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VOLTAMMETRIC BIOSENSORS BASED ON METALLIC NANOPARTICLES SYNTHESIZED FROM PLANT EXTRACTS: A SHORT OVERVIEW OF RECENT ACHIEVEMENTS

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Since the last decade of the 20th century, many scientific disciplines have heavily relied on materials with nanometer dimensions. Nanomaterials are already integrated into numerous biomedical and pharmaceutical applications, including the delivery of active substances to specific targets within the body. This has been demonstrated by their contribution to the containment of the recent COVID-19 pandemic. Graphene, silver, gold, and other nanoparticles possess exceptional physical and chemical properties, including increased thermal stability, improved conductivity, and the capacity to host various organic substrates on their surface area. In the past 20 years, a significant field of nanoparticle synthesis has emerged, where eco-friendly reducing agents found in numerous plant species are used. This brief review focuses on the outstanding performance of metallic nanoparticles synthesized using "green methods" in designing voltammetric biosensors. The major goal of this short review is to highlight some of the latest electrochemical advances in exploring metallic nano-systems obtained via phytosynthesis from plant extracts, covering the most notable achievements in the design of amperometric and voltammetric biosensors.

Keywords: metallic nanoparticles; green chemistry; electrochemical biosensors; voltammetry

ВОЛТАМЕТРИСКИ БИОСЕНЗОРИ ДИЗАЈНИРАНИ ОД МЕТАЛНИ НАНОЧЕСТИЧКИ ШТО СЕ СИНТЕТИЗИРАНИ ОД ЕКСТРАКТИ НА РАСТЕНИЈА: КРАТОК ПРЕГЛЕД НА НЕКОИ СКОРЕШНИ ПОСТИГНУВАЊА

Во последната деценија од 20-тиот век голем број научни дисциплини се базирани на материјали што имаат нанометриски димензии. Наноматеријалите веќе се интегрирани во многу биомедицински и фармацевтски апликации, а се значаен дел и во трансферот на активни супстанции до специфични цели во телото. Ова беше демонстрирано со нивниот придонес во справувањето со последната пандемија на COVID-19. Графенот, среброто, златото и другите наночестички поседуваат исклучителни физички и хемиски својства, вклучувајќи зголемена термална стабилност, подобрена спроводливост и способност за прифаќање различни органски супстрати на својата површина. Во последните 20 години се појави значајна област на синтеза на наночестички, во рамките на која се користат еколошки редуцирачки агенси што се наоѓаат во многу растенија. Овој краток преглед се фокусира на перформансите на метални наночестички синтетизирани со таканаречени "зелени методи" во дизајнирањето на волтаметриски биосензори. Главната цел на овој краток преглед е да се истакнат некои од последните електрохемиски достигнувања во истражувањето на метални наносистеми што се добиени преку фитосинтеза од екстракти на растенија, вклучувајќи ги некои од постигнувањата во дизајнирањето на амперометриски и волтаметриски биосензори.

Клучни зборови: метални наночестички; „зелена хемија“; електрохемиски биосензори; волтаметрија

1. INTRODUCTION

Electrochemical biosensors have found widespread use in a variety of fields, such as electrochemical analysis, biosensing, drug delivery, biomedicine, and pharmacy. This is due to their unique features, reflected mainly in highly expressed specificity. The transduction of chemical signals to electrical measurable parameters in electrochemical biosensors is achieved by applying various electrochemical techniques such as voltammetry, conductometry, potentiometry, and amperometry. Voltammetry stands as an invaluable electrochemical method, offering profound insights into the dynamic transformations occurring at electrodes within important physiological and chemical systems. Its applicability spans small ions to bulky lipophilic redox proteins and enzymes.[1–3] At the heart of voltammetry is the measurement of the energy of electrons exchanged between a defined analyte(s) and an electronic conductor, known as a working electrode. Consequently, the meticulous choice of the working electrode is deemed an essential undertaking when conducting voltammetric experiments. Only a limited number of materials, such as noble metals, mercury, or various carbon-based electronic conductors, have been reported to be suitable materials for working electrodes in the majority of voltammetric studies.[1,4] To effectively employ voltammetry for the examination of specific ions, drugs, or physiologically active systems at micromolar or even lower concentrations, it frequently becomes imperative to enhance the working electrode's surface by incorporating materials possessing superior conductive and chemical attributes compared to the unmodified electrode.[5] Over the past two decades, many nanomaterials have been explored as modifiers of various working electrode surfaces in voltammetric experiments.[6] Nanoparticles based on metals such as Au, Ag, Pd, and Pt, as well as some metal oxides and especially nanoparticles developed from different carbon materials, have been extensively used to modify working electrodes made mainly of carbon and Pt.[6–8] This has significantly bolstered the use of voltammetry in developing a wide array of voltammetric biosensors engineered for identifying crucial chemical and physiological compounds.[4,8] In the past 20 years, the so-called "green synthesis" of various metallic nanoparticles has been one of the most explored approaches in nanotechnology.[9–11] This approach entails the utilization of plant-derived reducing agents to produce nanoparticles with the desired size and characteristics. This brief summary underscores some of the recent key accomplishments in the realm of nanomaterials achieved through "green" synthesis and their pivotal role in advancing the field of voltammetric biosensors.

2. RESULTS AND DISCUSSION

2.1. *Nanoparticles – a short introduction*

The concept of "nanotechnology", introduced by Richard Feynman,[12] a Nobel Prize laureate in 1965, has ushered in remarkable progress across diverse domains, including nanomedicine, pharmacy, chemistry, physics, high-tech industry, the food sector, and numerous others.[13] Nanomaterials and nanoparticles exhibit distinctive properties that can be customized to yield novel and altered functionalities in contrast to their larger bulk counterparts. Their reduced size and extraordinary characteristics with respect to increased stability and conductivity have attracted interest in applications in chip technology. Also, the ability to finely adjust the properties of nanomaterials has opened up a wide range of uses in fields such as electronics, photovoltaics, biomedicine, and pharmaceuticals. Over the last two decades, the impact of nanotechnology in these areas has been enormous. Although nanoparticles (NPs) are a large class of materials, a widely accepted definition of NPs is “a three-dimensional material that has at least one dimension in its structure less than 100 nm.[13] In the last 15 years, a number of exceptional works have emerged, delving into crucial subjects like the synthesis, properties, functions, characterization, and applications of different types of nanoparticles. In general, the remarkable catalytic characteristics of nanoparticles (NPs), combined with their capacity to enhance surface area-to-volume ratios through size reduction, improved electronic conductivity, heightened durability, and enhanced compatibility with various substrates, render them exceptionally well-suited for utilization in electrochemical systems. Furthermore, a number of NPs, particularly those based on graphene, serve as ideal platforms for attaching functional groups, a noteworthy feature that enhances their selectivity toward specific substrates.[13] Many recent excellent reviews report on different properties, synthesis protocols, characterization, and applications of nanoparticles in electrochemical experiments.[14–16] This brief summary highlights the recent noteworthy achievements in the realm of nanoparticles produced using "green synthesis" and their role in advancing the development of voltammetric biosensors. The significance of green synthesis methods is on the rise as a promising pathway for the sustainable preparation of nanoparticles. Such methods result in nanomaterials that have decreased toxicity towards living organisms and the environment. Additionally, these approaches can offer further advantages, such as lower energy consumption and production costs than traditional synthesis methods, making them suitable for large-scale commercial production. Since many excellent reviews have already focused on methods of synthesis of green nanoparticles,[9,10,11,13] we will underline just some of the general concepts of this approach here.

2.2. *What is the "green synthesis" of nanoparticles?*

In general, producing nanoparticles and other nanomaterials often requires lengthy procedures that frequently utilize costly and harmful chemicals. Although these materials find widespread use in a variety of applications, most chemical methods for their synthesis are predominantly constrained by excessive energy consumption, elevated production expenses, the use of toxic substances, and the generation of undesirable by-products. As a result, there has been a growing need for the development of eco-friendly methods to produce nanoparticles, with the goal of reducing the potential for dangerous reactions and the generation of toxic waste. The primary objective of eco-friendly methods is to streamline the transition of nanoparticles from laboratory research to practical commercial applications while ensuring cost-effective production. So far, various affordable and uncomplicated methodologies have been devised for producing nanomaterials without the need for harmful substances and the readers are advised to explore some of those works.[13,15] The so-called "green protocols" have emerged as promising routes for preparing nanoparticles that reduce toxicity towards living organisms and the environment, thus promoting the use of non-toxic and renewable materials.[17] When discussing "green synthesis of nanoparticles", it typically refers to an environmentally conscious approach that represents a paradigm shift in chemistry. This approach aims to eliminate toxic waste, minimize energy consumption, and utilize environmentally friendly solvents, including water, mild organic acids, and ethanol or their derivatives. A simplified schematic description of the green synthesis approach of silver nanoparticles is given in Figure 1.

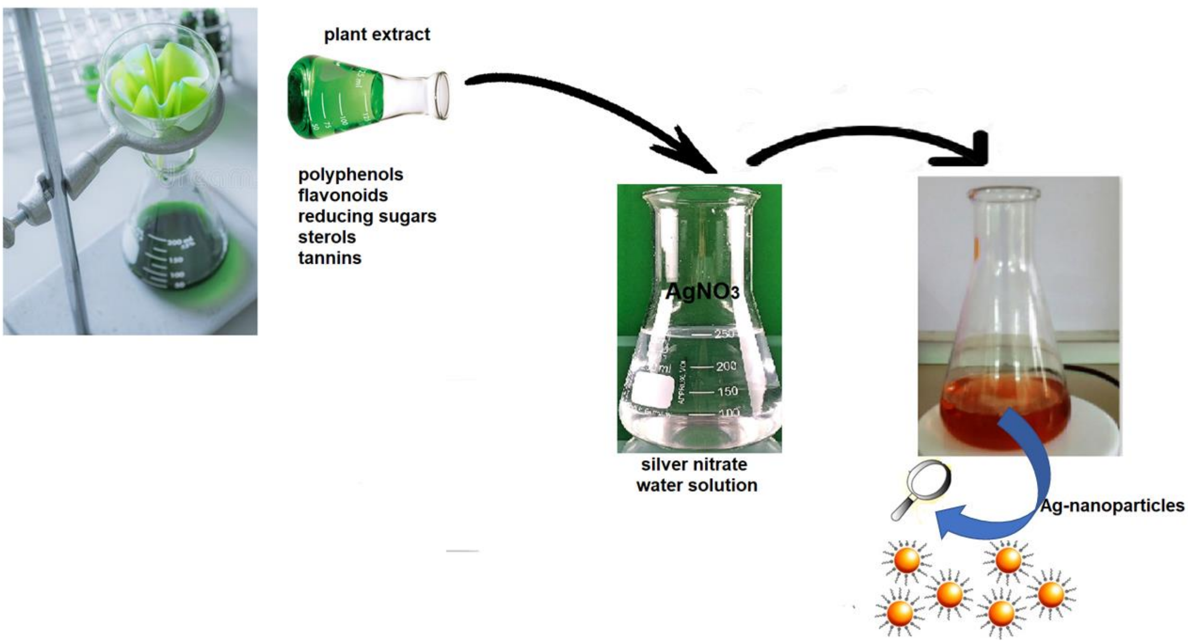

Fig. 1. A simplified scheme of the general protocol used in the "green synthesis" of silver nanoparticles

The general chemical approach for synthesizing colloidal metal dispersions in dilute solutions involves reducing the metal ions present in some sort of metal complexes in water solutions. In the classical scenario, one mainly explores reducing agents such as hydrazine and sodium borohydride to obtain nanoparticles. However, these are not ideal reducing systems because they tend to reduce all metallic ions simultaneously, which often leads to agglomeration of the created nanoparticles.[18] Incorporating eco-friendly materials like plant extracts, microorganisms, and algae as reducing agents comes with notable advantages. Generally, these biological extracts are blended with metal salt solutions, where they gradually catalyze the formation of nanoparticles with reduced dimensions. Metal ions present in water solutions can be reduced from a positive oxidation state to a zero-oxidation state via chemical reactions of various biosystems present in plants. It is well known that plant extracts contain a variety of metabolites and reductive biomolecules responsible for the reduction of metal ions, including terpenoids, flavones, ketones, aldehydes, amides, carboxylic acids, carbohydrates, proteins, and vitamins.[17] Among the many natural products present in the plants, polysaccharides, such as starch and chitosan, are also seen as excellent scaffolds for this purpose. In recent years, polysaccharides such as hydroxypropyl, beta-glucan, hyaluronic acid, or diaminopyrinidinyl have been successfully used to synthesize nanoparticles.[9–11,17] In addition, many alkaloids, polyphenolic compounds, terpenoids, some enzymes, and co-enzymes are recognized as very important reducing systems present in plant extracts.[19] In addition, harnessing antimicrobial plant extracts seen as in situ reducing agents and "capping agents" can contribute to creating engineered nanoparticles with enhanced antimicrobial properties.[20] The dimensions of nanoparticles are pivotal for exhibiting their antimicrobial properties, and these dimensions are effectively preserved by the capping agents.[21] Indeed, when the capping agent itself exhibits antimicrobial properties, it can further enhance the overall antimicrobial effectiveness of the synthesized nanoparticles.[20] Consequently, plants possessing intrinsic antimicrobial attributes can be employed to successfully create silver, gold, copper, or other nanoparticles with heightened antimicrobial capabilities.

Given the existence of numerous extensive reviews covering the synthesis protocols, properties, functions, and applications of metallic and metal-oxide nanoparticles using green methods,[9–11,17,19] this report concentrates explicitly on some important recent applications of metallic nanoparticles synthesized via green approaches in the advancement of voltammetric sensors.

2.3. *Voltammetric biosensors based on green metallic nanoparticles*

It is already well elaborated that numerous nanoparticles, particularly metal and graphene nanoparticles, exhibit remarkable catalytic properties. Integrating nanoparticles possessing catalytic attributes onto the working electrode's surface often takes place through self-assembly. This occurs when the working electrode is immersed in a solution containing nanoparticles for a specified duration. Voltammetric sensors and biosensors in which the surface of the working electrode is modified with nanoparticles have good potential for reducing overpotentials in numerous vital electrochemical reactions and very often affect the reversibility of certain redox reactions that are typically classified as electrochemically irreversible when studied on unmodified electrodes. Figure 2 illustrates the fundamental steps in designing voltammetric sensors using nanoparticles synthesized through green methods.

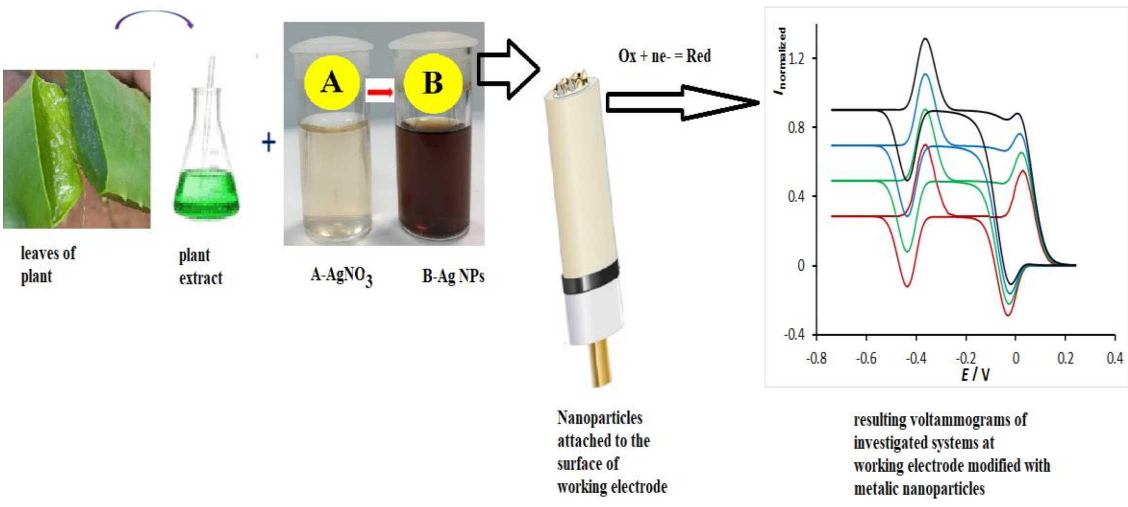

Fig. 2. Schematic representation of major steps involved in green-synthesized nanoparticle modification of a working electrode and the resulting voltammetric outputs

Table 1 offers a summary of recent significant achievements in the field of metallic nanoparticles derived from plant extracts. Because of their easily controllable green synthesis and superior electron-conductive properties, silver[22–44] and gold,[41–50] as well as bimetallic Au-Ag,[41,45,51] together with the copper-based[52–57] nanoparticles are largely explored nanomaterials in designing various voltammetric sensors. In addition, due to their excellent antibacterial properties, which are advantageous in the design of biosensors, silver nanoparticles are especially preferred nano-systems. Therefore, during the COVID-19 pandemic from 2020 to 2023, the use of Au and Ag-based NPs rapidly expanded, primarily in biosensing. Green methodology has also proven to be a successful approach in voltammetric applications of various metallic nanoparticles based on Zn,[58–62] Mg,[62,63] Sm,[62] Mo,[64] Fe,[57,65,66] Ni,[65,67] and Pb.[68] Since the recent review work[69] describes in detail the production, characterization, and application of plant-based synthesized nanoparticles, we refer the readers to that work[69] to get a deeper insight into the potential of "green" nanomaterials. A systematic overview of the application of green-synthesized metal-based nanoparticles in the design of specific voltammetric sensors is given in Table 1. Note that the green-synthesized nanoparticles listed in Table 1 have been mainly reported for their applications in voltammetric analyses of important chemical and physiological systems over the past 5 years.

Table 1

Data related to voltammetric detection of various substrates using metal-based nanoparticles synthesized through an eco-friendly process using plant extracts

Type of nano-particles (NP's)	**Type of electrode**	**Plant extract**	**Analyte/Remark**	**Detection limit/Remark**	**Reference**
Ag NP's	GCE	*Theobroma cacao linneu (Malvaceae)*	Superoxide radical	Assessment of antioxidant capacities of various assays	[22]
Ag NP's	Carbon paste electrode (CPE)	*Ocimum Sanctum* leaf	Cd(II) and Pb(II)	0.0891ppm for Cd(II) and 0.048 ppm for Pb(II)	[23]
Ag NP's	Polyaniline (PANI)–carbon paste electrode (CPE)	Dry *Artemisia* leaf	Pb^{2+} ions	0.04 μmol/l	[24]
Ag NPs	GCE	Leaf of *Salvia leriifolia*		Facilitated reduction of nitrite ions/antibacterial activity observed	[25]
Ag NP's	GCE	*Costus afer (Costaceae)*		Antibacterial activities observed	[26]
Ag NP's	GCE	*Ficus sycomorus* leaves	Bromocresol green	Detection limits of 1.5 × 10^{-5} mol/l and 1.3 × 10^{-5} mol/l, for monomer and dimmer, respectively.	[27]
Silver oxide NP's	Modified carbon-paste electrode	*Centella asiatica* and *Tridax plant* powder		Increased antibacterial and antifungal activity observed	[28]
Ag NP's	Modified GCE	*Cupressus sempervirens* L. (CSPE) pollen extract	H_2O_2	0.23 μmol/l	[29]
Ag NP's	Graphite electrode (GE)	*Rosa damascena* waste: post-distillation	H_2O_2 Vanillin	8.4 μmol/l for H_2O_2	[30]
Ag NP's	AgNPs/GCE-modified electrode	Dried leaf *Bardaqush* extract (DLBE)		Inhibited growth of microbial colonies observed	[31]
Ag NP's	GCE	Leaf extract of *Talinum triangulare* (TT)		Increased antimicrobial activities observed	[32]
Ag NP's	As-prepared Ag electrode	Leaf extract of *Datura metel*		Supercapacitor energy storage properties observed	[33]

Type of nano-particles (NP's)	Type of electrode	Plant extract	Analyte/Remark	Detection limit/Remark	Reference
Ag NP's	Glassy carbon electrode (GCE)	*Mimosa pudica* root extract	Significant antimicrobial properties against gram-positive and gram-negative microorganisms observed; much lower sensitivity towards dopamine detection	0.5 mmol/l detection limit of Dopamine	[34]
Ag NP's	Carbon paste electrode (CPE)	*Hagenia abyssinica (Brace)*		Lower charge transfer resistance observed at NPs modified electrode	[35]
Ag NP's	GCE	*Solanum mammosum*		Increased antimicrobial activity against Escherichia colli observed	[36]
Ag NP's	GCE	*Setaria verticillata*		Metal impurities of organic effluents detected	[37]
Ag NP's	AgNPs overlay on Ni foil as the working electrode.	*Datura metel* L.		Energy storage properties like supercapacitor observed	[38]
Ag NP's	GCE	*Talinum triangulare*		Significant antimicrobial properties against gram-positive and gram-negative microorganisms observed	[39]
Ag NP's	Various electrodes	Various plant extracts		Applied in different environmental analyses	[40]
Ag NP's, Au NP's, Ag–Au bimetallic NPs	Bare platinum (Pt) and modified Pt electrodes	*Solidago canadensis*		Pt/Au–Ag electrode was more electroactive with a greater current response than Pt/Au- and Pt/Ag-modified electrodes.	[41]
Ag NPs/Au NP's	GCE and screen-printed carbon electrode (SPCE)	*Rumex roseus* (RR)	H_2O_2	1.3 μmol/l	[42]
Au NP's	Comparing a phyto-AuNPs/GCE with an empty GCE	*Fragaria vesca* *Ribes nigrum* *Ribes uva-crispa*		Better performances in respect to detection of uric and ascorbic acid observed	[43]
Ag NPs, AuNPs, and Ag−Au bimetallic nanoparticles	Modified platinum electrode (PtE)	*Citrus sinensis*	Increased reversibility of ferrocyanide/ferricy anide redox probe observed	2.02 μmol/l	[44]
Au/Ag NP's	ITO	Grape seed extract	Resveratrol	Nanomolar concentration range	[45]
Au NP's and Ag NP's	Modified GCE	Flower extract of *Rosa damascena*		Increased reversibility of hexacyanoferrate redox couple	[46]
AuNPs at polyaniline (PANI) film	GCE	Grape	Resveratrol	87 nmol/l	[47]
Au NP's	GCE	*Magnolia kobus*		Suitable material for various biomedical determinations	[48]
Au NP's	Modified anthocyanin-based carbon paste electrode	Black rice extract	Lead, cadmium and copper	9.178 μg/l for Pb; 86.327 μg/l for Cd; 85.373 μg/l for Cu	[49]

Type of nano-particles (NP's)	Type of electrode	Plant extract	Analyte/Remark	Detection limit/Remark	Reference
Gold and palladium nanoparticles on graphene flakes (Au/PdNPs5 GRF)	GCE	Caffeic acid	Caffeic acid	6 nmol/l	[50]
Ag-Cu bimetallic NP's	GCE	*Citrus limon* – India		Increased reversibility of [Fe (CN)6]3-/4- in 0,1 mol/l KCl	[51]
$Cu/Cu_2O/CuO$	GCE	Polyphenols of pomegranate	Ethanol	0.09 μmol/l	[52]
Copper oxide NP's	Carbon paste electrode modified with polyaniline (PANI)	*Ficus elastica*	Cd^{2+}, Pb^{2+}, and Hg^{2+}	Cd^{2+}, Pb^{2+}, and Hg^{2+}(0.11, 0.16, and 0.07 μg l^{-1}, respectively)	[53]
CuO NPs	Pm-CuO/ITO electrodes	*Annona squamosa*	H_2O_2	574 μmol/l	[54]
CuO NP's	graphite electrode	*Caesalpinia bonducella* seed extract	Riboflavin	1.04 nmol/l	[55]
Nanocrystalline CuO	Carbon paste electrode modified using CuO NPs	*Aloe vera latex*	Paracetamol and D-glucose in 1 mol/l KOH solution	1 mmol/l both for para-cetamol and for glucose	[56]
Copper Ferrite ($CuFe_2O_4$) NPs	GCE	*Aloe vera* plant extract and *Flacourtia indica* root extract		Significant antimicrobi-al properties observed	[57]
ZnO NP's	GCE	*Carica papaya* seed	Silymarin	0.08 mg/l	[58]
ZnO NP's	Modified screen plate carbon	Citrus peels extracts		Enhanced catalytic activities and increased reversibility of standard redox couples observed	[59]
ZnO NP's	GCE	Sageretia thea natural extracts		Enhanced catalytic activity observed	[60]
$ZnSnO_3$ NP's	GCE	*Aspalathus linearis*		Improved reversibility of hexacyanoferrate in KOH observed	[61]
Sm NPs MgO, and ZnO NPs	Carbon paste electrode	*Cicer artinum* powder		Efficient removal of removal of rodhamin-B (rh-B) and malachite green (MG) dyes	[62]
MgO NP's	Carbon paste working electrode	*Withania somnifera*		Significant antibacterial activities observed	[63]
MoO_3 NP's	Electrode with graphite powder	*Centella asiatica* plant powder		Improved electrochemi-cal reversibility of standard redox couples	[64]
Nickel Ferrite ($NiFe_2O_4$) NP's	GCE	*Persa americano* seeds		Increased electrochemical reversibility of standard redox couples	[65]
Fe_3O_4 NPs	Modified screen-printed carbon electrode (SPCE)	*Callistemon viminalis*		Increased reversibility of various standard redox couples	[66]
NiO NPs	GCE	*Opuntia ficus indica* commonly known as cactus		Significant antimicrobi-al activity observed	[67]
PbO NPs	GCE	*Mangifera indica*		Increased antimicrobial activities observed	[68]

*GCE–glassy carbon electrode; CPE–carbon paste electrode; ITO–Indium tin oxide electrode

3. OUTLOOKS FOR THE FUTURE

Green chemistry is an emerging discipline focused on implementing principles that minimize the utilization and generation of hazardous chemical substances. Consequently, adopting greener techniques helps reduce the environmental footprint associated with industrial practices. Significant efforts have been made in the last 20 years to apply these methods as potential solutions to costly processes and to minimize the use of toxic materials inherent in traditional synthesis approaches. In this context, the synthesis of green nanomaterials is considered an optimal approach for mitigating the negative consequences of their production and use, thereby lowering many risks associated with nanotechnology. Currently, there is growing research interest dedicated to the production of metallic nanomaterials using various environmentally friendly synthesis protocols. Over the past 15 years, green nanomaterials have been swiftly integrated into developing voltammetric sensors designed for microbiological applications and quantitative determination of various analytes. While a significant number of voltammetric sensors based on "green nanoparticles" show potential utility for analysis across different fields, most of these devices have only been validated in laboratory settings. Due to the limited availability of commercially accessible voltammetric green nano-sensors, it is strongly recommended that precise and accurate validation studies be conducted for the practical deployment of these electrochemical sensors. Furthermore, it is imperative to conduct studies on the toxicity and degradation of these nanomaterials. All these concerns must be thoroughly addressed before the eventual commercial introduction of these sensors. While numerous authors detail specific voltammetric biosensors based on green-nano particles, challenges always arise from interferences within complex matrices when operating in real systems. The enhanced electronic conductivity of unmodified electrodes due to metallic nanoparticles makes their surfaces suitable platforms for attaching various ligands and receptors. The integration of green nanoparticles with specific ligands holds the potential to create highly specific voltammetric biosensors, which could eventually find applications in diagnostics in medicine or analytical purposes in chemistry.[70,71] Enhancements in this aspect are necessary before the realization of reliable voltammetric biosensors based on green nanomaterials. In a broader context, it is anticipated that voltammetric sensors utilizing "green" nanomaterials could pave the way for creating numerous practical analytical devices, offering viable alternatives to many costly diagnostic and instrumental systems.

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