed (V. K. Sharma, Yngard, and Lin 2009). The metal precursor is usually a metal salt in solution; the reducing agent may vary from organic compounds -such as ascorbic acid (Zain, Stapley, and Shama 2014)- to inorganic salts - like sodium borohydride (X. Wang et al. 2014)-. The stabilizing agents (such as polyvinylpyrrolidone (PVP), starch, sodium carboxyl methyl cellulose, etc.) allows the dispersibility of the nanoparticles in common solvents (Rac-Rumijowska et al. 2017). The systematic modification of the experimental parameters controls the morphology and uniformity of the final product. As an example, hydrazine co-reduction of $[AuCl_4]^-$ and $[PdCl_4]^{2-}$ complex anions was used to synthetized colloidal suspensions of Au_xPd_{1-x} nanoalloys. Besides, polymeric compounds of high molecular weight, such as polyvinylpyrrolidone (PVP) or polyvinyl alcohol (PVA) were used as surface capping agents (Zaytsev et al. 2017).

Peng and colleagues have elaborated a seed-mediated protocol in order to obtain hybrid Ag–FexOy nanoparticles that show plasmonic and magnetic characteristics (Peng et al. 2011). The method is based on the chemical reduction of Ag+ ions when Fe NPs are present with non-crystalline FexOy surfaces previously produced by thermal decomposition.

Chemical vapor deposition (CVD) is a bottom-up technique used for the generation of a large number of nanomaterials under different atmospheres. In this process, a volatile precursor (or multiple precursors) reacts to produce the desired material (Yu et al. 2015). Hierso et al. have proved the synthesis of bimetallic core-shell palladium-platinum NPs in a layered structure

through the CVD method using a metal-organic precursor (Hierso et al. 1998). Alternatively, Choi et al. have defined the CVD technique as a fast method to produce monodisperse nanoparticles, which can be easily scaled to larger volumes, for example highly monodisperse Pt-Co BMNPs (D. S. Choi et al. 2016). Another example is the synthesis of Pt_3Co intermetallic nanoparticles supported on ceria by CVD. (Saedy et al. 2017).

A sol-gel process is a bottom-up method that consists of the synthesis of nanomaterials by hydrolysis and condensation reactions. The main benefits of sol-gel processing are the high purity and uniform nanostructures achievable at low temperatures. BMNPs made of Au-Pd, Au-Ag, and Au-Pt can be generated in a single step by a sol-gel methodology and stabilized in liquid and solid matrices (Devarajan, Bera, and Sampath 2005).

Table 1. Physicochemical methods of synthesis of bimetallic nanoparticles

Method of synthesis	**Nanoparticle**	**Size (nm)**	**Morphology**
Seed-mediated	Ag-Fe3O4 (Peng et al. 2011)	5-20 nm each nanoparticle	2 nanoparticles together
Chemical reduction	Au-Ni(X. Wang et al. 2014)	2.3 - 2.7 nm	Quasi-spherical
	Ag-Au(Mukha et al. 2017)	5-15 nm depending on the ratio	Quasi-spherical
	Ag-Au(I. O. Shmarakov et al. 2014)	15-30 nm depending on the metal ratio	Quasi-spherical
	Ag-Au (Pal, Shah, and Devi 2007)	20-27 nm depending on the metal ratio	Quasi-spherical
Chemical Oxidation	$SrTiO_xNy$(J. Liu et al. 2018)	50-200 depending on the temperature	Quasi-spherical
Laser ablation	Pd–Pt (Nakamura and Sato 2015)	50–90 nm	Predominantly spherical
	Ag-Pd core-shell(Mottaghi et al. 2014)	2.4 - 3.2 nm	Quasi-spherical

	Ag-Ni(Xiao et al. 2011)	Varies	Irregular shape
	PEG-Fe-Au Alloy (Amendola et al. 2013)	15-40 nm	Spherical
Sol-gel	Ag-Pt-modified TiO_2(Zielińska-Jurek and Zaleska 2014)	15-30 nm	Quasi-spherical
CVD	(Pd-Pt)/SiO_2(Hierso et al. 1998)	1-15 nm	Layers
	Pt-Co(D. S. Choi et al. 2016)	1.2 - 1.8 nm	Spheroids
	Ni-Pd @ MIL-101(Hermannsdörfer et al. 2012)	2 - 3 nm	Spherical

Nanoclusters sources deserve a special mention within the physicochemical approaches in terms of nanoparticle synthesis. BMNPs can be produced using gas-phase synthesis using the so-called nanocluster sources. Although there is a rich variety of types of NP sources that can be used, each one with advantages and drawbacks (Huttel 2017), the most popular ones are the magnetron-based cluster sources. This technique involves two chambers separated by a wall with a pin-hole: the aggregation chamber where the NPs are formed and the deposition chamber where the NPs are collected. The sputtering process takes place in the first chamber, loaded with a low-pressure ideal gas (typically argon) and a negative voltage is administered to a metallic objective (the origin of atoms). The application of this voltage fractures the gas and constitutes a plasma formed by Ar^+ and Ar^{2+} ions (with ratio $Ar^{2+}/ Ar^+ << 1$) and electrons. The ions are accelerated towards the target and the atoms of the surface are ejected by momentum transfer, which aggregate in the aggregation zone to form NPs. The dimension of these NPs (typically 1−20 nm) is directed by the power applied to the target, the argon pressure, the position of the target in the aggregation zone, and the possible use of extra gas (usually helium). It is worth mentioning that the technique is called "magnetron sputtering" because magnets are placed behind the target, which helps to trap electrons over it and as a result increases the efficiency of the process, thus allowing for using lower pressure values and obtaining faster deposition rates. Finally, the second chamber is the collection chamber where only the NPs that go through the pin-hole is collected on a substrate. This chamber is usually maintained in conditions of vacuum or ultra-high vacuum in order to guarantee the chemical purity of the NPs. Besides, the substrate can be heated to promote thermal diffusion effects, which can alter the structure of the NPs (Llamosa Pérez et al. 2013).

With a single magnetron-based source, BMNPs can be fabricated by using a bimetallic alloyed target. In general, the elements present in the NPs are similar or the exact ones on the target, but the internal structure of the compounds depends on the atomic diffusion of the two kinds of atoms. As an example, Oprea et al. showed the fabrication of Fe-B NPs from a $Fe_{50}B_{50}$ target,

which was made of an internal Fe core while outside the shell with a combination of Fe and B oxides and oxynitrides (Oprea et al. 2015). They could be functionalized with polyethylene glycol (PEG) and exhibited superparamagnetic behavior at RT. Therefore they may be tentatively used as contrast agents in magnetic resonance imaging (Oprea et al. 2014).

By heating the substrate, one can use thermal-induced diffusion to modify the structure of the NPs, leading to the generation of perfectly-defined core-shell structures. That was the approach used by Llamosa Pérez and co-workers: with a $Co_{95}Au_5$ target and by heating the substrate, significant structural changes were found: the deposition at low temperatures (close to RT) induced the synthesis of an alloyed fcc CoAu core with an non-complete cobalt oxide shell, whereas the use of elevate deposition temperatures (up to 770 K) led to the generation of a pure hcp Co core with an intermediate Au shell and a compact outer cobalt oxide shell (Llamosa Pérez et al. 2013)

Another possibility to obtain a wide diversity of crystalline and chemical combinations at atomic level from an alloyed magnetron target is to apply high-power impulses instead of a continuous dc voltage, in the so-called high-power impulse magnetron sputtering technique (HiPIMS) (Mayoral and Martínez 2019).

However, the most powerful way that permits for fine-tailoring of the chemical composition of the NPs is to use a cluster source with multiple targets (Martínez et al. 2012; Oprea et al. 2014): with the aim to produce BMNPs, two targets, A and B, are thus needed in this strategy. Different NPs are produced when the relative position of the targets in the aggregation zone is modified. If targets A and B are placed together, i.e., their distance to the pin-hole are the same, NPs made of a homogeneous AB alloy are obtained (Martínez et al. 2012). In clear contrast, if the target A is located behind the target B, NPs are being made of an A core and a B shell, which is a route that can be used to obtain core-shell NPs beyond the limitations of thermal diffusion (Llamosa et al. 2014). Martínez et al. used this route with an Au target behind a Ti one, and the obtained NPs were oxidized in-flight to have Au core - TiOx shell NPs at the end (Martínez et al. 2017). Finally, it is worth mentioning that this type of cluster sources with multiple targets is commercially available ("Nanocluster Deposition Source" 2019).

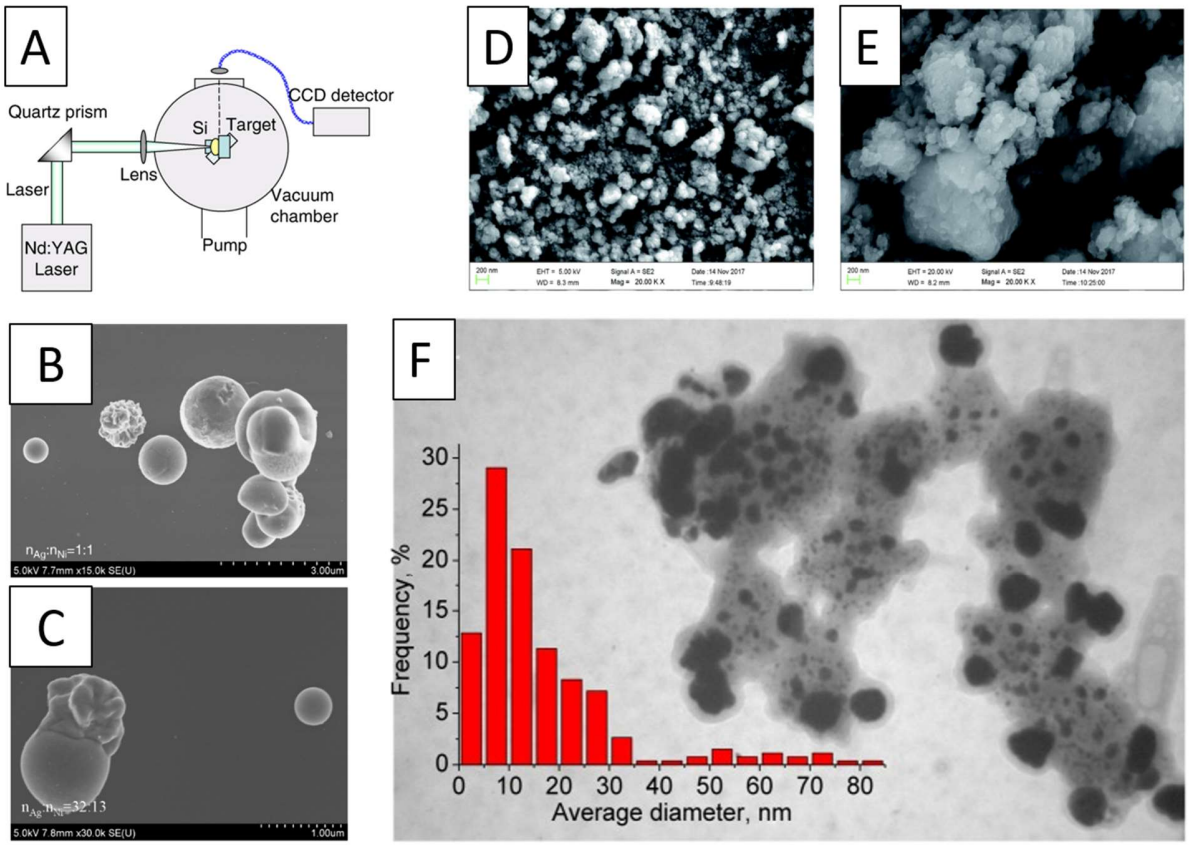

Figure 1. The schematic diagram of the experimental setup for the generation of Ag–Ni bimetallic nanoparticles by laser-induced plasma (A) (Xiao et al. 2011); Scanning electron microscopy (SEM) images of nanoparticles with a mole ratio of silver and nickel nAg:nNi = 1:1 and 32:13, respectively (B, C) (Xiao et al. 2011); SEM images of Ti3+ and N self-doped SrTiOxNy samples warmed at different temperatures and atmospheres: (D) T-130-Vac amd (E) T-200-Vac (J. Liu et al. 2018); and transmission electron microscopy (TEM) image and size distribution of particles in Ag/Au/Trp colloids (F) (J. Liu et al. 2018).

2.1.2. Green approaches.

The application of green chemistry basics to nanotechnology supposed improvement in the synthesis of nanomaterials in the direction of sustainability. Green nanotechnology was born as the promise of using environmentally-friendly, cost-effective and safe methods for generation of different nanomaterials (Makarov et al. 2014). Therefore, these processes can overcome the main restrictions of traditional physicochemical approaches –likewise, the generation of noxious by-products or the often uses of extreme reaction conditions- offering a suitable answer to environmental concerns (Kadzinski et al. 2018).

Therefore, several green nanotechnological approaches have been reported for the generation of nanostructures. These methods involve the utilization of living entities –for instance, microorganisms, fungi or plants- and biomaterials coming from different natural sources, like

fruits, biopolymers, and organic waste materials. It is important to know that each of these alternatives to the traditional chemical methods offers a different mechanism for the generation of the nanomaterials. However, the mechanisms still have as their basis, the use of a reducing agent, as polysaccharide, and a capping agent like protein or lipid.

The application of green methodologies for the production of bimetallic nanostructures is not widely reported as it could happen with other well-known nanoparticles, such as gold or silver. Nevertheless, some interesting examples can be found in the literature. In the next sections, the leading green synthetic approaches are explained together with some relevant examples, with some examples showed in Figure 2.

Bacteria-mediated synthesis

The use of bacterial populations as natural biofactories was one of the first reported methods. Since then, both Gram-negative and positive bacteria have been used for the successful generation of many hard systems with biomedical and technological applications (Thakkar, Mhatre, and Parikh 2010). It has been reported that these microorganisms can generate nanoparticles by converting metal ions into zero-valence metal nanoparticles, in a synthetic process that can be either intracellular or extracellular (Medina Cruz, Mi, and Webster 2018). In Table 2, examples of bacteria-mediated bimetallic nanoparticle synthesis are presented.

For instance, *Lactobacillus* strains in buttermilk can support the process of growing of Au-Ag alloy crystals of submicron size as a result of exposing them to the precursor ions without affecting the bacteria survival by the crystal growth (Pradeep 2002). Similarly, Pd–Pt nanostructures were generated both inside and outside the cells of *Shewanella oneidensis*, a facultative bacterium, with the ability to grow and resist in both aerobic and anaerobic media (Xu et al. 2019).

Table 2. Generation of bimetallic nanoparticles mediated by bacteria;

Bacteria	**Method of synthesis**	**Type of NPs**	**Size/ nm**	**Shape**
Lactobacillus	Extracellular	Au-Ag(Nair and Pradeep 2002)	100–500	Irregular
*Phormidium tenue (*marine cyanobacterium)	C-phycoerythrin pigment extracted from the marine cyanobacterium	Cd–S (Mubarakali et al. 2012)	5.1 ± 0.2	Spherical
Deinococcus radiodurans	protein extracts (Dps2)	Au-Ag (J. L. Li et al. 2018)	10–60	Spherical

Shewanella oneidensis	Intracellular and extracellular	Pd–Pt (Xu et al. 2019)	3–40	Spherical
Escherichia coli	coverage the cell surface and	Au–Pd core–shell(Deplanche et al. 2012)	16	Spherical
Cupriavidus necator	Extracellular	Au–Pd core–shell(Hosseinkhani et al. 2012)	10–50	Spherical
Spirulina platensis	Extracellular	Au-Ag(Govindaraju et al. 2008)	17-25	Core-shell

Fungi-mediated synthesis

Fungi are eukaryotic organisms that include yeasts, molds, and mushrooms. In the past years, there has been a rising need in developing biogenic synthesis methods of metallic nanoparticles using fungi (X. Zhao et al. 2018). As it happens with bacteria, the reduction of metallic salts by fungi may occur both intra- and extracellularly, using enzymes and proteins that these microorganisms produce naturally.

Interestingly, up-scale manufacturing of nanostructures from different fungal strains has demonstrated possible for scale-up processing, since they can be grown even *in vitro* (Siddiqi and Husen 2016). It is worth mentioning that for large-scale production of nanoparticles by biogenic synthesis, the use of fungi rather than bacteria is preferabl since it is faster to produce fungus biomass than bacteria biomass (Taherzadeh et al. 2003). Besides, the fungus mycelia have a large surface area for interaction (Pantidos 2014). Hence, the fungi can produce a high number of proteins, which may accelerate the process of the reduction of metallic salts. Some examples are given in Table 3, which shows previous studies into the synthesis of bimetallic nanoparticles utilizing fungi.

The filamentous fungus *Neurospora crassa* – a red bread mold- was analyzed and found to be propitious for the synthesis of bimetallic Au-AgNPs (Castro-Longoria, Vilchis-Nestor, and Avalos-Borja 2011), whereas crystallized and spherical-shaped Au-AgNPs were generated and regulated using a fungus, *Fusarium semitectum* in an aqueous media (Dasaratrao Sawle et al. 2008).

Table 3. Synthesis of bimetallic nanoparticles mediated by fungi.

Fungi	Nanoparticle		Size (nm)	Morphology
Fusarium oxyporum	CdS(Ahmad et al. 2002)		5-20	Spherical
Neurospora crassa	Au–Ag(Castro-Longoria, Vilchis-Nestor, and Avalos-Borja 2011)	70/30	3–90	Spherical
		50/50	3–110	
		30/70	4–45	
Fusarium oxysporum	Au–Ag(Senapati et al. 2005)		8–14	Spherical
Fusarium semitectum	Au–Ag(Dasaratrao Sawle et al. 2008)	50/50	10–35	Spherical
Volvariella volvacea	Au–Ag(Philip 2009)		50–100	Predominantly spherical
Yeast (instant dry)	Au–Ag(Zheng et al. 2010)		9–25	quasi-spherical

Plant-mediated synthesis

The use of plant extracts for generation of nanomaterials offers suitable and easy-to-scale-up approaches. The chemical composition of the extracts is full of compounds with diverse functional groups, like aldehyde, hydroxyl, carboxyl or amine groups. These groups are primarily responsible for the reduction of metal salts into zero-valence metals, conducive for the formation of nanoparticles with various shapes and dimensions (Shah et al. 2015). The compounds found in plant extracts help in the stabilization of the colloidal NP, preventing particle aggregation and controlling their morphology over time (Lu et al. 2014; Phan and Nguyen 2017)

In general, plant-mediated synthesis includes the preparation of a liquid extract, which consists of cutting finely or milling distinct pieces of the plant for instance stems, leaves, flowers or even roots until obtaining light and dried powder. Afterwards, this powder is added to a certain amount of water. The mixture is kept at a specific heat within a range of 25 to 100 ºC for a period that could be from a few minutes to several hours. Then, the solution is decanted or filtered to remove insoluble solid materials. Subsequently, the essence is combined with a solution of the metal salts at a specific temperature and desired pH with or without agitation (P. Singh et al. 2016; Kuppusamy et al. 2016; Velusamy et al. 2016)

In Table 4, different types of noble metal alloy NP using a variety of vegetable extracts made up of different parts of a living organism are shown. For instance, S. S. Shankar et al. synthetized Au-Ag core-shell extracellularly utilizing Neem -*Azadirachta indica*- leaf solution (S. S. Shankar et al. 2004). When compared to previous studies which use microorganisms like fungi, it was stated that the rates of reduction of the metal ions utilizing this leaf extract were significantly faster. Alternatively, leaves extract of *Cacumen platyclade* - evergreen coniferous tree in the cypress family- was used to synthesize spherical Ag-Pd nanostructures (Lu et al. 2014) and Au–Pd nanoparticles (Zhan et al. 2011), but also flower-shaped Au-Pd core-shell bimetallic nanostructures (D. Sun et al. 2014).

Similarly, Ganaei et al. demonstrated the efficient synthesis of bimetallic Au-Ag NP using a highly invasive soil weed coral vine (*Antigonon leptopus*) (Ganaie, Abbasi, and Abbasi 2016). The liquid extracts of the weed were found to be capable of reducing the metal ions and therefore generate aggregates of nanometric size, which were finally stabilized to avoid further aggregation processes. Similarly, Chopade et al. used tubers from *Dioscorea bulbifera* to synthesize Pt–Pd NP that were used as anticancer agents (Chopade et al. 2015).

Table 4. Generation of bimetallic nanoparticles mediated by plant extracts

Plant	Type of alloy NPs		Size/ nm	Shape
Cacumen platycladi	Ag–Pd(Lu et al. 2014)	3:1	11.9 ± 0.8	Mostly spherical
		1:1	9.1 ± 0.7	
		1:3	7.4 ± 0.4	
Cacumen platycladi	Au–Pd core–petals (D. Sun et al. 2014)~~(Zhan et al. 2011)(Zhan et al. 2011)(Zhan et al. 2011)(Zhan et al. 2011)(Zhan et al. 2011)~~		47.8	Flower-like
Cacumen platycladi	Au–Pd(Zhan et al. 2011)		~ 7	Spherical
Antigonon leptopus	Au–Ag(Ganaie, Abbasi, and Abbasi 2016)		8–176	Spherical, triangular and irregular shapes
Dioscorea bulbifera	Pt–Pd(Chopade et al. 2015)		20–25	Irregular shape
Ocimum basilicum	Au–Ag(Malapermal et al. 2015)		21 ± 11.53 (leaf extract) 25 ± 9.63 (flower extract)	Spherical
Azadirachta indica (Neem)	Au–Ag core – shell(S. S. Shankar et al. 2004)		50–100	Predominantly spherical

Agrimonia eupatoria	Cu–Pt core–shell(Dobrucka and Dlugaszewska 2018)	30	spherical
Muntingia calabura	Ag–AgCl–Au (Patra et al. 2017)	100–400	cubical

Biomolecules-mediated synthesis

Another green synthesis approach for the synthesis of bimetallic nanostructures is utilizing biopolymers such as chitosan, polyethylene glycol (PEG), poly(methyl vinyl ether-co-maleic anhydride) (PVM/MA) and starch, as well as other molecules, as can be seen in Table 5. These biopolymers serve as eco-friendly reducing and stabilizer agents in the synthesis reaction (Hebbalalu et al. 2013). Haiqing Li et al. used the biocompatible hyperbranched polyglycerol (HBP) as an active reducing and stabilizing agent for the generation of bimetallic nanoparticles (Au-Pt, Au-Pd, and Au-Ru) with high solubility in aqueous media (H. Li et al. 2010). The reports have shown that the Au-Pt spherical particles with a size of 4.5 ± 1.7 nm, while on the other hand, Au-Pd and Au-Ru particles did not have a uniform size and they showed irregular morphologies.

In another study, the amino acid tryptophan was employed for the synthesis of Ag–AuNPs due to their ability to act as both reducing and capping agent. The Ag–AuNPs presented size of 5–15 nm with a quasi-spherical morphology (I. O. Shmarakov et al. 2014). Furthermore, a particular type of starch, known as degraded pueraria starch (DPS), was used by Xia et al. to synthesize Au-AgNPs with a diameter of around 32 nm and with a nearly spherical morphology (Xia, He, and Li 2013).

X. Liet al. have recently reported an effective biological methodology related to the hydrolysis of cellulose with the aim to generate Ag-Pd alloy NP utilizing hydrothermal conditions (X. Li, Odoom-Wubah, and Huang 2018). Alternatively, a green approach to generate gelatin-capped bimetallic Au-Ag NP has been reported, with its principals on the interaction between silver nitrate or chloroauric acid with a 1.0 wt% liquid gelatin solution at 50°C. The developed process is environmentally friendly and reactive to chemiluminescence detection a specific drug in its bulk powder, pharmaceutical injections and biological samples (Alarfaj and El-Tohamy 2016).

Table 5. Synthesis of bimetallic nanoparticles by biomolecules

Biomolecules	**Type of Nps**	**Size/nm**	**Shape**
Polyglycerol (HBP)	Au–Pt(H. Li et al. 2010)	8.0 ± 1.8	spherical

	Au–Pd(H. Li et al. 2010)	7.8 ± 2.0	spherical
	Au–Ru(H. Li et al. 2010)	7.1 ± 1.3	spherical
Tryptophan	Au–Ag(I. O. Shmarakov et al. 2014)	5–15	quasi-spherical
Pueraria starch	Au–Ag(Xia, He, and Li 2013)	32 ± 1.6	spherical
Starch	Ag–Cu(Valodkar et al. 2011)	20 ± 1.6	spherical
Cellulose	Ag–Pd(X. Li, Odoom-Wubah, and Huang 2018)	59.7 ± 1.4	Quasi-spherical
Chitosan	Ag–Cu(Zain, Stapley, and Shama 2014)	–	–
Gelatin	Au–Ag (Alarfaj and El-Tohamy 2016)	30	spherical

Waste material-mediated synthesis

On the one hand, waste materials coming from natural sources, such as agricultural wastes, have been recognized as an environmental burden for society. On the other hand, they have been stimulated new gateways for the production of renewable, low cost and sustainable materials (Khatami et al. 2018). Nevertheless, few methodologies have been described for the generation of nanostructures using these raw materials with successful results.

The synthesis of BMNPs mediated by waste materials has been poorly explored, so it remains as an area of opportunity for future scientific research. S. Shankar et al. presented for the first time an economic and non-contaminant approach for the formation of a colloidal solution of Au-AgNPs utilizing *Lansium domesticum* fruit peel essence as a mixed reducing and capping agent (S. Shankar et al. 2014).

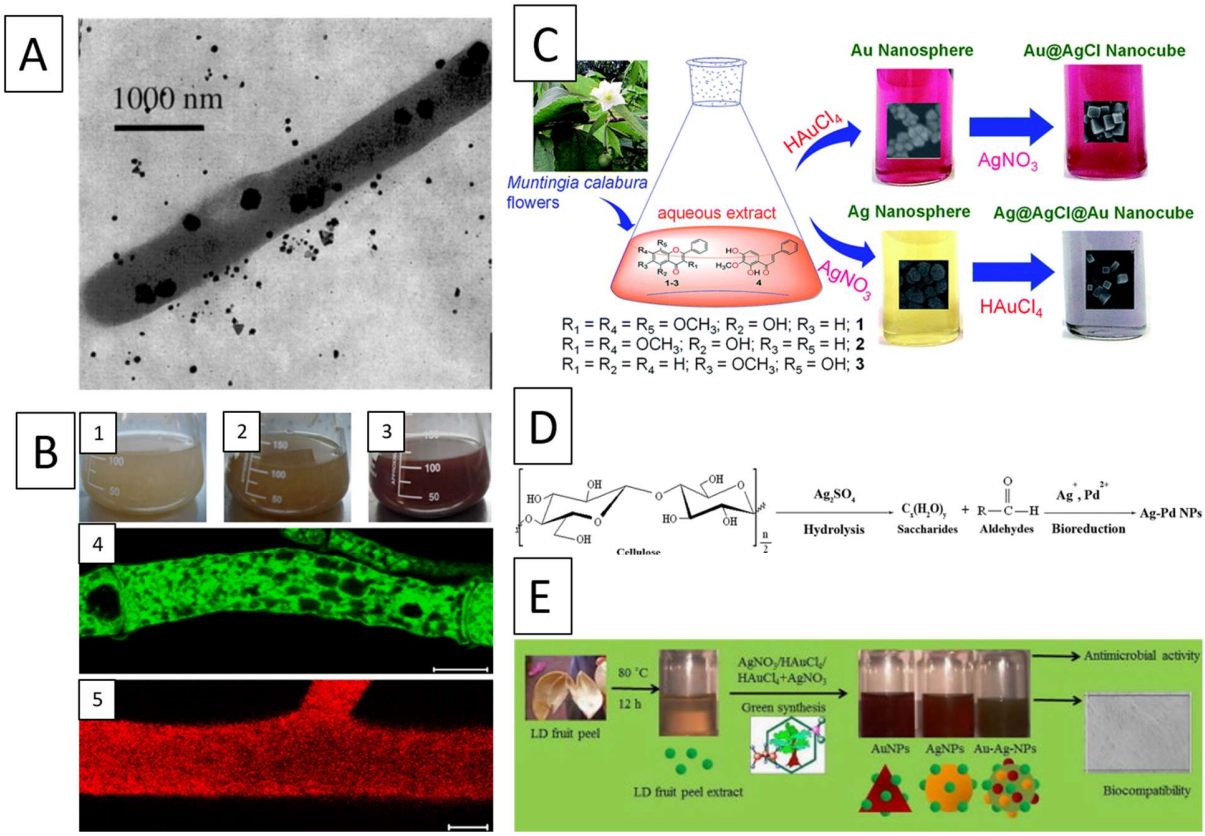

Figure 2. Electron micrographs of the growth of gold crystals in *Lactobacillus strains* (A) –Reprinted with permission from (Nair and Pradeep 2002). Copyright 10`9 American Chemical Society; N. crassa biomass exposed to liquid solutions of AgNO3 and $HAuCl_4$ (1) culture at time zero; (2) culture after 24 h in AgNO3; (3) culture after 24 h in HAuCl4; (4) hypha after 24 h in AgNO3 scanned under confocal microscopy (Abs/Em 420/515–530 nm); (5) hypha after 24 h in HAuCl4 scanned under confocal microscopy (Abs/Em 543/574–691 nm) (B) (Castro-Longoria, Vilchis-Nestor, and Avalos-Borja 2011); synthesis of metal nanoparticles using flower extract of *Muntingia calabura* (C) (Patra et al. 2017); The main reaction mechanism for the biosynthesis of Ag–Pd bimetallic NPs (D) (Patra et al. 2017); An economic and environmental friendly methodology created to produce colloidal solutions of and gold–silver-alloy (Au-AgNPs) nanoparticles using *Lansium domesticum* (LD) fruit peel extract (E) (Patra et al. 2017)

2.2. Bimetallic nanoparticles as biomedical tools.

In the next section, the successful application of bimetallic nanomaterials in the biomedical field will be explored as a potential solution towards cancer and bacterial infections, and as a tool to enhance biological imaging, drug delivery and biosensing.

2.2.1. Antimicrobial applications

The interaction between bacteria and humans has always been a complex and pivotal relationship with beneficial and undesired consequences. Living in a bacterial world as we do, pathogenic bacteria have learned how to infect humans. Fighting back was a laborious process until the

discovery of penicillin by Sir Alex Fleming in 1932 (Castro-Longoria, Vilchis-Nestor, and Avalos-Borja 2011). The antibiotic era was born, providing society with a wide range of antibiotics to fight infections. However, bacteria fought back, and they developed what is known as human-induced antibiotic resistance –different from natural antibiotic resistance found in the interaction between living organisms, such as fungi, with bacteria-. Different bacterial strains started developing resistance to the main antibiotics soon after their first use, hence the development of new formulations became a race for pharmaceutical companies (Ventola 2015). Therefore, humankind is approaching the post-antibiotic era, where infections that were easily treated in the past can now kill again (Zaman et al. 2017).

Nanotechnology has emerged as a potential solution to overcome the main limitations of antibiotics. Although it has been reported, bacterial-resistance to NP and other nanostructures is not prevalent amongst microorganism. For a long time, nanostructures composed by noble metals, like gold and silver have been used as powerful antimicrobial agents, decreasing the growth of bacterial populations (Shamaila et al. 2016; Salomoni et al. 2017). Nevertheless, bacteria are starting to develop resistance to them employing natural defense mechanisms (Panáček et al. 2018).

Therefore, new formulations are needed, enhancing antimicrobial approaches. The use of BMNPs as antimicrobial agents is not prominant in the biomedical field. A synergic antimicrobial effect can be achieved when different formulations of materials, such as silver nanostructures, are hybridized with other metal and oxide nanoparticles. For core-shell nanostructures, it is essential that one material act as a shell, while the other will form the core of the material (Chou and Chen 2007). Often, an enhancement of the antimicrobial properties – among others, as it will be discussed- is found compared to the monometallic formulation. Importantly, when talking about bimetallic nanoparticles –with some examples being showed in Figure 3- as antimicrobial agents, they can be found in literature as the individual nanostructure, with the presence of a coating made of different molecules or combined with different drugs.

For instance, Sankar Ghosh et al. reported a natural synthesis using sodium citrate as a reducing agent for the development of bimetallic Au-Ag core-shell NP. In the system, the AuNP were utilized as seeds for constant discharging of silver atoms on its surface (Banerjee et al. 2011). The structures presented antibacterial effects against Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and the two Gram-positive (*Enterococcus faecalis* and *Pediococcus acidilactici*) bacteria when working with low concentrated silver-shell, stronger efficiency was observed when treating Gram-negative bacteria. Y. Zhao's group showed that non-modified BMNPs of Au-Pt were powerful antibiotic materials, while pure Au NPs or pure Pt NPs did not display any antibacterial effect. A synthesis of the structures was achieved using a co-reduction of $HAuCl_4$ and K_2PtCl_4 with sodium borohydride in the vicinity of Tween 80 used as a stabilizer in water in an ice-water bath (Y. Zhao et al. 2014). They have explained that the mechanism that triggers the antibacterial activity is related to the dissemination of membrane potential and the increase of adenosine triphosphate (ATP) levels through using Au-Pt nanoparticles.

Besides, the formulation of bimetallic nanoparticles allows the combination with other molecules of biological interest. Holden's group produced Ag-Au alloy BMNPs covered with glutathione through a synthetic process of galvanization replacement between maltose coated AgNPs and

chloroauric acid ($HAuCl_4$) in an aqueous copolymer solution (Holden et al. 2016). They successfully brought into comparison the antibacterial properties of the Ag-AuNPs to pure AgNPs on *Porphyromonas gingivalis* W83, a pivotal pathogen in the development of periodontitis. They found that passivation of AgNP with metals like gold can produce less toxicity in eukaryotes.

Alternatively, Antonoglou et al. employed a reproducible, easy hybrid polyol methodology employing non-extreme temperature and solvothermal conditions with the aim to isolate bimetallic Cu-Fe nanoparticles polluted with non-oxide compounds (Antonoglou et al. 2017). Besides, they studied how 1,2-propylene glycol (PG), tetraethylene glycol (TEG) and polyethylene glycol (PEG 8000), with distinct physicochemical properties, can control the dimensions, structure, composition and the surface chemistry of the nanostructures.

Interestingly, the effect of antibiotics can be enhanced when combined with BMNPs. For instance, Naji M. et al. explored the profits of bimetallic AuAgNPs when used together with doxycycline- for burn infections (Fakhri, Tahami, and Naji 2017). The bimetallic nanoparticles, produced by core-shell method, showed the presence of a synergistic antibacterial effects of doxycycline coupled with the bimetallic nanoparticles when treating *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus* and *Micrococcus luteus*.

Belonging to the green chemistry approaches, some pathways have been reported for the production of BMNPs. For instance, R. Singh et al. showed the antimycobacterial properties of medicinal plants (*Barleria prionitis*, *Plumbago zeylanica*, and *Syzygium cumini*) -mediated synthesis of AuNPs, AgNPs, and Au-AgNPs, demonstrating strong effectivity, specificity, and selectivity to end with mycobacteria (R. Singh et al. 2016). In similar research, Akinsiku et al. described the production and modeling of AgNPs and silver/nickel allied BMNPs (Ag-NiNPs) using a plant-extract reduction method (Akinsiku et al. 2018). The antimicrobial properties of the nanoparticles were studied through the application of AgNPs as antibacterial and antifungal agents. Dlugaszewska J. used the *Agrimoniae* herbal essence to get bimetallic core-shell Cu-Pt NP, showing a maximum performance when treating Gram-negative bacteria (Dobrucka and Dlugaszewska 2018).

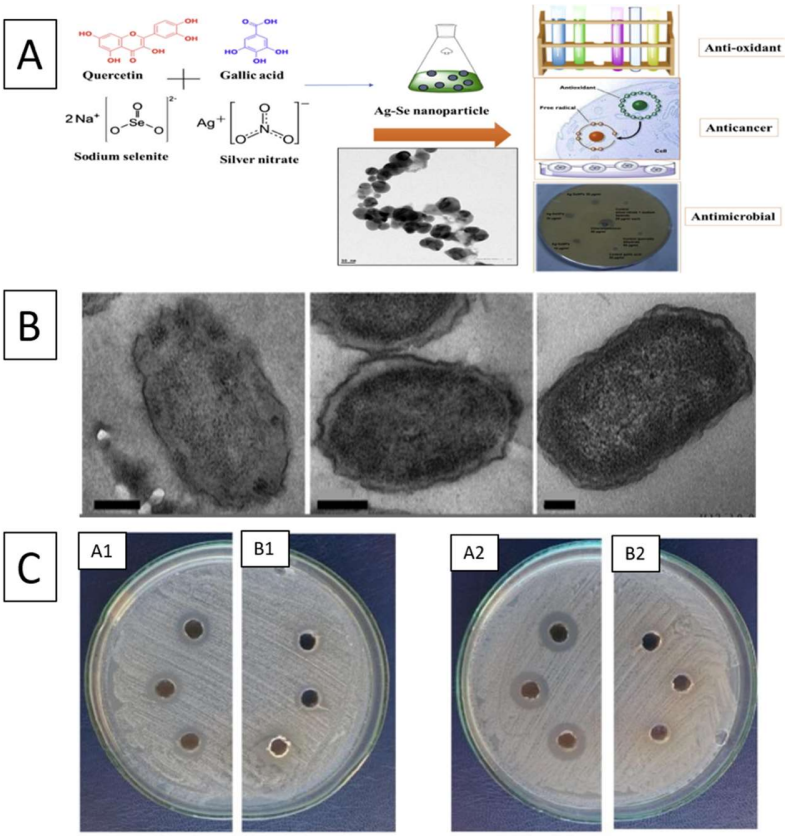

Figure 3. Methodology for the synthesis of stable, mono-dispersed high yielding bimetallic (Ag-Se) nanoparticles utilizing quercetin and gallic acid at room temperature (A) (Mittal, Kumar, and Banerjee 2014); Morphological changes of *Escherichia coli* when subjected to AuPt NPs (40 μg mL−1, 2 h) visualized with TEM; the NPs inferred blurring of the cytoplasm membrane, misplacing of the interior structure, and generation of a large-scale light area (B) (Y. Zhao et al. 2014); Antimicrobial effect of Cu-Pt nanoparticles (A1, A2) and *Agrimoniae herba* extract (B1–B2) facing *Staphylococcus aureus* (A1, B1) and *Escherichia coli* (A2, B2) (Dobrucka and Dlugaszewska 2018).

2.2.2. Anticancer applications

Cancer is defined as an abnormal growth of tissue where cells divide uncontrollably, leading to an exponential cell population growth and the death of healthy cells surrounding the cancerous tissue (Cooper 2000). In 2018, the global cancer burden rose to 18.1 million cases and 9.6 million cancer deaths. In the United States alone, there were approximately 1,735,350 cancer cases diagnosed and 609,640 cancer deaths in 2018 (Siegel, Miller, and Jemal 2018). With the current cancer survivors rate, the associated cost of treatments will be 157.77 billion US dollars by 2020 (Mariotto et al. 2011).

Humankind started using surgery as a cancer treatment. Nowadays, we live in the era of chemotherapy and radiotherapy (Arruebo et al. 2011). The first one involves chemical drugs that are introduced intravenously or orally, and that, upon entering the bloodstream, attack cancer cells, inducing cell-cell death (*Institute for Quality and Efficiency in Health Care: Executive Summaries* 2005). On the other hand, radiotherapy takes advantage of an ionic radiation dose in the tumour location, producing DNA damage that leads to cell failure (Gelband H, Jha P,

Sankaranarayanan R 2016). Often, both techniques are used in combination with each other to improve the efficacy of treatment.

Nevertheless, they both include essential limitations, such as a different effect on each patient, and harmful side effects like anaemia, organ damage, hair loss, and vomiting, among others (Ramirez et al. 2009). As a consequence of the above-mentioned limitations in chemotherapy and radiation therapy, several new treatments have arisen in the last decades, such as immune therapy, hyperthermia or gene therapy (Alberts et al. 2002).

The use of nanotechnology for cancer treatment has gained influence, as it is possible to overcome some current limitations regarding current imaging techniques and drug delivery approaches (Heath and Davis 2008). Specifically, nanoparticles can be synthesized with the ability to differentiate cancer cells from healthy cells, which enables tumour targeting, and is one of the potential advantages of nanotechnology for cancer treatment (Gmeiner and Ghosh 2015). Consequently, NP meet the essential cancer therapeutic requirements of efficacy and selective toxicity. One of the most encouraging nanomaterials for cancer treatments is gold nanoparticles (Jain, Hirst, and O'Sullivan 2012) since they are significantly stable, sensitive, and can be manufactured with elevated levels of precision. Moreover, there has been continued research to use them as drug carriers, photothermal agents, contrast agents, and radiosensitizers. Besides gold, silver nanoparticles (Yuan, Peng, and Gurunathan 2017) have been proposed as potential anticancer agents, with unprecedent cytotoxic characteristics and the ability to provoke apoptosis in a range of cancer cells (De Matteis et al. 2018).

BMNPs can offer an enhancement in their properties compared to monometallic nanostructures due to a synergetic effect between the two metals employed. The major concerns related to physicochemical features in relation to the biological performance of metallic nanoparticle are primarly their dimensions, shape, composition and charge among others; another key factor is the interaction with cancer cells. Besides, when combined with some techniques used in imaging or drug delivery for cancer, the improvement is typically related to this synergetic effect.

For instance, in an elegant study recently published, I. Shmarakov et al. proposed that the bimetallic Ag-Au composition could be utilized as improved anticancer materials because of their synergetic effect. Different colloidal solutions of Ag-AuNPs of alloy and core-shell type were analysed to obtain the antitumor performance as a function of the molar ratio of the metal and the atomic distribution of Au and Ag within NPs. The nanoparticles were tested *in vivo* with mouse Lewis lung carcinoma (LLC). Their results suggested that there was a significant dependence between the *in vivo* antitumor performance and the gold and silver interaction coming from their ordered atomic distribution (I. Shmarakov et al. 2017). Consequently, NPs with Ag core surrounded by Au shell showed maximum effectivity in comparison with all the NPs analysed towards LLC tumour growth and metastasizing inhibition.

Similarly, Kannan S. and Mishra SK. synthesized a silver-neodymium bimetallic nanoparticles system that was generated by a microwave-assisted polyol synthetic procedure. The structures confirmed magnetic resonance imaging (MRI), computed tomography (CT), and NIR trimodal imaging capacity and stated worthy temperature response to irradiation when NIR laser was used. The nanoparticles were functionalized using chitosan on the surface, delivering suitable

biocompatibility in addition to promoting the charging of paclitaxel, an anticancer drug (Mishra and Kannan 2017). Consequently, the bimetallic formulation supposes a combined therapeutic agent, giving the capacity to eliminate cancer cells *in vitro* at very low concentrations when compared to single therapy.

Hybrid Zn-Au NPs composed by zinc cores and gold shells were synthesized by Jongmin et. al., with the objective of providing them with *in vivo* discernibility through positron emission tomography (PET) once the zinc core was activated and also to give them the capacity to produce radiosensitization by the use of secondary electrons generated on the gold shell after being irradiated with different radiation founts (Cho et al. 2016). Quasi spherical zinc NPs (□5-nm diameter) were produced and then recovered with a □4.25-nm gold layer to generate Zn-Au NPs. After several tests, they concluded that the Zn-Au NPs synthetized in this research have the ability to be utilized as PET-imageable radiosensitizers for applications such as radiotherapy and PET tracers for molecular imaging.

Alternatively, a methodology utilizing the reduction of silver nitrate and tetrachlorauratic acid at the same time and also employing tryptophan (Trp) as a reducing/stabilizing agent was developed. The obtained Ag-Au-Trp NPs, with 5–15 nm size were capable of generating stable aggregates with dimensions ranging 370–450 nm and showed significantly less toxicity compared to Ag-AuNPs stabilized by sodium dodecyl sulfate (SDS), taking into account the estimation of biochemical parameters and oxidative damage produces considering a mouse model system. Ag-Au-TrpNPs demonstrated to have anticancer activity regarding a Lewis lung carcinoma model (I. O. Shmarakov et al. 2014). The results of the research reinforce the theory that the use of tryptophan in NP production successfully attenuates the potential hepato- and nephrotoxicity of NPs *in vivo*.

The bimetallic oxide nanostructures are known to enhance the carrier characteristics of the nanomaterials. For instance, Kumar and colleagues used ZnO-MgO BMNPs that were synthesized by precipitation process at low temperature. In order to elucidate the efficacy of the uptake and discharge of the anticancer drug, the adsorption, and liberation of doxorubicin was analyzed, and also the kinetics of the procedure. They deduced that ZnO-MgO nanoparticles would potentially be a powerful drug carrier in a drug delivery system (Kumar et al. 2015).

In a similar work, Alarfaj and El-Tohamy described the generation of gelatin-capped bimetallic Au-Ag NP with its principals on the interaction between silver nitrate or chloroauric acid with a 1.0 wt% liquid gelatin solution at 50°C. The structures were utilized to improve a sensitive consecutive injection of the chemiluminescence luminol-potassium ferricyanide system in order to determine the anticancer drug raloxifene hydrochloride (Alarfaj and El-Tohamy 2016). Therefore, they developed a method that is environmentally friendly and sensitive for chemiluminescence detection of the desired drug when found in bulk-powder form, pharmaceutical shots, and biological samples.

However, the nanoparticles show anticancer activity by themselves with no need for therapeutic drugs. As an example, a method of synthesis for the stable, mono-dispersed high yielding bimetallic (Ag-Se) nanostructures utilizing quercetin and gallic acid at RT was studied. A variety of features, for instance, the amount of quercetin, gallic acid and Ag-Se salt, pH, temperature and

reaction time, were investigated and improved to regulate the features of the nanoparticles (Mittal, Kumar, and Banerjee 2014). The generated Ag-SeNPs were used as anticancer entities for Dalton lymphoma (DL) cell, and in addition, when used *in vitro* they showed a decrease of 80% of its growth at concentrations of 50 µg/mL. Besides, a Fe/Zn bimetallic nanoparticle using *Coriandrum sativum* leaf essence acting like reducing agent were prepared by an ultrasonic assisted methodology. After generation, HeLa cancer cell line and normal cell line were tested *in vitro* to determine nanoparticles' cytotoxicity, showing 54.95% of cytotoxic effects at a concentration of 200 µg/ml when facing HeLa cancer cell line (Sathya, Saravanathamizhan, and Baskar 2018).

As mentioned in previous sections, over the last few years, green nanotechnology approaches have arisen as a novel solution for the production of bimetallic nanoparticles with biomedical applications. As an example, Chopade et al. demonstrated the quick and effective production of new Pt–Pd BMNPs by the use of a medicinal plant -*Dioscorea bulbifera*- acting as a reducing agent for the first time (Chopade et al. 2015). These nanostructures showed anticancer activity against HeLa cells. The bimetallic formulation exhibited more pronounced cell death -74.25%- in comparison to individual PtNPs (12.6%) or PdNPs (33.15%). Moreover, they reported an improved scavenging performance against 2,2-diphenyl-1-picrylhydrazyl, superoxide, nitric oxide, and hydroxyl radicals.

2.2.3. Imaging applications

Imaging is largely applied in the biomedical field for diagnosis because of the ability of these techniques to provide an interface between vision and intuition (Estelrich, Sánchez-Martín, and Busquets 2015). Conjugation of NP with targeting ligands, for instance, peptides, small organic molecules or antibodies, enables the development of targeted probes with elevated specificity (Nune et al. 2009). The interaction of these modified-metallic nanoparticles within natural tissue results in real-time monitoring of molecules and single cells, tissues, and organs *in vivo*. Metallic nanoparticles are being used in different modalities for imaging, such as X-ray (CT), positron emission tomography (PET), single-photon emission CT (SPECT), ultrasound, and MRI (Lindner and Link 2018), each of them has its strengths and limitations.

Nuclear imaging is a modality that generates data about biodistribution of radiolabelled drugs or other ligands; nonetheless, it particularly ends in noisy images which have low spatial resolution when compared with anatomic images. In this technique, emitted photons have to penetrate the massive lead parallel collimators in the first time which only permits photons emitted perpendicular respect the camera face to prosperously interreact with the imaging crystal (Hacker et al. 2015). Consequently, to improve the resolution of this imaging technique single photon emission tomography (SPECT) was developed, which obtaining volumetric images having a spatial resolution of ~7.5–10 mm. In the line of this research, bimetallic hybrid Zn-Au nanoparticles with zinc cores and gold shells were synthesized to allow them to be seen *in vivo* when the zinc cores is proton activated and also gave them the ability to provoke radiosensitization by using secondary electrons generated by the gold shell when irradiated by different radiation sources (Cho et al. 2016).

Another medical technique, PET helps reveal how biological tissues are functioning, using a radioactive drug, also called tracer, to show this activity. Radionuclides that decay with positron emissions, like Fluorine-18, Carbon-11, Iodine-124, and Oxygen-15, can be imaged with a PET scanner, that gives a higher spatial resolution (2–5mm for clinical scanners). The emitted positron easily finds an electron, ending in a reaction of annihilation where both photons present an energy around 511 keV and provokes trajectories around 180 degrees in contrary directions (Shukla and Kumar 2006). Reduced-quality imaging of positrons can be achieved utilizing SPECT having ultra-high energy collimators, on the other hand, the PET camera was particularly designed to take profit of the physical features of positron emitters (Rahmim and Zaidi 2008). Bo Pang et al. developed an easy methodology for radiolabelled Pd-Cu-Au core-shell tripods to utilize them in PET and image-guided photothermal cancer treatment when radioactive 64Cu atoms were directly introduced inside the crystal lattice (Pang et al. 2016).

CT was created by Hounsfield et al. in 1967, in one side motivated for the enhancement in not only computer processing power but also the capacity of x-ray imaging. Utilizing accesible computing technology, CT produced high resolution 3D - modelings of patients anatomy by the use of multiplane x-ray imaging and mathematical computer image regeneratin algorithms(Histed et al. 2012) CT is one of the convenient types ofimaging, however, it is not considered a targeted imaging modality without using specific contrast agents (Reuveni et al. 2011) Therefore, metallic nanoparticles have been used as a contrast agent for molecular and targeted imaging of tumors and cancers(Reuveni et al. 2011). For example, B. Li et al. have developed a multifunctional copper-bismuth sulphide (Cu-BiS) nanocomposite as a contrast agent for CT, IR thermal imaging and photothermal therapy (B. Li et al. 2015) This enables them to mix the NIR results with nanostructures-improved imaging results, like MRI or X-ray CT ones.

A special mention should be made with magnetic NP, which have been utilized in broad variety of applications due to their properties that are generated by their size, shape, composition, and the capacity of functionalization at the cellular and molecular level. Notably, their unique magnetic properties make them an interesting system to be used as contrast entity MRI. When going to the bimetallic configuration, the structures can also exhibit super magnetic properties, which makes them great aspirants to work as MRI contrast agents.

For example, and as can be seen in Figure 4, later progressions in the production and alteration of Fe-Pt nanoparticles, which have higher chemical stability compared to Fe and Fe-Co, have made them a viable option for MRI and CT (Q. Li et al. 2015; Senpan et al. 2009). These particles are formed through thermal annealing of the MgO-coated FePt-Fe3O4 NPs, after that an acid washing is done to eliminate MgO. Amendola et al. used laser ablation synthesis in solution to obtain PEG-FeAu NPs with excellent stability in air and in aqueous solutions, which exhibited good properties to act as harmful contrast agents for MRI (Amendola et al. 2013). In another work, J. Choi et al. enhanced imaging accuracy of Fe-based nanoparticle using a Gd-based coating (J. Choi et al. 2010). In this work, a dual-mode nanoparticle contrast has been reported; the T_1 contrast material, $Gd_2O(CO_3)_2$ (thickness=1.5 nm), is found on the shell for high T_1 contrast characteristics, and the superparamagnetic T_2 contrast material, $MnFe_2O_4$ of 15 nm, is found at the core. Therefore, $Gd_2O(CO_3)_2$ shell come into direct contact with water molecules, and $MnFe_2O_4$ core maintains a long-range magnetic field for the relaxation of water molecules.

Nevertheless, T_1 contrast agents are suitable for morphological assessment of the standard or pathological anatomy (e. g. for musculoskeletal applications), and T_2 contrast agent is suitable for detection of blood and of iron and calcification in many tissues (Chavhan et al. 2009) Therefore, these nanoparticles potentially can be applied to a large variety of biotargets with improved diagnostic exactness.

2.2.4. Drug delivery applications.

Nanostructures are often used in drug delivery applications. Nanoparticles' properties, such as the high-surface-to-volume-ratio and biocompatibility, enable an efficient loading and immobilization of a high amount of therapeutic agents including, synthetic drug molecules, proteins and peptides, oligonucleotide and antibodies, either on or inside these nanostructures (McNamara and Tofail 2015) When talking about BMNPs (Figure 4), tuneable and adjustable physical property and critical parameters, which can happen through using a combination of elements, make these synergetic structures appealing for biomedical applications (Sun, Lee, and Zhang 2008). Targeted delivery of drugs is an essential biomedical application that aids in avoiding the systemic administration of drugs and increases the therapeutic efficiency of drugs.

For instance, Kumal et al. have recently reported a gold-silver–gold core-shell-shell (CSS) nanostructure to deliver oligonucleotides-like plasmid DNAs, siRNAs, and miRNAs- by the use of NIR irradiation cleavage, which enables targeted delivery of RNAs to target locations under spatial and temporal regulation (Kumal et al. 2018). They have explained that the photothermal liberation of siRNA from the surface of CSS nanoparticles is particularly higher than the one from Au NPs when comparable conditions were used. Regulating the dimensions and ratio of the core and shell sizes has helped them in the tuning and optimization of release efficiency.

Similarly, Taylor et al. have used a combination of iron, zinc, and silver with superparamagnetic iron oxide nanoparticles, also known as (SPIO) for the therapy of antimicrobial-resistant biofilms (Taylor et al. 2012). In this work, Fe, Zn, and Ag have been separately conjugated to SPION to couple the antibacterial features of these compounds to the superparamagnetic characteristics of SPION. It is reported that this could improve the antibacterial activity of these metal salts and enables targeting bacterial infections (i.e., *Staphylococcus aureus*) in a magnetic field using superior magnetic properties of SPION.

Moreover, bimetallic nanoparticles have been also used as a drug carrier for cancer therapy. For example, Au-Pt (Au core and Pt shell) bimetallic nanoparticles were synthesized by V. Maney et al. and encapsulated inside chitosan coating through ionic gelation with tripolyphosphate (TPP). Also, doxorubicin (DOX) -most potent anticancer drug available- was encapsulated inside chitosan layer and delivered to different cancerous cells (e.g., human embryonic kidney cells (HEK293), breast adenocarcinoma (MCF-7), epithelial colorectal adenocarcinoma cells (Caco-2) and hepatocellular carcinoma cells (HepG2)) (Maney and Singh 2017). This novel combination has enabled them to encapsulate high amounts of DOX, and further induce a pH-triggered release at intracellular acidic conditions of cancerous cells to bring about selective cancer targeting.

Similarly, D. Dutta et al. have developed cationic bovine serum albumin (BSA) embedded (gold-silver) Au-AgNPs to carry a suicide gene payload into the cancer cells153 effectively. It has been explained that loaded plasmid DNA (pDNA, CD-UPRT) and Au-AgNPs induces apoptosis in HeLa cells through two different mechanisms. Specifically, suicide gene (CD-UPRT) converts the non-toxic prodrug 5-FC into 5-FU and other toxic metabolites, while A-uAg applies oxidative stress inside cells through ROS generation.

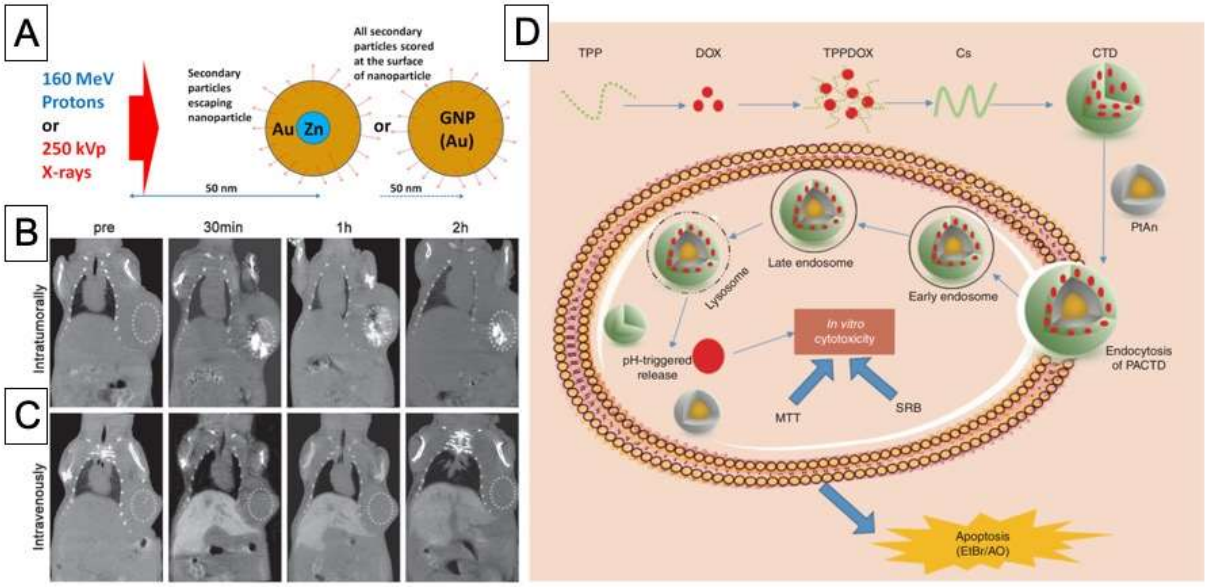

Figure 4. An incident proton or x-ray beam interacted with nonradioactive gold-coated zinc (Zn-Au NPs or gold nanoparticles (GNPs) placed in vacuum, as well as with the secondary particles. All secondary particles scored at the surface of NP (Cho et al. 2016); In vitro CT image of a intratumoral (B) and intravenous (C) injection of the solution of the Cu_3BiS_3 NPs. The position of tumor is labeled by the dotted circles (B. Li et al. 2015), and an schematic illustration of doxorubicin-encapsulated platinum-gold/chitosan BMNPs for sustained pH responsive release leading to site-specific in vitro biological activity and apoptosis (D) (Maney and Singh 2017).

2.2.5. Photothermal therapy applications.

Photothermal therapy (PTT) is a promising technique to fight against microbial infection and cancer (Rozanova and Zhang 2009). Initially, this form of therapy is a variation of photothermal ablation (PTA) therapy that utilizes light (NIR wavelength range (700–2000 nm)) to burn tumors. However, PTA may destroy healthy cells and tissues due to unspecific targeting of the light. Recently, nanotechnology has been shown as a potential way to remarkably enhance PTA by applying a near-IR laser light absorbing material, such as metallic/bimetallic nanoparticles, to the target sight in the body (H. Sharma et al. 2015). Unique advantages appended to PTT by nanotechnologies, such as high specificity and minimal invasiveness, has made this technique an excellent potential for treating cancer metastasis and bacterial infections. Moreover, owing to using bimetallic and metal alloy nanoparticles, PTT can be guided with multimodal imaging or combined with the other available therapies to perform more effective targeting (Figure 5).

For instance, Wang et al. have developed a dual-mode bimetallic nanoparticle for imaging, and photothermal therapy of SK-BR-3 breast cancer cells (C. Wang et al. 2009). In this work, the super magnetic properties of Fe_3O_4 and the photon luminescence effect of gold nanorods (Au_{rod}) make using a combination of diagnosis, imaging and therapy techniques possible. In another work, Fan et al. used a Au-coated Fe-based nanoparticle to target and destroyedy a multidrug-resistant (MDR) bacteria (i.e., MDR *Salmonella* DT104) (Fan et al. 2013). As reported, the plasmonic shell made of Au, in combination with the magnetic core of iron of developed nanoparticles has been used for targeted separation, in addition to selective photothermal eradication of a MDR pathogen.

NP based on noble metals, like Au, Ag, and Pt, are mainly utilized for PTT because they present enhanced biocompatibility, decreased toxicity and strong optical absorption in the near-IR (NIR, 700—1100 nm) (Yamada, Foote, and Prow 2015). For instance, Cheng et al. have used chitosan capped seedless branched-bimetallic Au-Ag NPs against oral cancer cell line (SAS) (Cheng et al. 2012). This work has proposed a quick, facile, and one-pot approach for making spiky star-shaped Au-AgNPs by adding aqueous $HAuCl_4$ to $AgNO_3$, and then mixing it with enough ascorbic acid acting as reducing agent. The morphology of the NPs is regulated by changing the ratio of gold to silver precursors.

Moreover, X. Liu et al. have developed Au-Pt nanostructures which are comprised of Au core and Pt nanobranches with a wide absorbance of NIR light and intense concentration of X-rays (X. Liu et al. 2017). To improve the stability of AuPt nanostructures, they have been PEGylated and have been used against 4T1 cells under irradiated of an 808 nm laser.

2.2.6 Biosensing applications.

The development of nanoscience and nanotechnology revealed the critical role of bimetallic nanoparticles in areas such as nano-bio-sensors, immune labeling, and microelectronics because of their unique optical, electrical and thermal characteristics (Yadi et al. 2018).

The distinct properties of nanoparticles, like the large surface-to-volume ratio, high electrical conductivity, favourable biocompatibility, excellent catalytic ability, and surface reaction activity provide metal nanoparticles enormous possibilities in improving sensor performance, a feature that can be extended to bimetallic configurations in the nanoscale. Therefore, they have been widely used to develop transducers for biosensors, based on the efficient combination of different components into a nanoscale hybrid structure, which enables to maintain the known characteristics of such components inasmuch to lead to novel features which are absent in each component individually.

For example, Gan et al. have developed an electrochemical immune-sensor that can selectively sense C-Reactive Protein (CRP) using antigen-antibody reaction on a bimetallic nanoparticle (Gan et al. 2013). CRP is primarily produced in the liver due to an acute inflammatory stimuli, that its concentration in blood abruptly increases in the acute-phase response of inflammation(Salvo et al. 2017). They used a supermagnetic iron oxide nanoparticles (Fe_3O_4) with a Au coating, achieving a well-assembled, biocompatible and environmentally safe metallic

component with high affinity for connecting to the amine/thiol ending groups of organic molecules. Thus, they contributed significantly to advancements in diagnostics and biological detection (Suk Fun Chin, Swaminatha Iyer, and Raston 2010; Zhou, Wu, and Xing 2012)

Alternatively, semiconductor nanocrystal quantum dots (QD) have been utilized for protease sensing using fluorescence resonance energy transfer (FRET) and bioluminescence by E. Chang et al., using the properties of these particles, since QDs are inorganic luminescent semiconductor structures (Chang et al. 2005). They typically are composed of a Cd-Se core, a zinc sulfide (ZnS) shell (Welser et al. 2011). QDs quenched by AuNP using different cleavable peptides have been used to investigate some proteases including chymotrypsin and collagenase (Medintz et al. 2006), thrombin (Jong Hyun Choi, Kok Hao Chen, and Strano 2006), and magnetic NP (Figure 5).

In another work, Chiriac et al. have developed a giant magneto-impedance (GMI) using Co-Fe magnetic microparticles (0.9–2 μm) for the determination of the small concentration of biomolecules (such as RNA) (Chiriac et al. 2005). It is explained that functionalized Co-Fe microparticles could successfully target biomolecules (i.e., ssDNA (single-stranded DNA), antibodies, proteins, enzymes) and form a dipole field under the external magnetic environment that was detected by the GMI sensor. Moreover, impedancemetric and conductometric are conventional approaches to develop immune sensors. For example, D. Lin et al. have developed an electrochemical impendence spectrum (EIS) in order to detect alpha-fetoprotein (AFP) by implementing Au-Pt nanodendrites (D. Lin et al. 2012). AFP is a key tumor marker cancer diagnosis in liver, testis, and ovary. A sandwich-type electrochemical immunosensor was generated using mesoporous graphene loaded Au-Pt nanodendrites, which are improved by poly-dopamine functionalized N-doped multi-walled carbon nanotube (PDA-N-MWCNT).

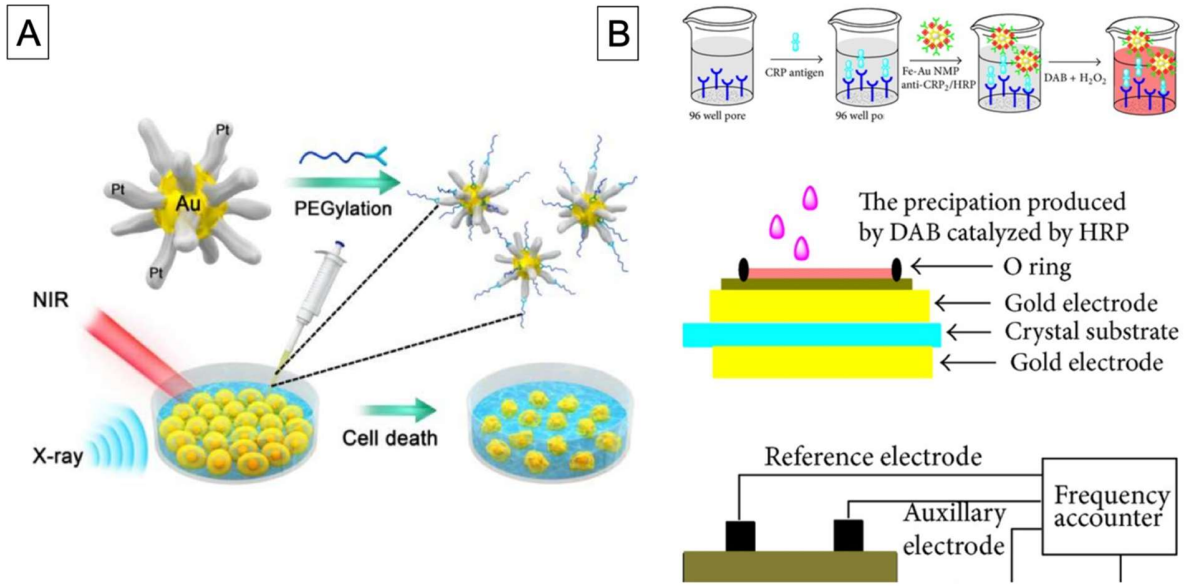

Figure 5. The illustration of the PEGylation and photothermal/radiation synergistic therapy application of the Au-Pt nanoparticles. Reprinted with permission from (X. Liu et al. 2017). Copyright 2019 American Chemical Society; Diagram of the generation of Fe-Au MNPs-anti-CRP2/horseradish peroxidase (HRP) conjugation and the

immunoassay methodology with the employment of Fe-Au MNPs-anti-CRP2/HRP as the signal tag (top) and the EQCM's measurement steps (middle) and detection system (bottom) (Gan et al. 2013).

3. The future of bimetallic nanoparticles.

Despite the outstanding advances in the development of efficient bimetallic nanoparticles for biomedical applications, there are still several challenges for the use of these nanostructures. For instance, one of the top concerns that have to be addressed is the limited control over the resulting particle size that most of the synthetic methods offer. In the case of monometallic Au- and AgNPs, it has been reported that there is a particle size-dependent cytotoxic effect on several cancer cell types (Pan et al. 2007; Gliga et al. 2014). For example, Pan et al. investigated the cytotoxicity of Au NPs in a particle size range of 0.5 to 15 nm (Pan et al. 2007) They found that the tested cells were susceptible to relativly small AuNPs (1.4 nm). In contrast, 15 nm-AuNPs were not cytotoxic at up to 60-fold higher concentrations. After extended research, it can be said that for noble metal-based BMNPs, there are no studies about the size-dependent cytotoxic effect of these nanostructures with a constant composition and atomic structure.

The next controversial issue is related to the mass transport across the original boundaries of the body, such as cellular membranes or intestinal barrier, where the biological affinity of the nanomaterials plays a pivotal role. Here, the use of BMNPs can enhance the biological affinity and mimic the conditions inside the body compared to other formulations. This behavior allows to efficiently induce cellular responses due to the nature of the different compounds employed in the nanosystem. For instance, N. D. Telling et al. evaluated the applicability of bacteria-mediated Zn- and Co-doped magnetite NP to use in biomedical fines, demonstrating that the magnetic particles response was modified once they interacted with cells producing a decline in their movement. This finding also shows that the medium-level dopant needs optimum magnetic characteristics in order to not modify their biological toxicity or influence osteogenic differentiation of the stem cells (Moise et al. 2017). Therefore, although reported toxicity of Co and Zn ions, these data suggest that iron oxide nanoparticles can be tuned to adequately modify their magnetic features without jeopardizing cellular biocompatibility.

Another important milestone is related to the need for developing new mathematical and computer models that contribute to a greater knowledge and prediction of chemical, physical and biological response to the presence of the nanostructures. These systems are challenging enough for the monometallic formulation, becoming even harder when two or more metals are incorporated within one single structure. However, several attempts have been made. For example, Akinsiku et al. have found that a theoretical model can clarify an experiment observation on the relationship between BMNPs penetration through peptidoglycan layers and the activeness of microbial species, depending on the nature of the nanoparticles and pore size of the layer (Akinsiku et al. 2018).

The nanotechnological inclusion in medical applications regarding bimetallic formulations is still a young field which needs more research, studies, and experiments.

4. Conclusion

Nanotechnology has undoubtedly risen as a powerful tool that benefits every aspect of society, from healthcare to environmental remediation, going through renewable technology and agriculture, with a meaningful economic impact that is expected to see exponential growth in time. Among all the potential nanotechnological applications, the utilization of nanoparticles in the biomedical area is leading to a novel horizon of techniques, developmental technologies, and improvements that are transforming the way that we fight diseases and pathogens. Despite this, the use of bimetallic formulations remains a field to be further explored, with plenty of unknowns and applications that need to be elucidated in order to build the better world that nanotechnology promises for humanity.

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