Metallic Nanoparticles: Potential Ecofungicide for Controlling Growth of Plant-pathogenic Fungi

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Summary: Development of nanoscience has provided several kinds of useful nanomaterials for biomedical applications such as drugs delivery systems, antibacterial or antifungal products and health care devices. Abundant studies of metallic nanoparticles have reported fortheir potential antibacterial property and exploited for practical applications. Moreover, several metallic nanoparticles have recently proven their strong inhibitory activity on plant-pathogenic growth. Thus, metallic nanoparticles could be utilized to develop a new generation of fungicides for agricultures inceusing of the chemical fungicides could pose some limitations such as harming to some beneficial microorganisms as well as human health.Moreover, accumulations of fungicide residues in agricultural products and underground water are also serious problems. Another drawback of fungicide usage is creating resistance of the harmful fungi which regenerates new strain of fungi without any known preventing approach. In the review, we focus on the effect of metallic nanoparticle on plant pathogenic microbes and the possibility of these nanoparticles in protecting plant thus providing currently knowledge of different metallic nanoparticles which have been reported their ability to control plant-fungal pathogens at laboratory scales and to treat fungi-infected plants.

Keywords: Metallic nanoparticles, Ecofungicide, Antifungal, Plant pathogen.

Introduction

It is reported that plant-pathogenic fungicaused tens ofbillions dollarsin crop loss[1, 2]. Although fungicides are still important tools for managing disease in agricultureand many chemical fungicides are available on market, some of them are quite expensive and createfungicide resistance. Moreover, accumulationsof these chemical fungicides in post-harvest fruits, soil and water areother severe problems causing toxicity for human health and environment[2]. Many efforts have been made to find alternative fungicides in purpose to reduce the burden for farmers[3].

In recent years, metallic nanoparticles (NPs) have beenemerging as an alternative candidate for the chemical fungicides due to theirwell-known biological properties which have exploited in medicine, industry and agriculture[4–10]. Many pharmacological applications of the NPsare proved involvinga wide range of properties such as antibacterial, antiplasmodial, anti-imflamatory, anticancer, antiviral, and antifungal activities[11, 22]. Treating and controlling growth of viral pathogens of metallic NPs classify them as the alternative agents since they have multiple binding sites, which can bind to viral membrane to control the function of such viruses [15].Hence, bio-based NPs are acting as effective virucidal compounds which inhibit cell-free virus and cell-associated virus [19]. Other studies also indicated that silver and gold NPs are promising antiviral drugs [16, 21]. AgNPs have clearly showed the membrane damaging ability in Candida species and also damaging ability in fungal intercellular components [17, 18].

Despite a number of papers have been published in this field, most of them focus on the antimicrobial activity of metallic nanoparticles. A part of these papers have reviewed biological properties of metallic nanoparticles which have been applied to alter several conventional household and industrial products. Up to now, nanofungicides, nanopesticides and nanoherbicides are still in the early stages of development which should be considered to extensively study and produce in order to apply in phytopathogens management [20]. Here, we would like to focus on the effect of metallic nanoparticle on plant pathogenic microbes and the possibility of these nanoparticles in protecting cultured plant. Therefore, the aim of this review is to summarize activities of some metallic nanoparticles against plant-pathogenic growth and their potential to apply in the agriculture as ecofungicides as shown in Fig. 1.

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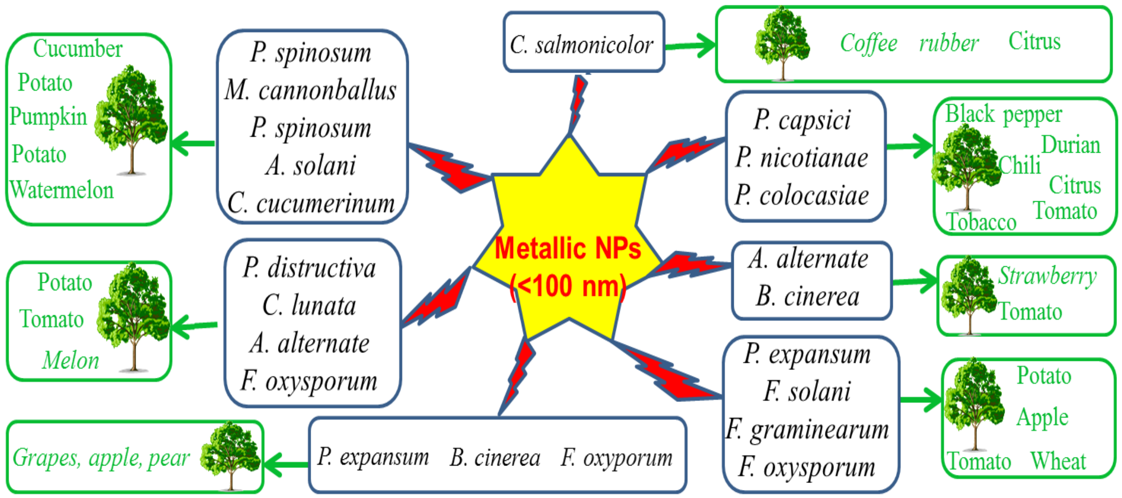

Fig. 1: Inhibitory and killing activities of some metallic nanoparticles against plant-fungal pathogens at laboratory scales and fungi-infected plants *in* agriculture fields.

Metallic NPs and Synthesis

Metallic nanoparticles have gained a lot of attentions due to their novel properties such as optical, catalytic, and antimicrobial, compared to their bulk metallic forms[23]. Up to now, several approaches have reported toproduce nanoparticles include chemical, physical and biosynthetic methods.

Approaches to produce nanoparticles are classified as “top down” and “bottom up” approaches. (Sepeur, 2008). In top-down method, nanoparticles are mainly synthesized by size reduction which can be achieved by various physical and chemical treatments (Meyers *et al*., 2006). However, these approaches have a major limitation since the surface chemistry and the physical properties of nanoparticles highly depend on the surface structure (Thakkar *et al*., 2010). Of bottom up approach, the nanoparticles can be synthesized either joining atoms, molecules or small particles (Mukherjee *et al*., 2001) (Fig. 2). The bottom up approach mostly relies on chemical and biological methods of production.

Among different types of nanoparticle production, chemical synthesis is known as the most popular method using in commercial scaledue to the high efficiency compared to other methods.However, biosynthesis manner which uses microorganisms and plant extract have recently been reported as alternative green methods. These methods are described in the following sections.

Chemical synthesis of nanoparticles

Chemical synthesis consists of different methods such as sol-gel, microwave, reduction, etc. Depending onavailable materials and facilities, appropriate method has been chosen[24-29].

In electrochemical method, synthesis of nanoparticles isoccurred at electrode-electrolyte interface. At anode, metallic bulksare dissolved to metallic ions and migrate to the cathode. Metallic ionsare reduced to metal atoms and stick together to become larger metal. Finally, those particles are precipitated resulting in nanostructured metal colloids[30].This method gives variety of advantages such as reducing the cost of performance, using common equipment, operating by environmental friendly and simply process comparing with other techniques[31]. In the sol-gel method, metal alkoxides or metal chlorides are precursors which are hydrolyzed and polycondensated to form nanoparticle network system containing a liquid phase. Drying step is conducted to remove liquid phase out of the gel. Polycondensation and mechanical properties of products can be enhanced by performance thermal treatment (calcinations) [32–34]**.**

Basic principle of reduction method is the formation of metallic atoms from reduction of metallic salt compound with the aid of reducing agents and dispersants or protecting agents[7, 24], [35]. In the method, concentration, reductant and dispersant or protecting agent play important rolesin size distribution and ultrafine size formation of the metallic nanoparticles (Fig. 3).

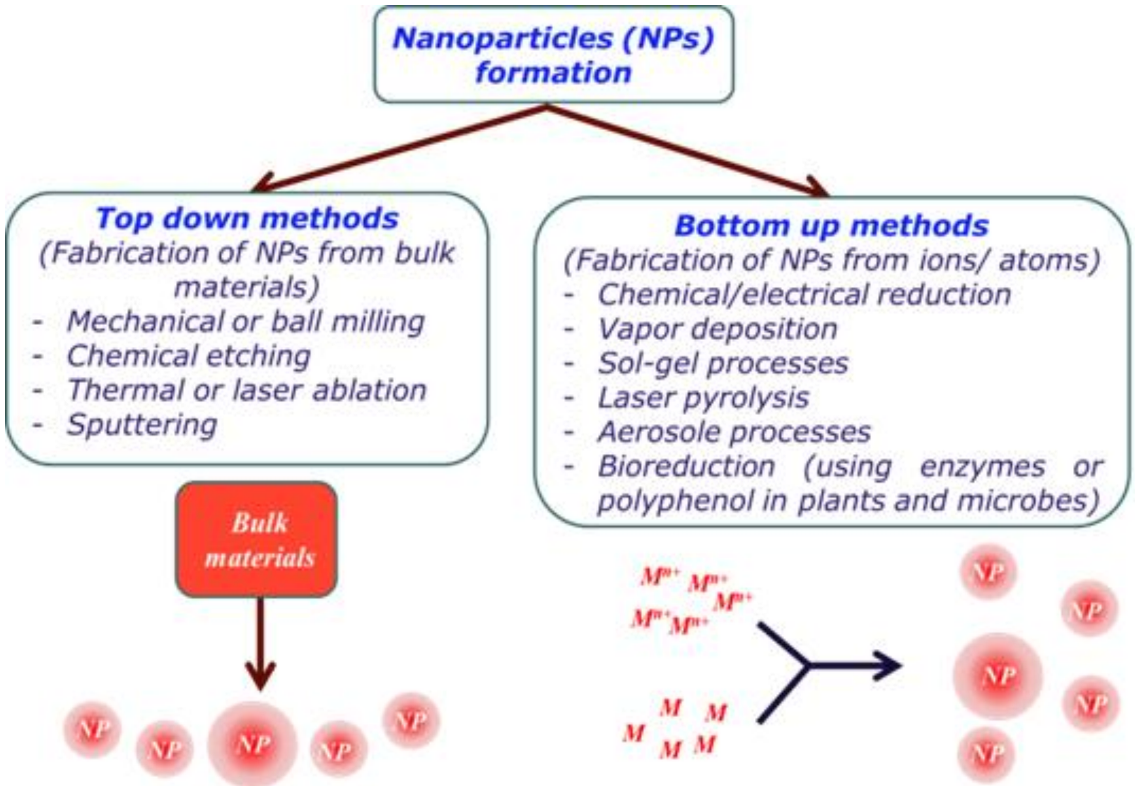

Fig. 2: Approaches for fabrication of nanoparticles for practical applications.

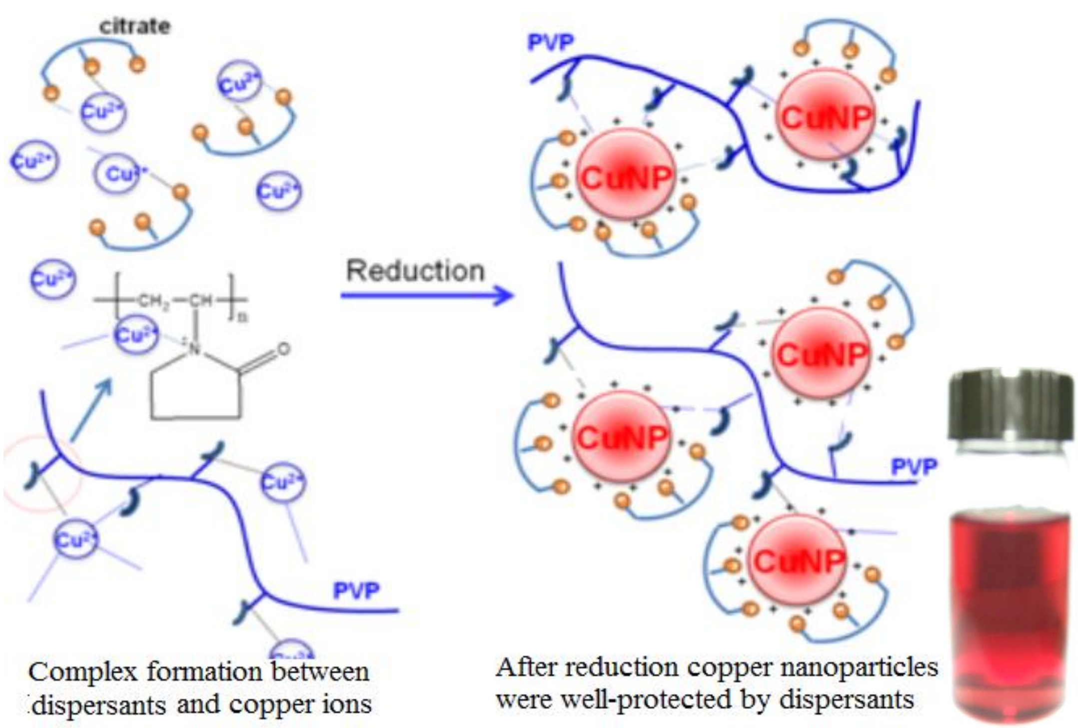

Fig. 3: Synthesis of the ultrafine Copper NPs with synergistic effect of citrate dispersant and PVP capping polymer on controlling size growth[20].

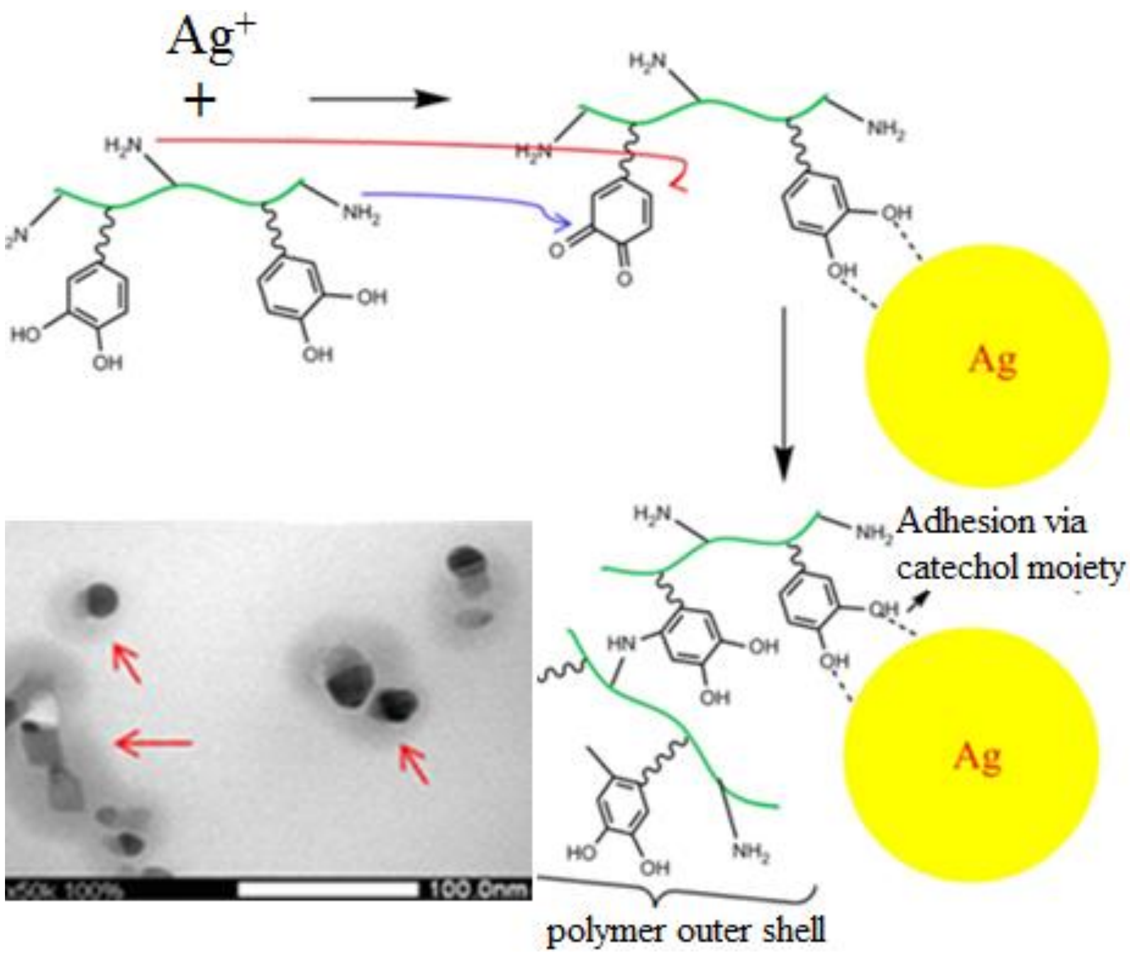

Fig. 4: Preparation of the silver core-chitosan shell nanoparticle via catechol-mediated reduction and adhesion.

In the reduction method, there has recently been an emerging approach in which silver and gold nanoparticles were produced and then protected by the polyphenol-functionalized polymers like chitosan dihydroxyphenylacetamide, hyaluronic acid-graft-catechol, 3,4-dihydroxyphenylalanine-containing poly(ethylene glycol), etc.(Fig. 4).

The approach could produce some metallic core-polymer shell nanoparticles without use of any reducing agent and protecting polymer as conventional method [26, 27, 36].

Physical method for synthesis of nanoparticles

Physically synthetic methods of nanoparticles are laser ablation, vacuum vapor deposition,pulsed wire discharge and mechanical milling[37–40].In the laser ablation method, the prepared copper nanoparticles at small size are dispersed in solvents. However, the process needs a high-power laser beam, a vacuum chamber and inner gas. The method is also similar to vacuum vapor deposition.Pulsed wire discharge takes place via evaporation of a materials to produce its vapor and then cooled by an ambient gas to form nanoparticles [41]. For mechanical milling method, this is a simple process and low cost production in large scale [38. 42].

Biosynthesis of nanoparticles

Despite the presence of chemical and physical methods, development of an eco-friendly synthetic procedure of nanoparticles recently has graspedlots ofscientists' attentions. Biosynthesis is known as useful method not only because of its reduced environ-73 mental impact compared with some of the physical and chemical methods, but also because of large production quantities. It is reported that nanoparticles produced by biosynthesis have well-defined size, morphology and are free of contamination [43–47].

The directionutilizing "natural bio-sources" such as soil microorganisms and plant extracts is prominent[43, 48–54].For example,several microbes like bacteria, yeast, fungi, and algae secrete enzymes can transform metal ions into desired metals [55–57]. Nanoparticles synthesis can be happened in intracellular and extracellular pathways.For instance, NPs were synthesized using *Verticilliumsp* by intracellular pathway[58]. Silver NPs formation using microorganism or synthesis of gold nanoparticles by *R.capsulata*are typically examples in extracellular synthesis [59].

Plant extract isa well-known biosynthesis method which has brought many benefits in various fields such as plant growth promotion, pathogen suppression and disease controldue to the abundant natural compounds contained in all plants such as alkaloids, flavonoids, reducing hexose, amino acids and other nutritional compounds [43, 54, 60, 61].The methodhas been reported is being cost effective and friendly environmental material for NPs production.Silver, zinc oxide and gold NPs were synthesized successfully from *Ocimumtenuiflorum*,*Solanumtricobatum*, *Synzygiumcumini*, *Centellaasiatica*, *Citrus sinensis*,*Kalopanaxpictus*,*Brassica oleracea*, *Matricariachamomilla*, etc.[54, 62–67].However, the most challenge in the synthetic method is controlling size and shape of NPs. The different hydrogen ion concentrations and temperature for extraction also affect the size and shape of NPs [68, 69].

Comparing between biological methods of synthesis, microbial synthesis is more readily scalable, friendly-environment and compatible with the use of the product for medical applications. However, production of microorganisms is often more expensive than the production of plant extracts[54].

Metallic NPs against plant-pathogenic growth

The increasing use of NPs has led to the growing of researches exploring antimicrobe mechanism of NPs. For instants, metallic nanoparticles can enter biofilms or they can change the metabolic activity ò bacteria [70, 71]. Basically, NPs have to contact with microbes to accomplish their antimicrobial function. There are different forms of contact such as electrostatic attraction, van der Waals forces, receptor-ligand and hydrophobic interaction [72]. After that NP can cross the bacterial membrane and interact with cell components of the microbes such as DNA, lysosomes, ribosomes and enzymes thus leading to oxidative stress, heterogeneous, alterations, changes in cell membrane permeability, protein deactivation, and change in gene expression [72–74]. The most important antimicrobe mechanisms are known as oxidative stress [75], metal ion release [76] and non-oxidative mechanisms [77]. According to the valuable properties of metallic nanoparticles, the following sections concentrate on specific metallic nanoparticles which can be served as potential ecofungicide for cntrollinggrowth of plant-pathogenic fungi.

Silver nanoparticles

Silver nanoparticles (AgNPs) are popular type of NPs, have being studied extensively and used as safely antibacterial agent due to various biological and antibacterial properties[9, 78–81]. The AgNPs release silver ions which can interact with disulphide bonds resulting in blocking functional characteristics of microbes [21, 50, 81]. AgNPs also have the ability to create reactive oxygen species causing irreversible damage to bacteria and also have a strong affinity in binding to DNA or RNA. The nanoparticles destroy hydrogen bonds in DNA double strands leading to DNA denaturation. Subsequently, these effects interfere with the microbial replication process and inhibit microbial growth [81].

Effect of silver ion on inhibitingPhytophthora(P.) pathogenic growth was first reported in 1993. Slade *et al.* indicate that silver ion is the most effect in the order: $Ag^{+} > Cu^{++} > Ni^{+} > Co^{++} > Zn'$. The$LD_{50}$for Ag^{+}, 0.11µM (11.4 ppb), compared with 1.84 µM (117 ppb) for Cu^{++}[82]. However, the silver ion is not stable for several practical applications. Recently, there has been an approach using nanoparticles for inhibiting plant-pathogenic growth. The nanoparticlessustainably release Ag^{+} resulting in maintaining its antimicrobial activity for a long period of time.Several studies reported thatAgNPs have exhibitedstrong activity against plant-pathogenic growth. Kim *et al*showthat10 ppm of AgNPs could inhibit significantly growth of A.brassicicola, A.solani, B.cinerea, C.cucumerinum, D.bryoniae, F. oxysporum, F.solani, M.cannonballus, P.spinosum, S.lycopersici[83]. Jo *et al* report that AgNPs with diameter ranging from 20 to 30 nm exhibiting a highly antifungal activity on two grisea plant-pathogenic fungi (Bipolarissorokinianaand Magnaporthe)[84].Disease symptoms on the Bipolarissorokiniana-inoculated perennial ryegrass were significantly reduced when the plant was treated with AgNPs (50 ppm) in comparison with the water control and AgCl (Fig. 5). These obtained results are very significant to apply in agriculture since the fungi are the causal agents of common root rot, leaf spot disease, seedling blight on rice, wheat and barley which cause significant yield losses[85].

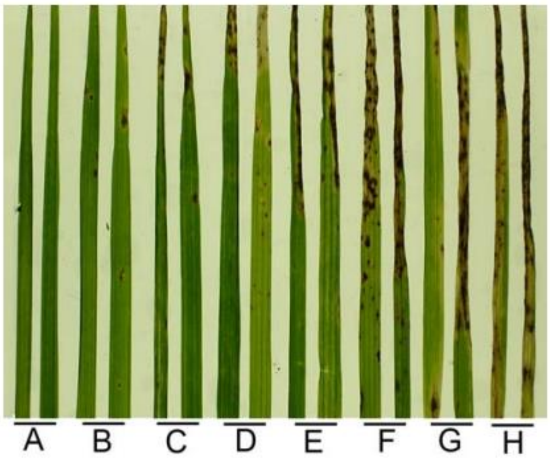

Fig. 5: Disease symptoms on leaves of perennial ryegrass were treated with A (AgNPs 50 ppm), B (AgNPs, 200 ppm), C ($AgNO_3$ 50 ppm), D (AgNPs 50 ppm + NaCl), E (AgNPs 200 ppm + NaCl), F ($AgNO_3$ 50 ppm + NaCl) G (AgCl 200 ppm), and H (water) [64].

Phu *et al*. indicate that the small size AgNPs (smaller 10 nm) exhibited aneffective dose (ED50) at 27.2 ppm for *Corticiumsalmonicolor* [86]. The microorganism causes pink disease on rubber resulting in a significant reduction of latex yield.In addition to mentioned studies, AgNPs-containing composites also show their potential application as a fungicide for plants. Ocsoy *et al*. fabricated DNA-Directed silver nanoparticles on graphene oxidecomposite which could apply in plant disease management. The AgNPs 18 nm in diameter were grown on graphene oxide exhibiting significant growth inhibition of *Xanthomonasperforans*on tomato leaves in comparison with commercial fungicide –Mancozeb [87]. Park *et al*. introduced a nanosizedsilica-silver solution (0.3 ppm AgNPs) exhibiting highly antifungal effect on green squash [88] (Fig.6).

Our previous studies indicate that chitosan silver core shell nanoparticles (9 ppm active silver) could inhibit upto80 % growth of *P.capsici*, *P.nicotianae*and*P. colocasiae*plant-pathogenic fungi [27].The *Phytophthora*fungi cause serious damage to durian tree black pepper/chili/tomato plant (*P. capsici*), tobacco, citrus (*P. nicotianae*), and taro (*P. colocasiae*) leading to dead plants and significantly decrease in productivity.BiosyntheticAgNPs (ranging from 6 to 38 nm)were produced from white radish against *Fusatiumoxysporum*(15 ppm) and*Fusariumsolani* (30 ppm) [89]. The approach could produce apromising antifungal agentto against the plant pathogenic fungi to control the plant diseases.

Copper Nanoparticles

Although AgNPs have been the most studies and applications than others, studies on fungal activity of copper nanoparticles (CuNPs) recently received huge attentions due to their appropriate cost compared with other NPs. The CuNPs have been proved the activity which against several pathogen fungi [7, 90].

Prachi *et al*. (2014) report that CuNPs have size ranging from 3 to 10 nm exhibiting significantly antifungal activity against different kinds of pathogenic fungi such as*Phomadistructiva*, *Curvularialunata*, *Alternaria alternate* and *Fusariumoxysporum* [91]. Our group indicated that the ultrafine CuNPs ranking 2-5 nm exhibiting a strong antifungal activity against *C. Salmonicolor* [7]. The in diameter was prepared via chemical reduction method. As aresult, at 7 ppm CuNPs concentration, 100% of the fungi were inhibited to grow due to the release of copper ion causing microbial membrane damage[7, 91]. The study also indicated that most of the overgrowth fungi were killed after 2nd spraying containing 7 ppm of CuNPs (Fig.7). A preliminary result obtained from treating diseased rubber trees with ultrafine CuNPs showed that disease indexwas reduced significantly after twice spraying in comparison with Validacin 5 L (a commercial fungicide for *C. Salmonicolor)*. These obtained results could offer the ultrafine CuNPs as an potential eco-fungicide for agriculture[5, 7].

Similar to CuNPs, the toxicity of the CuO NPs performed on*P. ultinum* and *P. aphanidermatum.* The study confirmed that the toxic metal released from the CuO NPs inhibited Fe uptake processes of*Pythium hyphae* resulting in antimicrobial effects of the metallic oxide NPs[92].

Zinc oxide nanoparticles

Zinc compounds exhibiteffective antibacterial and antifungal activities and play an important role as fungicides in agriculture[93–95]. Recent reports indicate that smaller sizes of ZnO present better antimicrobial activity than bigger sizes particles[96, 97]. He *et al*. show that ZnO NPs performed antiproliferativeactivity (inhibited over 80%) against*Botrytis cinerea* and *Penicilliumexpansum* plant-pathogenic fungi [98]. Antifungal efficacy of ZnO NPs was also evaluated to against *Fusariumoxyporum*strain. Approximately 77.5% fungal growth inhibition of *F. oxysporum* was achieved when 12mg L^{-1} concentration of ZnO NPs was applied [99]. Furthermore, the toxicity of the ZnO NPs toward *Pythium* was evaluated in which the growth of the *P. ultinum* and *P. aphanidermatum* were significant inhibited [92]. In another study, ZnO NPs (20-30 nm in diameter) were green-synthesized from weed plant exhibitedhighly antifungal activity on different fungal species including *Aspergillusflavus* and *Fusariumculmorum*. The study also indicates that small-sized ZnO NPs (20-30 nm in diameter) present strongly inhibiting ability compared to the large-sized NPs (82-86 nm) [100].The antimicrobial effect was explained thatZnO NPs could form the free radicals on the surface themselves; these radicals then damage the lipids in bacterial cell membrane leading to leaked and broken bacterial cell membrane[101, 102].

At the end of this review, several nanoparticles which could be potential ecofungicides to protect plants in agriculture owing to their highly inhibitory activity are summarized in the following Table.

Conclusion

The paper briefly presentsseveral effective synthetic methods of the antimicrobial metallic nanoparticles. These nanoparticles have been applied infood industry, household, cosmetic, pharmacy. Beside above-mentioned applications, these metallic NPs have recently performed a highly antiproliferative activity against several species of plant pathogenic fungi. These fungi have damaged and lost crops of economic plants. These NPs are exhibiting their strongly potential applications as ecofungicide in agriculture since theyperform bioactivity and preventthe fungicide resistance problem of several plant pathogenic fungi.

Table-1: A summarized table of some nanoparticles exhibiting a highly inhibitory activity against plant-pathogenic growth

Metallic NPs	Size (nm)	Conc. (ppm)	Inhibition (%)	Plant Pathogenic Fungi	Damage on plants	References
Ag/CHPA core-shell	<30	9	80 >90 >75	P. capsici P. nicotianae P. colocasiae	Durian, black pepper, chili, tomato, tobacco, citrus, and taro	[23]
AgNPs	6-38	15	60-80 75-90 55-75 50-75	P. expansum F. solani F. graminearum F. oxysporum	Apple, potato, wheat, and tomato	[68]
AgNPs	38	15	59.3 52.9	Alternaria alternate Botryticcinerea	Tomato and strawberry	[82]
AgNPs	7-25	10	>70 >70 >60 >50 >70	P. spinosum M. cannonballus P. spinosum A. solani C. cucumerinum		[62]
AgNPs	20-30	25	>80	M. grisea	Ryegrass	[63]
CuNPs	2-4	7-10	100	C. salmonicolor	Coffee andrubber	[7]
CuNPs	3-10	20 (µg/ disc)	22 mm 21 mm 18 mm 24 mm	P. distructiva C. lunata A. alternate F. oxysporum	Tomato, potato, melon	[69]
CuO NPs	<50	50-500	90 >60	P.ultinum P. aphanidermatum	Wheat, tomato	[71]
ZnO NPs	60-90	12 (mg L^{-1})	>80 >90	B. cinerea, P. expansum	Grapes, apple, and pear	[77]
ZnO NPs	75	12 (mg L^{-1})	>75	F. oxyporum, P. expansum	Apple, pear, and crops	[78]
ZnO NPs	<100	50	50 50	P.ultinum P. aphanidermatum	Wheat and tomato	[71]
ZnO NPs	20-30	25 (µg/ml)	>55%	A. flavus F. culmorum	Cereals, legume, and tree nuts	[79]

List of Abbreviations

NPs	Nanoparticles
AgNPs	Silver nanoparticles
AuNPs	Gold nanoparticles
CuNPs	Copper nanoparticles
ZnO NPs	Zinc oxide nanoparticles
CTAB	CetylTrimethyl Ammonium Bromide
PCR	Polymerase Chain Reaction
PVA	Polyvinyl alcohol

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Conflict of interest

The authors declare that they have no conflictof interest for this work.

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