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Review

Bio-Fabrication of Trimetallic Nanoparticles and Their Applications

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Citation: Roy, A.; Kunwar, S.; Bhusal, U.; Alghamdi, S.; Almehmadi, M.; Alhuthali, H.M.; Allahyani, M.; Hossain, M.J.; Hasan, M.A.; Sarker, M.M.R.; et al. Bio-Fabrication of Trimetallic Nanoparticles and Their Applications. *Catalysts* **2023**, *13*, 321. https://doi.org/10.3390/catal13020321

Academic Editors: Vitali A. Grinberg, Alexander D. Modestov and Anwar Sunna

Received: 28 November 2022
Revised: 9 January 2023
Accepted: 18 January 2023
Published: 1 February 2023

Abstract: Nanoparticles are materials whose size is less than 100 nm. Because of their distinctive physical and chemical characteristics, nanoparticles have drawn considerable interest in a variety of fields. Biosynthesis of nanoparticles is a green and environmentally friendly technology, which requires fewer chemical reagents, precursors, and catalysts. There are various types of nanomaterials, out of which trimetallic nanoparticles are receiving considerable interest in recent years. Trimetallic nanoparticles possess unique catalytic, biomedical, antimicrobial, active food packaging, and sensing applications as compared to monometallic or bimetallic nanoparticles. Trimetallic nanoparticles are currently synthesized by various methods such as chemical reduction, microwave-assisted, thermal, precipitation, and so on. However, most of these chemical and physical methods are expensive and toxic to the environment. Biological synthesis is one of the promising methods, which includes the use of bacteria, plants, fungi, algae, waste biomass, etc., as reducing agents. Secondary metabolites present in the biological agents act as capping and reducing agents. Green trimetallic nanoparticles can be used for different applications such as anticancer, antibacterial, antifungal, catalytic activity, etc. This review provides an overview of the synthesis of trimetallic nanoparticles using biological agents, and their applications in different areas such as anticancer, antimicrobial activity, drug delivery, catalytic activity, etc. Finally, current challenges, future prospects, and conclusions are highlighted.

Keywords: trimetallic nanoparticles; green synthesis; antibacterial; catalytic activity

1. Introduction

Nowadays, there is extensive research being conducted in the area of nanotechnology because of its enormous applications in both the industrial and medical sectors. The use of nanotechnology in a variety of fields, including chemistry, biology, and engineering, has produced advanced, effective, and unique products with improved features, particularly those that find biomedical applications [1–3]. The development of nanoparticles is considered to be one of the ground-breaking approaches to addressing significant issues in the world. They offer high catalytic activity as well as a high surface-to-mass ratio [4]. Nanoparticles (NPs) are effective, affordable, and eco-friendly solutions to current processing materials [5]. These synthesized nanomaterials have distinctive capabilities that are useful for tackling gaps in sectors such as health, energy production, drug delivery systems, and wastewater treatment [6–8]. There are various types of nanoparticles depending on their morphology and other characteristics. Fullerenes and graphenes, which are considered carbon-based nanoparticles, are used in electrical devices and also have medical applications [9,10]. Metallic nanoparticles, for example gold and silver nanoparticles, have been used in numerous applications such as biosensors, efficient drug delivery systems, active food packaging, and other medicinal uses [11]. Other varieties of nanoparticles include organic nanoparticles such as lipid-based, polymer-based nanoparticles, and inorganic nanoparticles.

Metallic nanoparticles have received the greatest attention among the numerous types of nanoparticles due to the usefulness of their biological features, nontoxic nature, and their distinctive properties [12,13]. Due to their unique optical, electrical, and magnetic properties, metal nanoparticles have been investigated for a variety of applications [14]. Metallic nanoparticles can be classified into monometallic, bimetallic, and trimetallic nanoparticles, depending on the composition or the total number of metals or metal oxides present. It has been observed, by different studies, that the most intriguing results are produced when metal nanoparticles are mixed together. As a result, the bi or trimetallic nanoparticles have better characteristics or qualities than the monometallic ones. Compared to monometallic nanoparticles, multimetallic nanoparticles, composed of various metals, provide a unified system that can display unique features [15]. When compared to monometallic or bimetallic nanoparticles, trimetallic nanoparticles exhibit more catalytic activity [16], more antibacterial effect [17], diversified shapes [18], highly selective detection and sensitivity [19], high level of stability [20], and chemical transformation [21]. These promising features are a result of the combined or multifunctional effects of the three metals that make up trimetallic nanoparticles. These trimetallic nanoparticles have been shown to exhibit remarkable properties like, increased photocatalytic activity, increased antimicrobial activity, and other therapeutic activities. One study reported the synthesis of trimetallic nanocomposites of Ag/Cu/Co for their antifungicidal activity against *Candida auris* infection [22].

Trimetallic nanoparticles are mainly formed by the combination of three different metals. The trimetallic catalysts are considerably more effective than bimetallic catalysts. Trimetallic nanoparticles are synthesized using different physical, chemical, and biological processes [23,24]. Physical methods include microwave irradiation, ultrasonic-assisted synthesis, hydrothermal, and adsorption. Whereas, chemical methods include reduction using various chemicals such as sodium borohydride, the co-precipitation method, etc. [25]. Various studies have reported using chemical synthesis to prepare Au/Pt/Pd [26], Co/Zr/Sb [27], and many other trimetallic NPs. However, most of these physical and chemical methods are costly and can be a threat to the environment. The production of trimetallic nanoparticles via biological methods is thought to be a more practical and environmentally friendly approach. In the biological method of synthesis, which is also known as green synthesis, of trimetallic nanoparticles, plant extracts or microorganisms are used, which serve as reducing, stabilizing, and also capping agents. Since biological agents contain various secondary metabolites, including flavonoids, terpenoids, enzymes, alkaloids, antioxidants, fungal metabolites, algal metabolites, etc. [28], which are considered to be reducing, capping, and stabilizing agents. These synthesized trimetallic nanoparticles are characterized by using different methods, including UV-vis spectroscopy, scanning electron microscopy (SEM), transmission electron microscopy (TEM), X-ray diffraction (XRD), energy dispersive spectroscopy (EDS), etc. (Figure 1).

After characterization of the synthesized nanoparticles, they can be used in a variety of fields, such as medicine, as an antibacterial agent [29], or in wastewater treatment by degrading different dye molecules [30]. Similarly, there have also been reports of the cytotoxicity shown by biologically synthesized trimetallic nanoparticles against different cancer cell lines. In this review, an overview of the biosynthesis of trimetallic nanoparticles using different biological agents, and their promising applications in biomedical and environmental remediation is discussed.

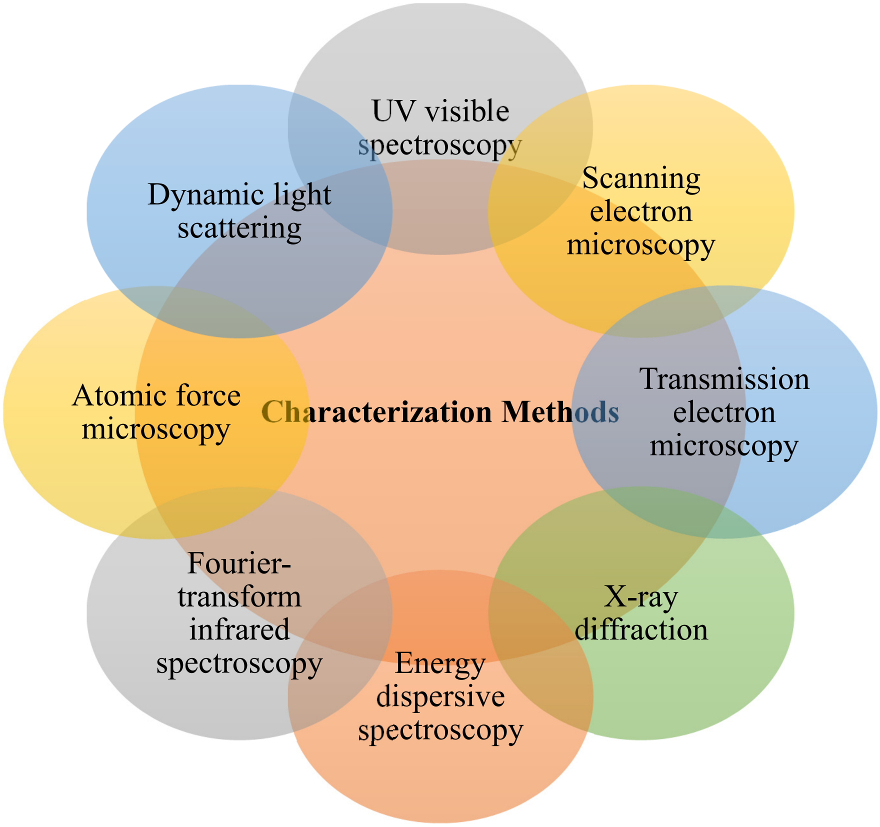

Figure 1. Different methods for characterization of nanoparticles.

2. Different Types of Nanomaterials/Nanoparticles

Depending on various factors, including structure and shape, size, and different physical and chemical characteristics, nanomaterials have been divided into multiple types, such as organic, inorganic, and carbon-based nanomaterials (Figure 2).

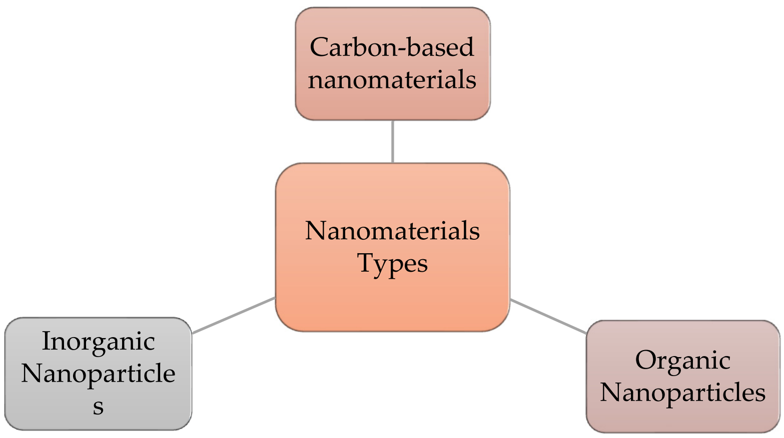

Figure 2. Different types of nanomaterials.

Inorganic NPs have many advantages compared to organic NPs in terms of their low toxicity and biocompatibility. Inorganic nanoparticles include metal nanoparticles, metal oxides, and ceramic nanoparticles [31]. Inorganic nanoparticles that are synthesized from metals such as gold, silver, copper, palladium, etc., are known as metal nanoparticles. Copper oxide and zinc oxide are some examples of metal oxides. Due to their wide variability of sizes [32] and variety of physical properties, these nanoparticles have diverse applications. Metallic nanoparticles are smaller in size than organic nanoparticles; hence, they provide a larger space for functionalization, whereas ceramic nanoparticles are inorganic nanoparticles that are hollow and porous in nature. Ceramic inorganic nanoparticles are commonly used during catalysis and for imaging purposes [33]. Metallic nanoparticles are divided into three categories based on how many metals or metal oxides are involved: monometallic, bimetallic, and trimetallic [34]. Other inorganic nanoparticles employed in biological applications include gold nanoparticles, magnetic nanoparticles, and quantum dots.

3. Trimetallic Nanoparticles

A "triple core-shell structure" has been proposed for the construction of trimetallic nanoparticles. A single element creates a core, another element covers the core to create an interlayer, and a third element covers the interlayer to create a shell [35]. The second metal cannot help tune the desired qualities in terms of particle size, shape, and surface morphology. However, by moving the electron density from the initial hold metal into the surface catalytic organization, it can increase the catalytic effectiveness [36]. In order to efficiently change the functions of bimetallic and trimetallic nanoparticles, triple core-shell particles have been produced with significant features. When compared to similar monometallic nanoparticles, the physical combination of nanoparticles, such as Ru-Pt in solution, exhibits more catalytic activity. The highly versatile history of catalytic materials has improved from single monoatomic catalysts, particularly Pd, Pt, and Au, which are in nanoscale, to bimetallic structures. Studies have reported that nanoparticles such as Pd, Rh, and Pt readily form a bimetallic structure with an Au core in an aqueous solution. Currently, a thorough evaluation of the Ag-core nanoparticle production is available, due to Ag being cheaper, and it shows significant individual catalyst activity. Trimetallic nanoparticles are more efficient than mono or bimetallic ones because of their distinctive properties such as antimicrobial, catalytic activity, etc. Synergism significantly increases the catalytic activity of trimetallic nanoparticles against microbes [37]. These nanoparticles, furthermore, have increased functional activity in medical applications such as cancer treatment [19].

Zhang and Toshima [38] reported a comparative analysis between the activity of bimetallic nanoparticles (BNPs) and that of trimetallic nanoparticles (TNPs). These results affirmed that the higher activity of TNPs towards glucose oxidation is due to their synergistic catalytic action. They also concluded that the effects of electronic charge transfer between the various components, and geometric effects, result in electronic structure alteration, which improves catalytic activity. Additionally, when another metal species is added, nanocatalysts undergo structural modifications that lead to increased activity [38]. In a study with carbon nanotubes (CNTs)-Pd/Au/Pt trimetallic NPs, they showed good electrocatalytic performance and stability exhibited synergistic effects [39]. There have also been several studies that entertain the idea of changing or adjusting the size, composition, and morphology of the monometallic counterparts of these trimetallic structures to regulate their functions for various purposes [40].

3.1. Physical Synthesis

Techniques like microwave irradiation, ultrasonic-assisted synthesis, thermal, and others fall under the category of physical approaches to synthesizing trimetallic nanoparticles (Table 1).

3.1.1. Microwave-Assisted Synthesis

One of the widely used, quick processing techniques for the creation of trimetallic nanoparticles is microwave irradiation. The ability to adjust the size distribution of the nanoparticles for various applications is a significant benefit of utilizing this technology [41]. The La/Cu/Zr/Carbon dots [42], and Au-Pt-Ag [43] trimetallic nanoparticles, have been synthesized using this technique, for photocatalytic and antimicrobial activity, respectively.

3.1.2. Ultrasonic-Assisted Synthesis

Ultrasound can raise the temperature or the pressure in a solution, and as a result of the higher temperature, tiny metal nanoparticles form quickly. Highly porous trimetallic Pt/Au/Ru alloy nanoparticles were fabricated with the help of ultrasound. Compared to conventional Pt nanoparticles, the 77 nm nanoparticles produced significantly increased electrocatalytic activity in the synthesis of formic acid [44]. Sonochemical synthesis has also been used to create trimetallic Pd/Co/Pt nanoparticles with a core shell of Pd and Co [45].

3.1.3. Laser Synthesis

Laser irradiation synthesis is a very effective method for creating trimetallic nanoparticles without the use of a surfactant or the addition of chemicals. With this technology, high-purity nanomaterials can be created without additional contaminants, while also saving both money and the environment. A study on laser synthesis has been conducted for the synthesis of Al_2O_3-AgAu trimetallic nanocomposites. With an approximate size of 15 nm, the nanoparticles produced were polycrystalline [46].

Table 1. Synthesis of trimetallic nanoparticles using physical method.

Trimetallic Nanocomposites	Method	Shape	Size	Activity	Methods of Characterization of NPs	References
Au/Pt/Ag	Microwave Irradiation	Dark nanofluid	20 nm	-	XRD, SEM, Surface enhanced Raman scattering (SERS)	[47]
Pt/Au/Ru	Ultrasonic-assisted	Nearly spherical (Highly porous)	77 nm	Highly electrocatalytic toward formic acid oxidation	TEM, XRD, XPS	[44]
Al_2O_3@AgAu	Laser synthesis	Polycrystalline	15 nm	Catalytic activity	UV-vis, TEM	[46]
La/Cu/Zr/Carbon dots	Microwave Method	Fibrous	30–100 nm	Adsorption/Photo catalytic activity in order to remove organic pollutants	FTIR, XRD, TEM, UV-vis, SEM	[42]
Au/Pt/Ag	Microwave Method	Nanofluid	20–40 nm	Antibacterial activity	UV-vis, XRD, TEM, HR-TEM, SEM, and MIC	[43]
Au/Pt/Pd/reduced graphene oxide	Physical adsorption on GCE(glassy carbon electrode)	Spherical	80–100 nm	Electrochemical catalyst for the reduction of H_2O_2 and diagnosis of breast cancer cells	TEM, EDX, XRD	[48]

FTIR: Fourier-transform infrared spectroscopy; FESEM: Field emission scanning electron microscopy; AFM: Atomic force microscopy; HRTEM: High Resolution Transmission Electron Microscopy; XPS: X-ray photoelectron spectroscopy; VSM: Vibrating-sample magnetometer; CLSM: Confocal laser scanning microscopy; TGA: Thermogravimetric analysis; EDX: Energy dispersive X-ray spectroscopy; TEM: Transmission Electron Microscopy; HPLC: High Performance Liquid Chromatography; CV: Cyclic Voltammetery; STEM: Scanning Transmission Electron Microscopy; EDX: Energy dispersive X-ray spectroscopy; TG-DSC: Thermogravimetry Differential Scanning Calorimetry; ICP-MS: Inductively coupled plasma mass spectrometry.

3.2. Chemical Synthesis

Techniques such as chemical reduction, co-precipitation, and hydrothermal methods, etc., fall into the category of chemical approaches to synthesize trimetallic nanoparticles (Table 2).

3.2.1. Co-Precipitation

One of the chemical synthesis methods for trimetallic nanoparticles is co-precipitation, which involves nucleation, growth, and agglomeration. This process often results in the co-precipitation of the necessary metallic ions from general media in various forms, including oxalates, citrates, formates, hydroxides, and carbonates. To create the final powder, these precipitates are calcined at the appropriate temperature. Because this method does not include the use of any organic solvent, this process is quick and straightforward, and it requires less energy at low temperatures, which makes it easy to control the composition and particle size. Co/Zr/Sb nanoparticles have been synthesized using the co-precipitation method. The obtained nanoparticles were observed with SEM to have dark cores surrounded by other shells, with an average size of 20.5 nm [27].

3.2.2. Hydrothermal Method

This process involves creating nanoparticles at high vapor pressure and temperature in aqueous solutions. Single crystals are produced with this method, which depends on the solubility of the precursor minerals in the reaction mixture in an autoclave at high pressure. The solubility of substances like precursors or surfactants in hot water affects the crystal formation. Consequently, this procedure is simple to apply and gives precise control over the product's shape, size, and crystallinity. Highly porous trimetallic Pt/Ni/Cu nanoparticles, with an approximate size of 40 nm, were produced using the facile hydrothermal technique [49].

3.2.3. Chemical Reduction

By reducing the suitable components to the zero-valent state, the chemical reduction process is utilized to create trimetallic alloy nanoparticles. The core of the reduction process is formed by the metal cations with the highest oxidation reduction potential, which precipitate first, followed by the deposition of the second and third precursors as the shell. In a study, Au/Pt/Pd trimetallic nanoparticles that appeared to be dog bone-shaped, were synthesized when CTAB (cetyltrimethylammonium bromide) capped Au attached to Pt and then Pd via the successive ascorbic acid reduction pathway [50]. The seed-mediated reduction process has been hugely utilized to synthesize trimetallic nanoparticles, for example, Au/Pd/Ru, Pt/Au/Ag, Au/Pd/Pt, and many others. Reduction by sodium borohydride is also a go-to method to fabricate trimetallic nanoparticles. Appearing as chain-like agglomerates, Fe-Cu-Ag nanoparticles, with an approximate size of 75 nm, have been synthesized via the sodium borohydride reduction process. Galvanic displacement processes, which are utilized to create porous nanoparticles, may be viewed as a chemical reduction process [51]. Highly porous Ag/Au/Pt nanocages were synthesized using the galvanic replacement method [52].

Table 2. Synthesis of trimetallic nanoparticles using the chemical method.

Trimetallic Nanoparticles	Method	Shape	Size	Activity	Characterization	Reference
Au/Pt/Pd	Rapid Injection of $NaBH_4$	Round	1.7 nm	Catalytic activity for aerobic glucose oxidation	UV-vis, TEM, HR-TEM	[53]
Au/Pt/Pd	CTAB capped Au attached with Pt and then Pd by the ascorbic acid reduction pathway	Dog-bone shaped	75–90 nm	Efficient ethanol electrooxidation reaction	UV-vis, TEM, HRTEM, EDAX, XRD, XPS, FTIR, Raman analysis	[50]
Co/Zr/Sb	Method of co-precipitation	Dark cores encircled by additional shells	18–23 nm	Reductive coupling of nitroarenes to the azoxyarenees	FTIR, SEM, EDX, VSM, TEM, XRD	[27]

Table 2. *Cont.*

Trimetallic Nanoparticles	Method	Shape	Size	Activity	Characterization	Reference
Pt/Au/Ag	Seed mediated growth process	Spherical	40–50 nm	Electrocatalysts for glycerol oxidation	TEM, HPLC	[54]
Fe/Cu/Ag	Sodium borohydride reduction	Spherical (appear as chain-like agglomerates)	60–90 nm	Degradation of methyl orange dye in water	XRD, XPS, EDX, TEM	[55]
Au/Pd/Pt	Seed mediated growth	Cluster of island	55 nm	Photoelectrocatalyst activity	SEM, TEM, SERS, HRTEM, Cyclic voltammetery (CV)	[56]
Au/Pd/Ag	Seed mediated co-reduction	Polyhedral Structure	30 nm		TEM, STEM (Scanning TEM), XRD, EDX	[57]
Au/Pd/Ru	Seed mediated growth	Porous	110 nm	Catalytic activity for the degradation of azo-based dyes and the reduction of PNP	TEM, FE-SEM, EDS, UV-vis	[58]
Cu/Zn/Mn	Co-precipitation method	Spherical with agglomeration	90 ± 3 nm	Electrochemical glucose sensor, degradation of methylene blue dye, and antibacterial against *E. coli*	Uv-visible spectroscopy, FTIR, SEM, HR-TEM, XRD, EDAX, XPS, TG-DSC	[59]
Sn/Zn/Cu	Chemical reduction	Core-Shell structure	20 nm		Electron Microscopy, XRD	[60]
Ag/Cu/Pt	Chemical reduction	Core-Shell Structure (Spherical)	32.89 ± 4.35 nm		TEM, XRD, EDS	[61]
Fe/Ag/Pd	Seedless and co-reduction	Nano and capsule-like	Capsule like 93, Nanolike: 50	catalytic activity for the hydration of formic acid in an aqueous solution to produce hydrogen	UV-vis, TEM, XRD, EDX	[62]
Cu/Ni/Zn	Co-precipitation method	Agglomerated	7 ± 2 nm	Antibacterial efficacy against *Escherichia coli*, *Staphylococcus aureus*	XRD, FESEM, UV-vis, FTIR, TEM	[63]
Ag/Au/Pt	Galvanic replacement reaction	Porous nanocages	70 nm	Trace fluorescent dye detection	UV-vis, TEM, HR-TEM, XRD	[52]
Pt/Ni/Cu	Facile hydrothermal method	Porous	40 nm	Boost the methanol oxidation's activity and stability	XRD, TEM, HR-TEM, SEM	[49]

3.3. Biological Synthesis

Trimetallic nanoparticles may be produced most affordably, and in an environmentally friendly manner, via green synthesis or biological synthesis. Different plants, microorganisms, and biodegradable waste can be used as a source to synthesize these nanoparticles (Figure 3).

3.3.1. Plants

To synthesize nanoparticles, various plant components, including leaves, seeds, roots, and flowers, can be employed [64]. Plant extracts are considered to be reducing, capping, and stabilizing agents due to the presence of bioactive compounds such as flavonoids, terpenoids, enzymes, alkaloids, and antioxidants [65] (Figure 4). Various studies reported the synthesis of trimetallic nanoparticles utilizing plant extracts. One of the first instances of using plant extracts for the synthesis of mixed metal NPs was in 2007, when *Brassica juncea* seeds were used to synthesize Au/Ag/Cu alloy trimetallic nanoparticles [66].

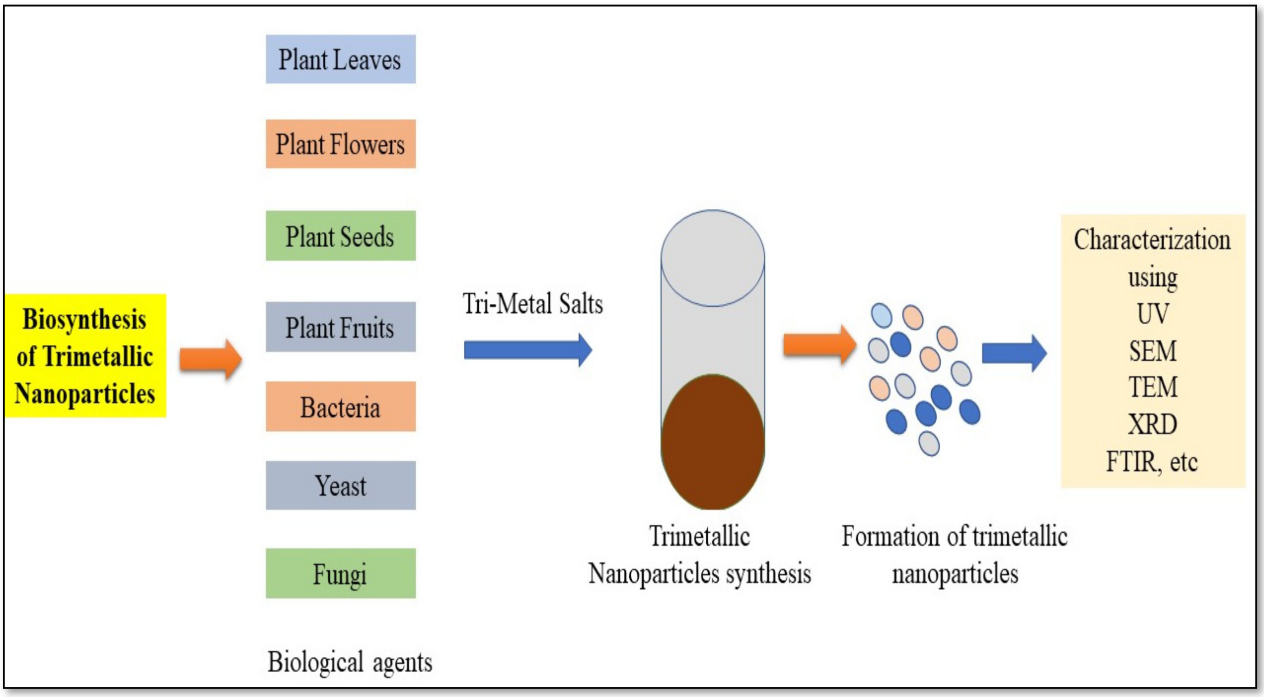

Figure 3. Biological synthesis of trimetallic nanoparticles.

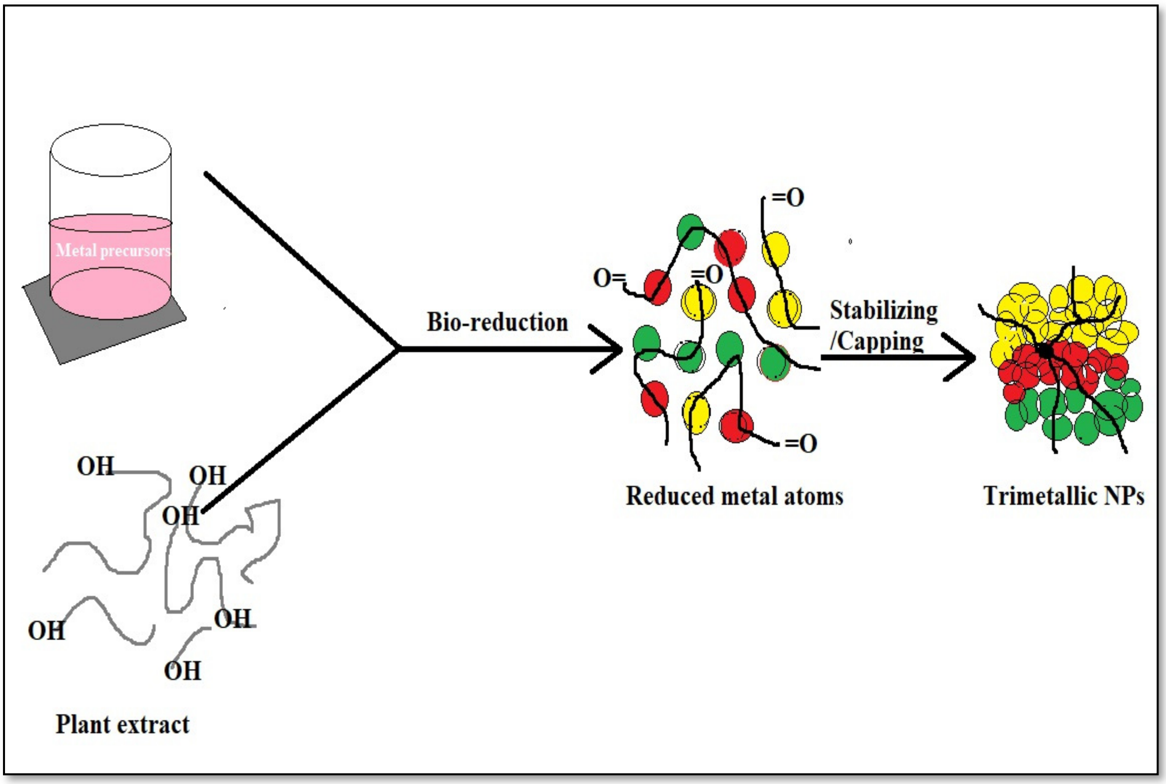

Figure 4. Role of plant extracts in trimetallic nanoparticles formation.

Furthermore, another study found that the use of aqueous leaf extracts at room temperature was a reliable method for producing Cu/Cr/Ni trimetallic oxide nanomaterials [67].

Using an aqueous extract of *Salvia officinalis*, we synthesized and tested the fungicidal properties of Ag/Cu/Co trimetallics. Additionally, *Origanum vulgare* extract was used for Cu/Co/Ni trimetallic NPs synthesis. Various trimetallic nanoparticles have been synthesized, using various plant extracts, which possess a wide range of applications (Table 3).

Utilizing abundant agricultural resources is a sustainable approach to creating nanoparticles, and a productive strategy to use and manage plant waste and biomass [68]. Post-harvest agricultural and industrial debris such as rice husks, wheat straw, fruit peel, sugar cane bagasse, wood dust, and unwanted herbs, shrubs, or other plants that are generally burnt, can be used as green sources for the production of trimetallic nanoparticles [69].

Table 3. Synthesis of trimetallic nanoparticles using the biological method.

Agent	Trimetallic Nanocomposites	Shape	Size	Activity	Characterization Method	References
Lamii albi flos	Au/Pt/Ag	Spherical	40 nm	Antimicrobial against *Enterococcus faecalis* and *Enterococcus faecium*	UV-vis spectroscopy, FTIR, SEM, TEM, AFM	[70]
Salvia officinalis	Ag/Cu/Co	Spherical	3.25 nm	Fungicidal against *Candida auris*	FTIR, SEM, TEM, EDX, XRD, TGA	[37]
Eryngium campestre and *Froriepia subpinnata*	Cu/Cr/Ni	Cube-like/Plate-like	14.15 nm using mixed leaf extract	Antibacterial efficacy against *Escherichia coli* and *Staphylococcus aureus*	TEM, UV-vis spectroscopy, XRD, FTIR, EDX, FESEM	[67]
Origanum vulgare	Cu/Co/Ni	Nanoflake-like	28.25 nm	Photocatalytic dye degradation	UV-vis, SEM, TEM, XRD, FTIR, TGA, DTG, EDX	[71]
Brassica juncea	Au/Ag/Cu	Spherical	~5–50 nm	NA	STEM, EDX, HAADF, FTIR	[66]
Meliloti officinalis	Au/Zno/Ag	Spherical, triangular and hexagonal	~20 nm	NA	UV-vis spectroscopy, SEM, FTIR, TEM, AFM, XRD	[72]
Syzygium aromaticum and *Aegle marmelos*	Ag/Au/Pd	Spherical	8–11 nm	Glucose oxidation and antimicrobial against *E. coli*	Uv-vis spectroscopy, TEM, SEM, FT-IR	[29]
Platycodon grandiflorum	Fe/Ag/Pt	Spherical	~10–20 nm	Lowering of 4-nitroaniline and decolorization of rhodamine B	UV-vis spectroscopy, XRD, FE-TEM, FTIR, VSM	[73]
Coriandrum sativum	Au/Ag/Sr	Almost spherical	70 nm	Gas sensing	UV-vis, FE-SEM, FTIR, XRD	[74]
Echinops persicus	Cu/Cr/Ni			Antibacterial efficacy against *E.coli*, *B.cereus*, *S. aureus* Catalytic activity towards quinolines and spirooxindoles Action of cytoxicity against human colon cancer (HT29) cells	TEM, FE-SEM, UV-vis, EDX, XRD, FTIR, EDX, DLS	[75]
Coriander sativum	Ni/Cr/Cu	NA	NA	Antibacterial and antifungal	UV-vis, XRD	[76]
Verbena ofcinalis	Au/CuO/ZnO	Mostly spherical	35 nm	Antileukemia	UV-vis, FTIR, TEM, AFM	[77]
Gum Kondagogu from *Cochlospermum gossypium*	Ag/Au/Pd	Regularly dispersed and spherical	10–45 nm	Catalytic degradation of 4-nitrophenol	XPS, UV-vis, XRD, FTIR, SEM, EDX, TEM, ICP-MS, DLS and PALS	[78]

Table 3. *Cont.*

Agent	Trimetallic Nanocomposites	Shape	Size	Activity	Characterization Method	References
Caesalpinia bonduc	Ag/Bi/SnO_2	Agglomerated, with edge having irregular shapes	NA	Photocatalytic activity	XRD, SEM, SAA, EDX, FTIR	[79]
Astragalus membranaceus	Au/Fe/Ag	Ant-shaped nanoparticles	100 nm	Strong catalytic activity for the production of beta, alpha and, beta-dichloroenones	UV-vis, XRD, TEM, HRTEM, AFM, EDS, XPS	[15]
Vitex agnus-castus	Au/CuO/ZnO	Spherical and locally agglomerated	5–25 nm	Dye degradation by catalytic activity	TEM, AFM, SEM, UV-vis, FT-IR	[72]
Malus Domestica Peels	Pd/Pt/Co	NA	NA	Hydrogen production and photocatalytic activity	UV-vis, FTIR, XRD	[80]
Shewanella oneidensis MR-1	Pd/Au/Fe	Nanorods	200–300 nm	Catalytic reduction of nitroaromatic compounds	TEM, XRD, EDX, XPS, VSM, FTIR, CLSM, TGA	[81]

3.3.2. Other Biological Agents

Microorganisms such as bacteria, fungi, viruses, and even yeast are also used for the synthesis of trimetallic nanoparticles due to their ability to collect and detoxify heavy metals through different reductase enzymes [82]. This approach offers a non-hazardous, affordable, and reliable method for creating trimetallic nanocomposites of varied shapes, sizes, compositions, and physicochemical properties. Numerous species of yeast and fungus, such as streptomyces and Neurospora, have also been employed to create nanoparticles due to their great tolerance for metals, particularly when considering the high biomass concentration of metal ions in cell walls [65].

4. Applications

There are numerous biomedical, as well as environmental, applications of trimetallic nanoparticles, and this area has a scope for growth in this field, with advances being made on a regular basis. Some of the applications of trimetallic nanoparticles are described hereafter.

4.1. Biomedical Applications

4.1.1. Antimicrobial Activity

One of the leading causes of serious health issues is foodborne disease caused by infectious agents. Currently, antibiotics are the only source of treatment against pathogenic microorganisms such as bacteria and fungi. However, due to the unsound use of antibiotics, many pathogens have become resistant to them. The prevalence of infectious disorders caused by bacteria resistant to many drugs has increased, especially methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa* resistant to fluoroquinolones. In order to solve this problem, the use of alternative antibacterial agents such as metallic nanoparticles have been highly targeted. Metallic nanoparticles have powerful, targeted, and prolonged antibacterial interactions with bacteria and biofilms at lower doses because of their tiny dimensions and high surface area-to-volume ratios.

Numerous studies have shown that trimetallic nanoparticles exhibit excellent antimicrobial activity compared to that of bimetallic and monometallic nanoparticles. In one study, Au/Pt/Ag was synthesized by the green synthesis method, by using leaf extract of *Lamii albi flos*. The acquired Au/Pt/Ag nanoparticles demonstrated outstanding antimicrobial properties against harmful strains of bacteria such as *Enterococcus faecalis* and *Enterococcus faecium*, both planktonic as well as sessile [70]. In their study, the authors attributed the antimicrobial effect to the combined synergistic effects of the trimetallic nanoparticles, with various activities towards the microbes, including their contact with cell membranes, resulting in structural changes in permeability and disruption, production of free radicals, inactivation of essential enzymes by reaction between thiol groups and metal ions released by the nanoparticles, and damage to microbial DNA as well as RNA damage. Similarly, in another study, the synthesis of Cu/Cr/Ni trimetallic nanoparticles was performed using mixed extracts of *Eryngium campestre leaves* and *Froriepia subpinnata*. The synthesized trimetallic nanoparticles showed rapid inhibition of growth of pathogenic strains of *Escherichia coli* and *Staphylococcus aureus* [67]. Similarly, Ag/Au/Pd nanoparticles showed antimicrobial properties against the pathogenic strain of *Escherichia coli* bacteria [29]. SEM analysis showed significant alterations in the cell wall. Furthermore, in a study, biosynthesized Cu/Cr/Ni trimetallic oxide nanoparticles, using *Echinops persicus* flower extract, demonstrated notable inhibitor activity against various bacteria such as *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus cereus* [75]. Antibacterial properties against the strains were studied using diffusion methods as well as Minimum Inhibitory Concentration (MIC). The findings and observations made it abundantly evident that Cu/Cr/Ni NPs are far superior to their matching single-metal nanoparticles in terms of their remarkable catalytic and antibacterial activity. Some trimetallic nanoparticles have also shown remarkable anti-fungicidal activity. For example, Ni/Cr/Cu trimetallic nanoparticles fabricated using extracts of *Coriander sativum* as a capping agent, showed dose-dependent inhibition against two fungal and two bacterial pathogens [76]. When the corresponding zone of inhibition (ZOI) was measured using the well diffusion method, its antibacterial ability against two fungal species, *Aspergillus flavus* and *Penicillium* sp., and two bacterial species, *Escherichia coli* and *Staphylococcus aureus*, was determined. All four pathogen species, showed dose-dependent inhibition. Trimetallic oxide NPs' antibacterial ability can be used in medical research, environmental sciences, and the pharmaceutical industry. In another instance, the synthesis of CuO/NiO/ZnO via the co-precipitation technique has shown remarkable inhibitory capabilities against bacteria such as *Escherichia coli* and *Staphylococcus aureus*. When observed via FESEM it showed lysis of the cell walls of bacteria because of the action of the trimetallic nanoparticles [63]. These studies have been found to be a pioneering path in the field of medical research. Hussein et al. [83] reported the synthesis of Ru/Ag/Pd nanoparticles from garlic tunicate leaf, with the particle size ranging from 50 to 90 nm and the shape being spherical. Synthesized Ru/Ag/Pd nanoparticles showed a potential antimicrobial activity against *Aspergillus favus*, *Aspergillus niger*, *Candida albicans*, *Candida glabrata*, *Escherichia coli*, and *Bacillus cereus*. Abdelsattar et al. [84] reported the synthesis of silver-cobalt-ferrite nanoparticles using Citrus limon, which were 20 nm with a spherical shape. They showed that, due to the antibacterial activity of the nanoparticles, 25 µM of the nanoparticles was able to kill *Salmonella* bacteria and 62.5 µM inhibited their growth.

4.1.2. Anticancer

Cancer is the leading cause of increasing deaths worldwide. Therefore, the early diagnosis and treatment of cancers is crucial. The employment of nanotechnology-related instruments has been encouraged to hunt for novel treatment approaches. There have been reports of cytotoxicity shown by biologically synthesized trimetallic nanoparticles against different cell lines. For example, in a particular study, Au/CuO/ZnO synthesized from *Verbena officinalis* showed cytotoxicity against the established jurkat cell line to test for antileukemia activity. The MTT assay showed that a concentration of 6 µmol was enough to give 100% activity, with the IC50 value of 1.08 µmol for the culture carried out for 24 h [77]. The analysis showed that the effectiveness depended on the concentration of the nanoparticles and the duration of the culture. Low concentrations of the synthesized trimetallic nanoparticles were shown to cause late apoptosis in the cultured cells, while higher concentrations caused necrosis. Because gold and silver nanoparticles are least toxic to human cells, trimetallic nanoparticles, including the Ag-Au combination, can be fabricated and applied in different cancer therapies. The current, intensive investigations using metal nanoparticles may result in the development of new medicinal treatments for various cancers. Chaturvedi et al. [85] reported synthesis of Au/Pt/Ag trimetallic nanoparticles from *Pleurotus florida* which were spherical in shape and ranged in size from 4 to 10 nm. Synthesized trimetallic nanoparticles were tested against the triple negative breast cancer cell line (mda-mb-231), and the highest 10% cell viability was reported at 100 µg/mL concentration of nanoparticles. The antileukemia activity of the synthesized Au/CuO/ZnO nanoparticles was evaluated, and cell viability was rapidly reduced in the range of 80 to 20% at a nanoparticle concentration of 0.1–4 µmol. Hussein et al. [83] reported that the synthesis of Ru/Ag/Pd nanoparticles from garlic tunicate leaf and synthesized trimetallic nanoparticles showed potential antiproliferative activity against HepG2, Caco-2, and K562 cell lines. Abdelsattar et al. [84] reported the synthesis of silver-cobalt-ferrite nanoparticles using Citrus limon, which has anticancer activity against HEPG2 and MCF7 cell lines, with an IC50 of 43.5 and 35.5 µg/mL.

4.1.3. Biosensors

Nanoparticles have come to light for their remarkable characteristics, such as catalytic activity, optical properties, etc. In a recent study performed by Nie, Ga, Ai & Wang, Pd-Cu-Au trimetallic nanocomposites were applied for the detection of glucose and H_2O_2. This is because Pd-Cu-Au showed excellent catalytic activity with respect to peroxidase enzymes and tetramethylene benzidine in the presence of hydrogen peroxide. The respective detection limits (LOD) of H_2O_2 and glucose were 5 nM and 25 nM [86]. Furthermore, to enhance the catalytic activity of nanoparticles, more metal nanocomposites can be incorporated into different alloys. For example, Cu/Au/Pt nanoparticles with strong plasmonic absorbance for imaging in the near-infrared were prepared using a simple one-pot synthesis method for biosensing and theranostics applications [87]. Many studies have demonstrated that trimetallic nanoparticles can also be used for the diagnosis of cancer. An H_2O_2 sensor that can track the release of H_2O_2 from live breast cancer cells was created using nanocomposites of Au/Pt/Pd and reduced graphene oxide [48]. Likewise, Pd-Fe-Ni trimetallic alloy NPs, produced on a glassy carbon electrode, were applied for the biosensing of biotin [88]. Additionally, in another study, a trimetallic nanocomposites decorated MXene nanosheet was used as an electrode for the platform assay to detect carcinoembryonic antigens [89].

4.1.4. Drug Delivery System

The aim of an ideal drug delivery system is to target the infected cells effectively, with low cytotoxicity. To avoid the limitations of traditional drug delivery systems, smart carriers have been fabricated from organic materials such as liposomes, or inorganic materials such as gold nanoparticles and carbon nanotubes [90]. Trimetallic drug carriers, with the core made up of gold and shell containing organic polymers, can infiltrate the biological environment of the human body [91]. Trimetallic nanoparticles serve as the basis for the gradual and precise release of drugs at a rate and location that obviate the limitations of conventional diagnostic and therapeutic approaches.

4.2. Catalytic Degradation of Heavy Metals and Toxic Pollutants

Trimetallic nanoparticles have gathered attention from scientists around the world due to their excellent catalytic degradation properties and other oxidation-reduction properties. In one study, trimetallic nanocomposites were used to enhance the performance of electrocatalysts. The facile ultrasonic-assisted method was used to create nanocomposites (NCs) with highly porous features and perpendicular pore channels. Such Pt/Au/Ru NCs effectively retain the structural stability of the catalysts, while also producing highly accessible surface-active sites, both of which are ultimately beneficial for increasing the electrocatalytic activity and durability. These characteristics also enhanced the performance of electrocatalysts toward formic acid oxidation [44]. Trimetallic nanoparticles have also been widely used for wastewater treatment. La/Cu/Zn/carbon dots were synthesized using the microwave method and used to remove malachite dye and ampicillin antibiotic from wastewater treatment [36]. The adsorption and photocatalysis processes make up the fundamental removal mechanism. On the surface of trimetallic nanocomposites (TNCs), dye and antibiotics are absorbed. La/Cu/Zr/CQDs TNCs are exposed to light to produce electron-hole pairs, which can then combine with water molecules to release hydroxyl and super oxide radicals, which causes the mineralization of antibiotic and dye molecules. In this study, after 4 h of photoirradiation under adsorption in the dark, followed by photocatalysis and a coupled adsorptional/photocatalysis process, 96% of the antibiotic ampicillin and 86% of the color malachite green (MG) were destroyed. The removal findings under these condition are better for MG solely because the absorbed antibiotic and dye molecules were more easily damaged by free radicals than the dissolved antibiotic and dye molecules. In light of various adsorptional/photocatalytic applications of the La, Cu, Zr, and CQD TNCs for the remediation of emerging pollutants, including pharmaceutical by-products, pesticides, and chlorophenols, the findings obtained are highly encouraging. Likewise, Au/Pd/Ru fabricated by using a one pot protocol using reduction of cobalt nanoparticles, showed efficiency towards the degradation of azo dyes, which resulted in the removal of color from the wastewater [58]. It is well known that aquatic life is severely harmed by effluents containing azo dyes. The colors released as industrial waste by the textile or other related industries not only pollute the environment, but also endanger human health. This experiment aimed to achieve facile catalytic degradation of dyes, as these dyes cannot be easily degraded. The nanocatalyst demonstrated excellent catalytic reactivity in the degradation of azo-based dyes and the reduction of PNP. In addition, dolochar sorption, from solid industrial waste dolochar, was used to eliminate the hazardous amines created during azo dye degradation. The nanocatalyst demonstrated effective color removal, and hazardous amines, created in situ from industrial waste water, were removed by straightforward sorption on a porous solid waste (dolochar), which is considerably more practical than the conventional biological procedures. They also showed how solid waste can be produced from wastewater, which is useful for waste management. This is the pioneering example of the trimetallic porous Au/Pd/Ru NP system, which is significant from both a synthetic and a catalytic standpoint. Trimetallic nanoparticles have also shown high catalytic efficiency for aerobic oxidation of glucose, as shown by the study of Zhang et al. [53], where Au/Pt/Pd NP with an alloy structure was synthesized by reducing ions with rapidly injected $NaBH_4$ [53]. Despite being a similar size, the catalytic activity demonstrated by Au/Pt/Pd (60/10/30) nanoparticles for the oxidation of glucose was three times higher than by pure Au. The strong catalytic activity is believed to be a result of the Pd and Au components in the Au/Pt/Pd TNP having transferred electronic charges to one another. From these findings, it can be seen that trimetallic nanoparticles have proven to be very efficient in terms of catalytic degradation of heavy metals and other toxic pollutants.

4.3. Active Food Packaging

Different properties should be taken into account when making packaging materials, such as the flexibility of the materials, the hardness, and the inertness of the food packaging materials, along with various other properties. Plastic polymers, for example polyethylene, fulfill the criteria mentioned above. However, these plastic polymers take hundreds of years to degrade, and biopolymers are also not particularly suitable alternatives as they do not possess magnetic, optical, and other physical as well as chemical properties. Hence, scientists have shifted their focus towards producing active food packaging materials composed of trimetallic nanomaterials. Trimetallic NPs like Au/Fe/Ag and Fe/Ag/Pt, have the potential to be effective antimicrobials in food packaging applications [92]. If incorporated with biopolymers, these trimetallic nanoparticles enhance the shelf life of food materials. However, scientists should consider safety-related issues when developing these materials.

5. Current Challenges/Future Perspectives

In terms of the creation of environmentally friendly methods for the fabrication of trimetallic nanoparticles, the progress has been massive. However, the synthesis of trimetallic nanoparticles using green resources is still hampered by numerous obstacles or gaps that scientists and researchers around the world must overcome. Although this method is cost-effective and environmentally benign, there may be issues with material choice, optimal conditions, and the quality of the final product [93]. There are difficulties when choosing plants, because of their age and the concentration of metabolites required to synthesize those nanoparticles in their leaves, for example. So, information about the conditions in which the plant is growing should also be considered when selecting the material for the synthesis process [94]. The long reaction time and excessive energy usage are some of the concerning issues with the biological synthesis process. The lack of knowledge of the mechanisms underlying biosynthesis, and the difficulty of obtaining precise chemical reactions to describe the synthesis process, are significant barriers to green biosynthesis. Therefore, the precise process by which the plant extracts function as stabilizing, reducing, or capping agents remains a mystery to this day. Because of the possibility of obtaining nanoparticles with variable sizes and shapes when different extracts are used, problems might also occur in the final products of nanoparticles. The ability of manufactured nanoparticles from green synthetic methods to remove harmful contaminants has also been the subject of numerous studies, and in some of these studies the particles are only marginally effective at doing so [95]. To address these gaps and challenges, researchers must first understand the mechanisms underlying the bioreduction and stabilization of these nanoparticles using plants. They must also accept that this task cannot be successfully completed without taking into account the phenomenon as a whole and all relevant variables. Additionally, since these materials are readily available, and will aid in the bioremediation process, the utilization of biowastes such as wheat straw and rice bran in the synthesis of these nanoparticles should be encouraged.

There is a greater prospect for the applications of trimetallic nanoparticles. Scientists from all over the world are working to find the best possible green synthesis method to apply it in various uses such as inducing antileukemia [77] activity using these trimetallic nanoparticles. It is important to support in vitro research on these trimetallic nanoparticles to determine their effectiveness against different cancer cell lines. Numerous studies have revealed that these plant-derived nanoparticles are only minimally hazardous to humans. Therefore, employing them to treat numerous diseases, including cancer, would be a major medical breakthrough. Therefore, it shouldn't come as a surprise that they will be an essential part of the new generation, given the advancements nanotechnology has made in the field of medicine so far.

6. Conclusions

There are various methods that have been widely used for the fabrication of trimetallic nanoparticles. However, biological synthesis is highly encouraged because it is environmentally friendly and economical. Trimetallic nanoparticles exhibit better applications than bimetallic or monometallic nanoparticles. These nanoparticles have novel applications including effective drug delivery, removal of antibiotics, active food packaging, diagnosis, treatment of cancer, etc. Different parameters such as temperature, incubation time, and concentration of metal ions are essential for the synthesis of trimetallic nanoparticles. However, information on the biocompatibility of trimetallic nanoparticles is still not adequate, and more research is required in this domain to increase the efficiency of industrial processes and also biomedical applications.

Author Contributions: S.K., U.B. and A.R. conceptualized and designed the manuscript, participating in drafting the article and/or acquisition of data, and/or analysis and interpretation of data; S.K., U.B., A.R., S.A., M.A. (Mazen Almehmadi), H.M.A., M.A. (Mamdouh Allahyani), M.J.H., M.A.H.,

M.M.R.S. and M.F.N.A. prepared the figures and tables, edited and revised the manuscript critically. All authors have read and agreed to the published version of the manuscript.

Funding: The authors would like to thank the Faculty of Medicine, Universiti Kebangsaan Malaysia, for the approval and funding of this research (Approval code: FF-2020-016).

Data Availability Statement: Available data are presented in the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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