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Clove (*Syzygium aromaticum*)-mediated metallic nanoparticles: Synthesis, characterization, and possible pharmacological and industrial applications

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Abbreviations

AFM	atomic force microscopy
AgNPs	silver nanoparticles
AlNPs	alumina nanoparticles
AuNPs	gold nanoparticles
CB	clove bud
CuNPs	copper nanoparticles
CuONPs	copper oxide nanoparticles
DLS	dynamic light scattering
FeNPs	iron nanoparticles
FTIR	Fourier transform infrared spectroscopy
GC-MS	gas chromatography/mass spectroscopy
h	hour
IC_{50}	50% inhibitory concentration
MgONPs	magnesium oxide nanoparticles
MIC	minimum inhibitory concentration
min	minutes
MnONPs	manganese oxide nanoparticles
MNPs	metal nanoparticles
MoNPs	molybdenum nanoparticles
NiNPs	nickel nanoparticles

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NPs	nanoparticles
NR	not reported
PdNPs	palladium nanoparticles
sec	seconds
SEM	scanning electron microscopy
TEM	transmission electron microscopy
TiO_2NPs	titanium oxide nanoparticles
UV-vis	ultra violet-visible
ZnONPs	zinc oxide nanoparticles
ZnSNPs	zinc sulfide nanoparticles

1. Introduction

Nanotechnology offers practical applications to different fields, stretching from chemical techniques to environmental and medicinal innovations. This is mainly because nanomaterials have completely different physicochemical from individual atoms, compounds, and bulk materials (Etheridge et al., 2013). Nowadays, NPs are being explored for a plethora of industrial applications such as electronics, energy, water purification, agriculture, and cosmetics (Kargozar and Mozafari, 2018). Different types of NPs have been studied extensively for biomedical applications like drug delivery, medical imaging, diagnosis, and therapeutics (Ramos et al., 2017).

Several metal precursors have been used to synthesize MNPs in mono and multimetallic forms. MNPs possess unique optoelectrical properties due to their localized surface plasmon resonance, which can be utilized in several applications (Khan et al., 2019). Applying these MNPs in the different fields is dependent on the type of metal(s) used. To exemplify, the metal silver has been historically known for its antibacterial activity (Clement and Jarrett, 1994), and consequently, AgNPs are mainly studied for their antibacterial potential (Le Ouay and Stellacci, 2015). Plant phytochemicals have enabled researchers to green synthesize and stabilize MNPs without the need for applying expensive, toxic, and environmentally harmful materials in the conventional chemical synthesis methods (Gour and Jain, 2019). Besides contributing to the synthesis, these phytochemicals surround the MNPs rendering them more biologically active (Afreen et al., 2020).

The widely used Indonesian spice *Syzigium aromaticum* (L.) (clove) belongs to the family Myrtaceae (Batiha et al., 2019). The aromatic, nail-shaped CB is a clove's dried, unopened flower bud (Adaramola and Onigbinde, 2016). The traditional use of cloves is known, which is also supported by the scientific reports that investigated the clove's extracts, essential oil, and isolated compounds for their antiseptic (Meeker and Linke, 1988), antibacterial (Ajiboye et al., 2016), antifungal (Kaur et al., 2019), antiviral (Cortés-Rojas et al., 2014), and anticancer activities (Banerjee, 2005). Clove essential oil has enormous applications in the food, sanitary, biomedical, pharmaceutical, active packaging, and cosmetics industries due to its biological properties, including antioxidant, antimicrobial, antiseptic, analgesic, and anticancer activities (Nowak et al., 2012). A recent review by Batiha et al. (2019) summarizes the reports describing the traditional use, chemical constituents, and the pharmacological actions of different clove components.

2. Role of clove phytochemicals in the synthesis

The green chemical reduction of the metal salts by plants involves many phytochemicals found in their extracts. These reducing phytochemicals can reduce the metal ions to their pure atoms (e.g., Ag^{3+} to Ag^0). The electron donor functional groups can achieve this to complete the reduction step. Afterward, the agglomeration of these reduced metal atoms occurs, leading to the development of oligomeric clusters followed by the formation of the MNPs (Iravani et al., 2014). Depending on the chemical nature of the plant phytochemicals, the stabilization of the formed MNPs can be done without adding external stabilizers. However, when using the plant extract in the synthesis of the MNPs, it is not easy to single out a particular phytocomponent that is responsible for the reduction and stabilization of the MNPs because of the presence of several and different phytochemicals in the plant extract (Ovais et al., 2018). Therefore, only speculated mechanisms were reported to explain the mechanism of the MNPs synthesis using plant extracts (Dauthal and Mukhopadhyay, 2016). Till now, phytochemicals such as phenolics (e.g., flavonoids, phenolic acid, and terpenoids), organic acids, and proteins are deemed accountable for the synthesis of the MNPs (Ahmad et al., 2019; Mallikarjuna et al., 2014; Ovais et al., 2018).

Several studies also have suggested that different phytochemicals of different functional groups (e.g., R—CH, C—O, C═O, N—H, C—N, and O—H) from *S. aromaticum* (Table 1) are responsible for the synthesis of MNPs (Bagyalakshmi et al., 2019; A. Jain et al., 2018; Kanneganti et al., 2014; Kumar et al., 2017; Lakhan et al., 2020; Maheswari et al., 2020; Parlinska-Wojtan et al., 2018; Rajesh et al., 2018; Sathishkumar et al., 2018; Shanthi et al., 2017; Wang and Bai, 2020). These studies based these conclusions on analyzing the FTIR spectra of the CB or clove leave extracts and the produced MNPs.

The chemistry of *S. aromaticum* has been investigated, and this spice is known to include flavonoids, tannins, phenolic acids, and sesquiterpenes. GC-MS analysis has shown that more than 75% of clove essential comprises terpenoid eugenol (Jirovetz et al., 2006). The functional groups in the terpenoid structures are believed to have a significant role in synthesizing and stabilizing MNPs (Ur Mashwani et al., 2016). Several of the studies reviewed herein also suggested that eugenol is mainly responsible for synthesizing MNPs from CB. The following mechanism was suggested for the MNPs synthesis from eugenol: the presence of strong electron-withdrawing methoxy and allyl groups in the *ortho* and *para* positions to the O—H group facilitates the release of proton and renders eugenol in anionic form. Afterward, resonating anionic structures of eugenol are formed (Fig. 1), and two electrons are released in the process (Kaur et al., 2013; Parlinska-Wojtan et al., 2018). This is also justified by the presence of transmittance of C—O and C═O peaks and the disappearance of the O—H in the FTIR spectra of the generated MNPs from CB (Parlinska-Wojtan et al., 2018).

Eugenol is practically insoluble in water (Yuwono et al., 2002), and hence the use of water to extract eugenol and essential oils, in general, has shown less yield compared to the use of other organic solvents and distillation methods. Clove oil yield was low as 0.44%, with eugenol content less than 5% when macerating the buds with water for isolation for five days (Shafira et al., 2020). The study showed that the highest eugenol content could be obtained using the Soxhlet apparatus (Shafira et al., 2020). Another study also detected lower clove oil yield (around 15%) when using water than other solvent systems such as 80% acetone and 80% methanol (Adaramola and Onigbinde, 2016). Eugenol was not even detected in the water extract of *S. aromaticum* in one study using thin-layer chromatography

Table 1 Summary of the different types of MNPs from *S. aromaticum*.

Metal nanoparticles	Size (nm)	Shape	Applications	Plant part used	General comments on the synthesis	Reference
AgNPs	30–60	Spherical	NR	Buds	Synthesis was done using microwave	Deshpande et al. (2012)
	20–149	Spherical	NR	Buds	Stirring at room temperature for 24 h	Vijayaraghavan et al. (2012)
	90	Quasi-spherical	Substrate for detection of explosives	Buds	Tested variable volumes of clove extract and silver salt	Sil et al. (2014)
	59 to 98	Polydispersed	Wound healing and antimicrobial	Buds	Stirring at room temperature for 24 h	Varalakshmi et al. (2015)
	12 to 85	Polydispersed	Antimicrobial	Buds	Stirring in the dark for overnight	Parlinska-Wojtan et al. (2018)
	5.0 to 40	Spherical	Anticancer		Stirring at different temperatures for 10 min	Kumar et al. (2017)
	23	Mostly spherical	Antimicrobial/ dye degradation	Buds	Different volumes and concentrations	Ajitha et al. (2019)
	50	Polydispersed	Antimicrobial	Buds	Stirring at 27°C for 1 h	Kaur et al. (2013)
	25 to 50	Cubic	Antimicrobial	Eugenol from buds	Synthesis from eugenol	Tekin et al. (2019)
	31 to 72	Polydispersed	Antimicrobial	Clove essential oil	Synthesis from clove essential oil under different pH levels	de Maciel et al. (2019)
	>200	Spherical	Antibacterial	Clove essential oil	Microemulsion technique	Gao et al. (2017)
	9.42	Spherical	Antibacterial/ antidiatom	Buds	Stirring in dark for 24 h	Lakhan et al. (2020)
AuNPs	100 to 300	Mainly triangular when using 1:1 clove extract to gold salt	NR	Buds	Optimization by using different volumes of the CB extract	Singh et al. (2010)

Table 1 Summary of the different types of MNPs from *S. aromaticum*—cont'd

Metal nanoparticles	Size (nm)	Shape	Applications	Plant part used	General comments on the synthesis	Reference
	5.0 to 100	Irregular	NR	Buds	Stirring the CB extract with the metal salt for 1 h	Raghunandan et al. (2010)
	NR	Irregular	Anticancer	Buds	Same methodology as reported in Raghunandan et al. (2010)	Raghunandan et al. (2011)
	NR	Square	NR	Buds	Mixing the CB extract into preheated (at 50°C) gold salt solution	Sharma et al. (2017)
FeNPs	50 to 100	Spherical	NR	Buds	Stirring the aqueous extract with $FeCl_3$ at 50–60°C, followed by stabilization with 1% chitosan and 1% PVA	Pattanayak et al. (2013)
	NR	Spherical	NR	Buds	Mixing Fe(I) and Fe(II) sulfate solutions with the CB aqueous extract at room temperature	Sujin Jeba Kumar et al. (2020)
	13.5	Spherical	Water treatment	Buds	Reaction at pH 4, precipitation of clove-FeNPs occurred after 40 min	Mondal and Purkait (2018)
	52	Irregular	Anticancer	Buds	Stirring the aqueous extract with $FeCl_3$ at 70°C for 5 min, followed by incubation at room temperature	Bagyalakshmi et al. (2019)
PdNPs	10 ± 1.42	Spherical	Catalysis	Buds	Mixing Palladium Chloride with a premixed solution of *S. aromaticum* and acacia water extracts at pH 9 and 55°C	Saxena et al. (2018)

Continued

Table 1 Summary of the different types of MNPs from *S. aromaticum*—cont'd

Metal nanoparticles	Size (nm)	Shape	Applications	Plant part used	General comments on the synthesis	Reference
	4.49	Spherical	Catalysis	Leaves	Wet impregnation of clove leaves and palladium chloride followed by stirring for 3h at 50°C	Wang and Bai (2020)
	20 ± 5	Spherical	Anticancer	Buds	Stirring with Palladium Chloride solution at 70°C for 30min	Shanthi et al. (2017)
ZnSNPs	165.9	Spherical	Antimicrobial/ photocatalysis	NR	*S. aromaticum* was used to cap the ZnSNPs synthesized using zinc sulfate and thiourea	Sathishkumar et al. (2018)
	46	Spherical	Antimicrobial	Buds	Stirring with zinc sulfate for 2h	Sathishkumar et al. (2017)
ZnONPs	35.69	Triangular/ hexagonal	Antifungal	Buds	Synthesis was done using combustion method with zinc nitrate	Lakshmeesha et al. (2019)
	NR	NR	Antibacterial	Buds	Stirring methanol CB extract with the metal precursor for 1h followed by thermal annealing	Osaili et al. (2019)
	50	Hexagonal	Photocatalysis/ Antimicrobial/ Antioxidant	Buds	Used ethanol CB extract	Anvarinezhad et al. (2020)
CuNPs	15	Spherical	Antimicrobial	Buds	Stirring with copper acetate for 15min at 30°C	Rajesh et al. (2018)
	NR	Spherical	Antimicrobial	Buds	Stirring the CB aqueous extract with copper nitrate at pH 14	Aziz and Jassim (2018)

Table 1 Summary of the different types of MNPs from *S. aromaticum*—cont'd

Metal nanoparticles	Size (nm)	Shape	Applications	Plant part used	General comments on the synthesis	Reference
CuONPs	NR	NR	Antibacterial	Buds	Stirring methanol CB extract with the metal precursor for 1 h. The NPs were recovered by annealing	Osaili et al. (2019)
MgONPs	2.0 to 4.0	Spherical	Colorimetric detection of Fe^{+3}	Buds	Stirring with magnesium acetate for 30 min at room temperature	Jain et al. (2018)
	~7.0	Mostly spherical	pH sensing	Buds	A similar procedure was reported (Jain et al., 2018) and modified with L-lysin	Jain et al. (2019)
MnONPs	4.0	Spherical	Electrochemical sensing of P-nitrophenol	Buds	Optimization by varying the concentration and volume of the metal salt and CB extract as well as the temperature	Kumar et al. (2017)
AlNPs	3.0 to 5.0	Spherical	NR	Buds	Microwave-assisted synthesis	Hasanpoor et al. (2017)
TiO_2NPs	9.5	Spherical	Anticancer/ Antibacterial	Buds	Modification of chemically synthesized TiO_2NPs with CB aqueous extract via hydrothermal method	Maheswari et al. (2020)
MoNPs	19.47	Spherical	NR	Buds	Stirring the extract with the metal salt for 15 min at 60°C until complete evaporation, followed by calcination at 700°C	Kanneganti et al. (2014)

Continued

Table 1 Summary of the different types of MNPs from *S. aromaticum*—cont'd

Metal nanoparticles	Size (nm)	Shape	Applications	Plant part used	General comments on the synthesis	Reference
NiNPs	40	NR	Antimicrobial	Buds	Stirring the extract with the metal salt for 15 min in a 1:1 ratio	Pavan et al. (2016)
Ag-Au-PdNPs	11.61 ± 6.5		Catalysis/ antimicrobial	Buds	One-step chemical reduction of the metal precursors using CB in combination with *Aegle marmelos* leaves extract	Rao and Paria (2015)
Ag-AuNPs	Variable according to the ratio of the metal salts	Polydispersed	Catalysis	Buds	Chemical reduction with different ratios of the metal salts at room temperature for 15 min	Sharma et al. (2020)

(El Ghallab et al., 2019). Therefore, presenting any assumption regarding the role of eugenol in the MNPs synthesis should be made with caution, specifically when using the water extract. Indeed, most of the reviewed papers herein described the synthesis of the MNPs from CB water extract. On the other hand, only a few described the synthesis from CB essential oil (de Maciel et al., 2019), isolated eugenol (Tekin et al., 2019), or CB extract using other organic solvents or techniques, e.g., steam distillation (Varalakshmi et al., 2015), hexane (Lakshmeesha et al., 2019), 30% ethanol (Anvarinezhad et al., 2020), or 80% methanol (Osaili et al., 2019).

2.1 AgNPs

AgNPs have unique physicochemical properties and are employed in different biological applications. The use of colloid silver, silver salts, and other silver products has been documented since ancient times (Alexander, 2009). Silver is mainly known for its antimicrobial uses, and consequently, many studies aimed to evaluate the effect of AgNPs against microbes (Dube et al., 2020; Majoumouo et al., 2019; Yin et al., 2020). Other studies also reported the wound healing (Konop et al., 2016), anti-inflammatory (Abdelhafez et al., 2020), and anticancer activities of AgNPs (Barua et al., 2017).

The aqueous phyto-constituents of CB produced AgNPs of the broad particle size range (20–149 nm) at room temperature using silver nitrate solution for 24 h (Vijayaraghavan et al., 2012). To accelerate the nanoparticles synthesis, Deshpande et al. used microwave radiation to synthesize

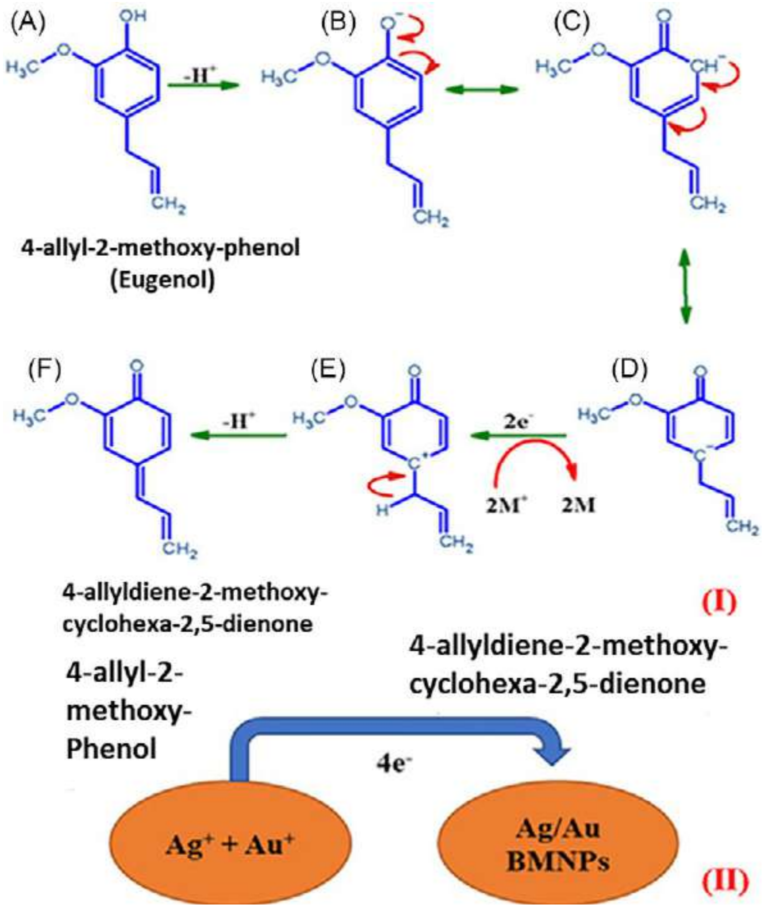

FIG. 1

Suggested mechanism of MNPs synthesis by eugenol (Sharma et al., 2020).

clove-AgNPs in a remarkably short time (120 s) (Deshpande et al., 2012). From the FTIR results, the authors suggested that the water-soluble polyphenolic (flavonoids) content of the CB was responsible for the reduction and the stabilization of the clove-AgNPs (Deshpande et al., 2012). The same methodology was adapted by Parveen et al. to reproduce clove-AgNPs with similar characteristics (Parveen et al., 2018). In this study, the clove-AgNPs, formulated in a cream form, were further evaluated for their wound healing properties. The cream containing 5% clove-AgNPs exhibited faster wound healing (28 days) compared to the 3% clove-AgNPs cream (46 days) (Parveen et al., 2018). The 5% clove-AgNPs cream wound healing mechanism was attributed to the increased collagen deposition, fibroblast production, and the reduction of macrophages (Parveen et al., 2018). Another study also reported the fabrication of clove-AgNPs based sponge dressing with antimicrobial activity, which showed almost 97% wound healing in rats compared to only 58% in control-treated rats (Varalakshmi et al., 2015).

Clove-AgNPs exhibited significant antimicrobial activity when tested with various bacteria and fungi. Parlinska-Wojtan et al. (2018) found that 40 X dilution of clove-AgNPs (original concentration was not reported) had bacteriostatic activity against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*, whereas the aqueous clove extract did not have any bacteriostatic action. Another interesting study was conducted by Ajitha et al. (2019), in which the authors tested different volumes of *S. aromaticum* aqueous extract and different concentrations of silver nitrate solution. The transmission electron microscopy (TEM) analysis data revealed an inverse proportional relationship between the concentration of silver nitrate and the size of the clove-AgNPs; the reverse was true concerning the volume of the *S. aromaticum* aqueous extract (Ajitha et al., 2019). Zone inhibitions produced by the clove-AgNPs indicated strong antimicrobial activity, with the largest zones observed against *Pseudomonas* spp. and *Bacillus* spp. (Ajitha et al., 2019). By observing the changes in UV-vis spectra, the authors also assessed the catalytic activity of phyto-mediated AgNPs, which reduced the absorbance of three pollutant organic dyes, viz., 4-nitrophenol, methylene blue, and rhodamine B (Ajitha et al., 2019). Another study showed that clove-AgNPs have more antibacterial activity against *E. coli*, *S. aureus*, and *Salmonella typhi* strains than the CB aqueous extract (Sameen et al., 2014). A study by Kaur et al. (2013) showed that clove-AgNPs have bactericidal effects against the growth of *Bacillus subtilis*. Tekin et al. (2019) adapted the same methodology from Kaur et al. (2013) to synthesize AgNPs from isolated eugenol (eugenol-AgNPs) from the methanol extract of *S. aromaticum*. The zone inhibitions of the eugenol-AgNPs showed antibacterial activity against *E. coli* and *S. aureus* but less antifungal activity against *C. albicans* (Tekin et al., 2019). de Maciel et al. (2019) synthesized AgNPs from the essential oil of *S. aromaticum*. Their UV-vis, DLS, and TEM analysis data showed that the synthesis could be optimized by varying the pH conditions (de Maciel et al., 2019). For instance, the AgNPs synthesized at pH 8.0 gave spherical NPs an average size of 35.5 nm, while the synthesis at pH 10 formulated NPs of different shapes with an average diameter (37.9 nm) according to their TEM micrographs (de Maciel et al., 2019). The pH variable AgNPs also showed different antimicrobial activity as determined by the broth microdilution assay. For example, the AgNPs at pH 8.0 gave MIC values of 60 and 80 μL/mL against *E. coli* and *S. aureus*, respectively. On the other hand, the AgNPs at pH 9.0 had an MIC of 100 μL/mL against both bacteria (de Maciel et al., 2019). The AgNPs produced from clove oil via the microemulsion method inhibited the growth of *E. coli* and *S. aureus*. This activity was decreased upon removal of clove oil from the AgNPs by ultrasonic cleaning, which shows the role of clove oil in enhancing the antibacterial activity of AgNPs (Gao et al., 2017). The study by Lakhan et al. (2020) showed that clove-AgNPs inhibited the growth of marine community bacteria using the disk diffusion method. The clove-AgNPs inhibited the growth of the marine algae *Nitzschia closterium*. The number of the algae was significantly decreased after the treatment with clove-AgNPs in a dose-dependent manner. This inhibition was found consistent for seven days. On the other hand, the CB extract did not show similar antidiatom activity (Fig. 2). The authors concluded that clove-AgNPs could be utilized to prevent microorganisms responsible for the formation of micro-fouling in artificial marine surfaces (Lakhan et al., 2020).

The anti-inflammatory effects of clove-AgNPs were also reported. Varghese et al. compared the anti-inflammatory activities of aqueous clove extract and its AgNPs. The results showed that clove-AgNPs induced higher scavenging activity and protein denaturation inhibition in a dose-dependent mode, reducing anti-inflammatory responses (Varghese et al., 2017). Moreover, clove-AgNPs downregulated the in vitro expression of interleukin-1 beta by 80% compared to 60% achieved by the aqueous clove extract. Unfortunately, the authors did not report the physical characteristics of the clove-AgNPs, such as their size or morphology.

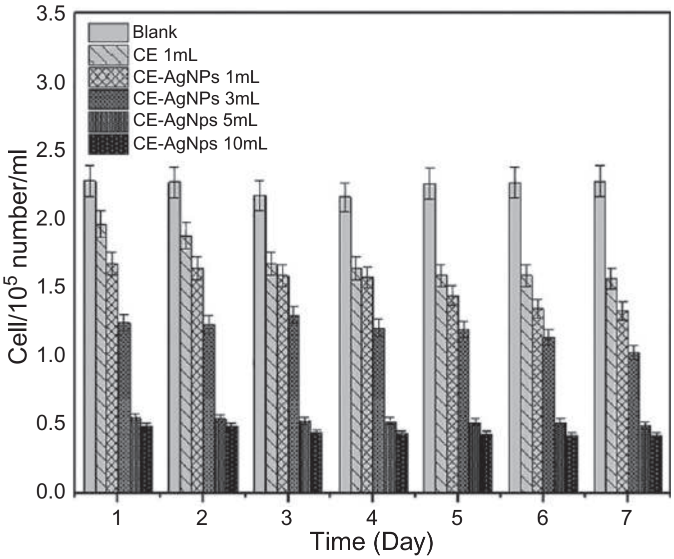

FIG. 2

Effect of clove-AgNPs (denoted CE-AgNPs) and CB aqueous extract (denoted CE) treatment on the *N. closterium* diatom cell number (Lakhan et al., 2020).

The anticancer actions of clove-AgNPs were also studied. Venugopal et al. showed that clove-AgNPs were able to induce cell death by increasing the treatment concentrations. The calculated IC_{50} value of clove-AgNPs was 60 and 50 μg/mL against breast and lung cancer cell lines, respectively. On the other hand, the aqueous extract of *S. aromaticum* exhibited less anticancer effect with an IC_{50} value of 70 μg/mL against both the cell lines (Venugopal et al., 2017). Furthermore, the frames obtained from the fluorescent microscope of the cells stained with acridine orange, ethidium bromide, and DAPI revealed that clove-AgNPs induced cell death via apoptosis (Venugopal et al., 2017).

2.2 AuNPs

AuNPs have attracted the attention of biomedical researchers globally not only because of their unique optical and electrical properties and ease of synthesis, but also for two main reasons: first, AuNPs are proven biocompatible agents due to their chemical and physical stability (Hu et al., 2020) and secondly, S- and N-containing AuNPs are easy to be functionalized with biologically active molecules attributed to the ability of AuNPs to form stable chemical bonds with S- and N-containing organic molecules (Bai et al., 2020).

One of the first reports about the synthesis of AuNPs from clove (clove-AuNPs) was done by Singh et al. (2010). The resultant clove-AuNPs varied in size distribution and morphology by changing the ratio between the CB aqueous extract and the gold salt (Singh et al., 2010). The authors used L-cysteine to functionalize the clove-AuNPs, useful for future biological conjugation (Singh et al., 2010). In the same year, Deshpande et al. mixed solutions of macerated aqueous extract of *S. aromaticum* and gold salt to synthesize clove-AuNPs in 1 h. Different methods were utilized, such as UV-vis, TEM, SEM, and AFM analyses, to characterize the clove-AuNPs, and the formation of the NPs has attributed to the water-soluble flavonoids as shown by FTIR results (Raghunandan et al., 2010). Later, the same methodology was used with modification to synthesize clove-AuNPs in 4 h (Hameed et al., 2014). The synthesized clove-AuNPs inhibited the urease and carbonic anhydrase enzymes, which can be useful in treating many diseases such as glaucoma, epilepsy, and stones formation prevention (Hameed et al., 2014). Also, to explore the anticancer potential of clove-based AuNPs, different cancer cell lines were treated with biofabricated AuNPs from CB (Raghunandan et al., 2011). The results from the XTT assay showed that clove-AuNPs had an IC_{50} as low as 20 μg/mL on HeLa (human cervix), HEK-293 (human kidney), and HT-29 (human colorectal) cell lines, and 30 μg/mL against K-562 (leukemia). The authors suggested that the antiproliferation activity of clove-AuNPs was due to their irregular morphology and the free-radical scavenging as indicated by the nitric oxide assay (Raghunandan et al., 2011).

2.3 FeNPs

The number of studies reporting the green synthesis of FeNPs is fewer compared to the reports pertaining to the green synthesis of Au- and AgNPs. It is mainly because reduced iron is easily oxidized in solution due to its particle instability and high aggregate tendency attributed to its low surface charge. Therefore, it is more difficult to obtain FeNPs (Sujin Jeba Kumar et al., 2020). Additionally, due to the superparamagnetic properties, modifiable surfaces, and low toxicity (Chang et al., 2011), FeNPs have been highly considered for cancer treatment, mainly as a drug carrier (Kanagesan et al., 2013). FeNPs are also useful in catalysis because of their uniform distribution in solutions, high reactivity, and ease of separation owing to their magnetic properties (Sujin Jeba Kumar et al., 2020).

A study conducted by Sebastian et al. evaluated the ability of 24 plant water extracts collected from peninsular India (Sebastian et al., 2018). FeNPs were only synthesized from the water extract of eight plants, including the leaves water extract of *S. aromaticum*, which immediately produced the FeNPs (clove-FeNPs) (Sebastian et al., 2018). Interestingly, the amount of phenolics in the reaction medium was reduced after the synthesis by more than 20%, citing the role of phenolic contents of *S. aromaticum* in the formation of clove-FeNPs (Sebastian et al., 2018). In another study, CB aqueous extract was used to produce multiphase FeNPs instantaneously (Sujin Jeba Kumar et al., 2020). Other plants were also tested but did not give positive results. However, the XPS analysis confirmed the presence of both Fe^{2+} and Fe^{3+} to determine the phases of the FeNPs (Fig. 3). Furthermore, the authors established the superparamagnetic behavior of the produced clove-FeNPs, which render these NPs useful as drug carriers or for hyperthermia treatment of cancer (Sujin Jeba Kumar et al., 2020).

Nowadays, there is increased usage of magnetic nanoparticles in catalysis owing to their high dispersibility, increased reactivity, and ease of separation. This is facilitated by their magnetic properties, nanosize, and having both homogenous and heterogeneous catalysis properties. Therefore, Clove-FeNPs were evaluated for their water detoxification properties. As a result, the clove-FeNPs loaded on a polymeric membrane were found to reduce nitrobenzene to aniline and adsorb fluorides, which can be utilized to remove harmful nitro-containing compounds and fluorides from water (Mondal and Purkait, 2018).

One study by Thenmozhi et al. (2019) successfully combined the anticancer properties of both the FeNPs and *S. aromaticum* by loading the methanolic extract on PVP-stabilized FeNPs (Thenmozhi et al., 2019). The MTT results showed that the biofunctionalized FeNPs inhibited the growth of the MCF-7 cell line (breast cancer) (Thenmozhi et al., 2019). A follow-up study on the same NPs

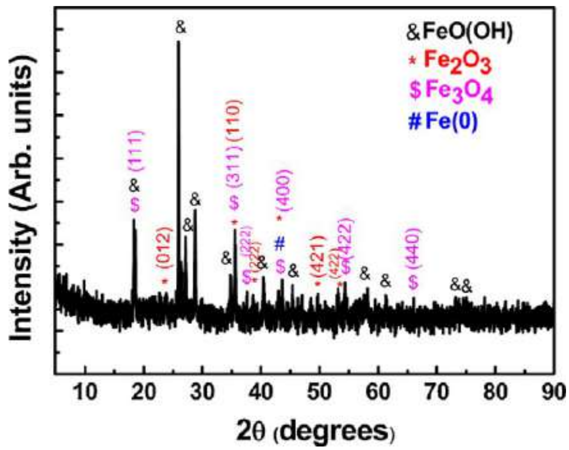

FIG. 3

XRD pattern of the multiphase clove-FeNPs (Sujin Jeba Kumar et al., 2020).

confirmed, using flow cytometry assays, that these NPs induce apoptosis on MCF-7 by triggering caspase-3, caspase-8, and caspase-9 (Thenmozhi, 2020). Furthermore, clove-FeNPs enhanced bee venom's antioxidant and anticancer activities against lung cancer (Bagyalakshmi et al., 2019). The authors described the biological effect of mixing clove-FeNPs with bee venom at different ratios. Based on the DPPH assay, it was found that the ratio 1:1 possessed higher antioxidant effects with IC_{50} of 56 μg/mL compared to 66 μg/mL when testing the bee venom alone. Furthermore, the same mixture ratio induced more than 50% cell death at a 250 μg/mL concentration after 4 h of incubation with lung cancer cell line (A549) (Bagyalakshmi et al., 2019). The limitation in this study was the absence of a comparative study to show the anticancer effect of bee venom and clove-FeNPs individually in their results.

2.4 PdNPs

Like other metal nanoparticles, PdNPs have been studied because of their imitable optical, electronic, and chemical properties, useful in several industrial and biomedical applications. However, unlike the NPs from other noble metals, PdNPs are more considered for applications such as catalysis, sensors, and fuel cells (Saxena et al., 2018). Pd metal is highly considered in catalysis as it is efficient in regulating various chemical processes such as oxidation, carbon-carbon, and carbon-heteroatom bond formation, hydrogenation, and carbonylation dehalogenations (Tsuji, 2004). For example, Pd is used as a catalyst in Suzuki coupling reaction, which, due to its mild conditions and tolerance for functional groups, is essential in synthesizing building molecules for several pharmaceutical compounds (Martin and Buchwald, 2008). The catalytic activity of PdNPs is further enhanced because of their high surface-to-volume ratio and unique SPR (Wang and Bai, 2020). Furthermore, PdNPs can be easily immobilized on different solids, which allows their recycling from the reaction medium upon catalysis (Monguchi et al., 2017).

Saxena et al. used a combination of the CB extract and the plant surfactant (acacia) to produce PdNPs (Clove-PdNPs) in a controlled pH medium (Saxena et al., 2018). The fabricated clove-PdNPs were successfully immobilized on glass and wafer silicon slides using the evaporation-induced self-assembly technique. The authors compared the chemical and electrical catalytic ability of both the immobilized and free clove-PdNPs. The heterogeneous catalytic activity of the immobilized clove-PdNPs was observed by reducing nitrobenzene in the presence of sodium borohydride, which was found to be higher than the free PdNPs. Clove-PdNPs immobilized on a fluorine-doped tin oxide glass surface (anode) exhibited higher current density and lowered charge-transfer resistance when compared to the free clove-PdNPs (Saxena et al., 2018). These results indicate the potential use of clove-PdNPs in fuel cells.

Furthermore, Wang and Bai explored the catalytic efficiency of clove-PdNPs synthesized from clove leaves powder for Suzuki coupling reaction (Wang and Bai, 2020). Using micro-infrared spectroscopy, the synthesis of clove-PdNPs was attributed to a hydroxyl functional group found in the phenolic, polysaccharides, and flavonoids content of clove leaves. The clove-PdNPs were also found to increase the yield of 4-bromonitrobenzene and phenylboronic acid (products in Suzuki coupling reaction) by 98%. This percentage was decreased to 91% after seven reaction cycles. However, the percentage remained the same after removing the catalyst (clove-PdNPs), which shows that clove-PdNPs are excellent heterogeneous catalysts for Suzuki coupling reaction (Fig. 4) (Wang and Bai, 2020).

The potential use of clove-PdNPs in cancer treatment was also investigated. Shanthi et al. (2017) reported a selective dose-dependent inhibition of HeLa cells by clove-PdNPs ($IC_{50} = 15$ μg/mL after 48 h of incubation). This selective cytotoxicity was evident by the higher IC_{50} value against normal cells (H8 cell line) ($IC_{50} = 45$ μg/mL after 48 h incubation). The authors utilized confocal microscopy to show the internalization of the clove-PdNPs inside the nucleus at different time intervals, with 80% of the NPs taken up by the cells after 48 h. The study concluded that the clove-PdNPs internalization in HeLa cells was accomplished via endocytosis (Shanthi et al., 2017).

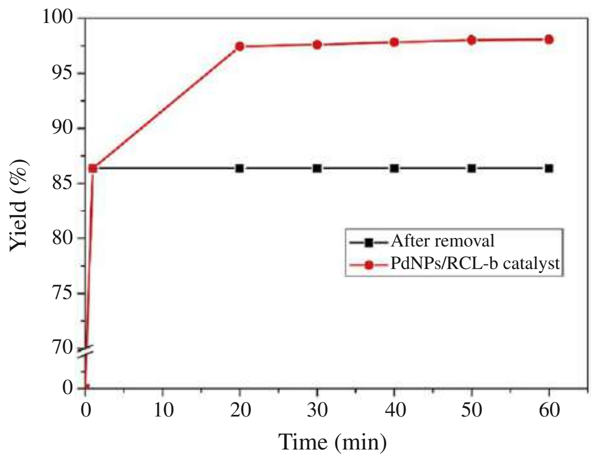

FIG. 4

Yield of Suzuki reaction using clove-PdNPs (denoted: PdNPs/RCL-b) at different time intervals (Wang and Bai, 2020).

2.5 ZnSNPs/ZnONPs

Zn is a nontoxic semiconductor metal of II–VI group with promising applications due to its direct gap energy (~3.63 eV), high refractive index, and dielectric constant (Liu et al., 2006; Rahchamani et al., 2015; Wang et al., 2010). ZnSNPs were therefore considered in several applications in optoelectronics, solar cells, sensors, photocatalysis, and as an antimicrobial agent (Azizi-Lalabadi et al., 2019; Khalafi et al., 2019; Lee et al., 2020; Mishra et al., 2013; Sarkar et al., 2016).

A study used the methanol extract of *S. aromaticum* to cap the ZnSNPs synthesized chemically using thiourea as a reducing agent (Sathishkumar et al., 2018). The bandgap of ZnSNPs from thiourea was 3.85 eV as calculated from the UV-vis spectrum; however, the addition of the *S. aromaticum* was found to increase the bandgap of the ZnSNPs to 4.12 eV. Additionally, the ZnSNPs incorporated with *S. aromaticum* methanol extract increased the photocatalytic degradation of methylene blue and methyl orange dyes compared to the photocatalytic effect of ZnSNPs from thiourea only (pure ZnSNPs). Also, the *S. aromaticum* mediated ZnSNPs exhibited a potent antimicrobial effect, which was significantly higher than the antimicrobial activity of pure ZnSNPs (Sathishkumar et al., 2018). A similar antimicrobial activity was also detected for the ZnSNPs synthesized entirely from CB (clove-ZnSNPs) (Sathishkumar et al., 2017). The disc diffusion assay showed that the highest inhibition zone detected for clove-ZnSNPs was 25 mm against *C. albicans* compared to 16 mm from the positive control (Sathishkumar et al., 2017). Another study by Lakshmeesha et al. (2019) synthesized ZnONPs from CB hexane extract (clove-ZnONPs) via the combustion method. The clove-ZnONPs were found to have antifungal activity by inhibiting the growth of *Fusarium gra*min*earum* (plant pathogen). The authors also studied the possible antifungal mechanism attributed to ROS formation, the increase in lipid peroxidation, and the reduction of ergosterol levels (Lakshmeesha et al., 2019). The ethanol CB extract was also used to produce ZnONPs with bactericidal activity against *E. coli* and *S. aureus* (Anvarinezhad et al., 2020). Interestingly, the degree of bactericidal activity was changed by changing synthesis parameters, specifically the CB extract volume and zinc salt concentration (Anvarinezhad et al., 2020). Osaili et al. (2019) synthesized ZnONPs and CuONPs either via thermal annealing or by using the methanol CB extract. The study compared the antibacterial activity of the different synthesized NPs (individually and in combination) against different foodborne pathogens, *E. coli* and *Listeria monocytogenes*. It was found that the methanol CB extract enhanced the antibacterial activity of the NPs against *E. coli* but not L. *monocytogenes*. The best antibacterial activity could be attained when a mixture of clove-ZnONPs and clove-CuONPs was used (MBC = 300 μg/mL) rather than using the individual NPs (MBC = 350 and above 400 μg/mL for clove-ZnONPs and clove-CuONPs, respectively) (Osaili et al., 2019).

2.6 Other mono-MNPs

Several researchers have explored the use of CuNPs in several applications such as electrical, catalytic, optical antibacterial, and antifungal applications (Bogdanović et al., 2014; Jain et al., 2015; Mohindroo et al., 2016; Pham et al., 2019). The abundance and low cost of Cu are advantageous compared to other expensive metals such as Au, Ag, and Pt (Gawande et al., 2016). Cu has been known as an effective antimicrobial agent with minimum toxicity on the body. However, the exact mechanism in which Cu exerts its antimicrobial activity remains largely speculative. Recently, it was suggested that the release of Cu ions from the Cu-based nanomaterials inside the bacterial cells drives the antimicrobial activity of Cu (Bastos et al., 2020). CuNPs were synthesized from CB (clove-CuNPs) after mixing the aqueous extract with copper acetate solution for 15 min (Rajesh et al., 2018). The biosynthesized clove-CuNPs showed antibacterial and antifungal activities with an 8.0 and 6.0 mm zone inhibition against *Bacillus* spp. and *Penicillium* spp., respectively (Rajesh et al., 2018).

Jain et al. reported the biosynthesis of amorphous MgONPs from CB aqueous extract (clove-MgONPs). The synthesis was done at room temperature. Moreover, the authors optimized the synthesis by changing reaction parameters such as reaction time, the concentration, and the volume of magnesium acetate and the CB aqueous extract (Jain et al., 2018). The clove-MgONPs produced were utilized for colorimetric detection of Fe^{+3}. Although Fe^{+3} is the most abundant transition metal and is involved in several metabolic processes (Aisen et al., 1999), still Fe^{+3} biological imbalance can lead to several ailments, e.g., anemia, diabetes, liver, kidney, and heart diseases (Que et al., 2008). The results from this study detected a shift in the maximal absorbance of the clove-MgONPs from 347 nm to 358 nm and a color change from pale yellow to black after the addition of Fe^{+3}, indicating the ability of the NPs to sense Fe^{+3} in solution. These observations were not detected upon the addition of other metals to the clove-MgONPs, which also indicates the selectivity of sensing toward Fe^{+3} (Jain et al., 2018). Jain et al. (2019) formulated simple, reliable, nontoxic, and affordable nano-based pH paper strips (ranging between 2.0 and 13.0) based on L-lysine-modified MgONPs that were synthesized by the green approach using the CB aqueous extract.

CB extract was also used to synthesize MnONPs (clove-MnONPs) (Kumar et al., 2017). The reaction parameters were changed to optimize the synthesis. The optimization was monitored by observing the UV-vis spectra of the produced clove-MnONPs using different volumes, concentrations, and ratios of the CB extract and the metal salt. MnONPs are widely used in contaminant sensing. Therefore, the authors used cyclic voltammetry, differential pulse voltammetry, and amperometry to show that clove-MnONPs can specifically detect P-nitrophenol (Kumar et al., 2017).

TiO_2NPs are another type of metallic nanoparticles reported from CB. TiO_2NPs have been shown to have antibacterial and anticancer activities (Abdel-Ghany et al., 2020; Abdolmajid et al., 2019; Behnam et al., 2018; Santhoshkumar et al., 2014). Maheswari et al. used *S. aromaticum,* individually and mixed with other plants, to investigate the possibility of enhancing the antibacterial and anticancer activities of the chemically synthesized TiO_2NPs from isopropyl alcohol (Maheswari et al., 2020). The study utilized the XRD and UV-vis techniques to confirm the incorporation of the plant extracts into the TiO_2NPs by comparing the spectra of the free and plant-modified TiO_2NPs. The study has found that the clove modified TiO_2NPs inhibited the growth of the KB oral cancer cell line more than the free TiO_2NPs. Furthermore, the clove-TiO_2NPs gave the highest inhibition zones against several bacterial strains compared to the free and the other plant-modified TiO_2NPs (Maheswari et al., 2020).

2.7 Multi-MNPs

MNPs can be categorized into mono- and multimetallic (bi- or tri-metallic) NPs according to the number of metals involved in the synthesis. Bi- and tri-MNPs can be formulated as alloy or core-shell structures. The synthesis of the multi-MNPs in solution is usually accomplished by the successive reduction of the metal precursors (Venkatesan and Santhanalakshmi, 2010). Due to the different metals' synergistic effects, multi-MNPs present enhanced physicochemical properties and greater efficiency in several industrial and nanomedicine applications, especially in catalysis (Nasrollahzadeh et al., 2020; Sharma et al., 2019).

A study by Rao and Paria (2015) was successful in synthesizing Ag-Au-Pd-NPs in alloy using a mixture of the CB and *Aegle marmelos* leaves aqueous extracts (ratio 1:1) in combination with the natural surfactant *Acacia* (Rao and Paria, 2015). The quick synthesis was done by the successive reduction of Ag, Au, and Pd salts at 50°C in a controlled pH medium. The study utilized the catalytic activity of the formed tri-MNPs in glucose oxidation to gluconic acid (important compound in food and pharmaceutical industries) with a conversion rate of 80% in just 190 min. The authors attributed this high catalytic activity to the electron charge transfer between the three metals, which leads to higher electron density at the catalytic site. Further, the study also showed that the Ag-Au-Pd-NPs have antibacterial activity against *E. coli*. This activity was determined by disc diffusion assay, and the morphological changes in the bacteria were also observed using SEM. The authors concluded that the biofabricated Ag-Au-Pd-NPs could produce gluconic acid with antimicrobial protection of the reaction medium during the manufacturing process (Rao and Paria, 2015). A recent study also explored the catalytic activity of bimetallic Ag-Au-NPs alloy from CB aqueous extract (Sharma et al., 2020). The authors described the effect of varying the metal salts mixture ratios on the physicochemical characteristics of the formulated bi-MNPs.

Moreover, the study also synthesized the respective monometallic NPs (Clove-AgNPs and clove-AuNPs) and compared the antioxidant of all the NPs using three different assays (ABTS, DPPH, and hydroxyl radical scavenging assays), which showed that the bi-MNPs have greater antioxidant activity compared to the individual NPs synthesized from CB. This antioxidant activity was attributed to the phytochemicals of the CB extract capping the NPs. Furthermore, three organic dyes (methylene blue, methyl orange, and P-nitrophenol) were used to study the catalytic activity of the NPs. The results indicated that the catalytic activity of the bi-MNPs is higher than the mono-MNPs owing to the higher number of Au and Ag interfaces in the bi-MNPs available for the redox process (Sharma et al., 2020).

3. Conclusions

The clove's extracts and bio-components have been shown to have a rich source of phytochemicals that can synthesize MNPs using cost-effective and safe methods. Most of the methodologies reported for the MNPs from clove followed typical chemical reduction fundamentals. The data have shown that more studies are needed to determine the clove's chemical component responsible for reducing and stabilizing the MNPs. The clove-mediated MNPs have exhibited interesting pharmacological activities that can be utilized in biomedical applications in the future, for example, as antibacterial and for wound healing. Additionally, clove-MNPs can play a role in industrial applications like water treatment and fuel cells.

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