

Review

Responses of Medicinal and Aromatic Plants to Engineered Nanoparticles †

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† This article is sincerely dedicated to Dr. Elena Masarovičová, Professor of Plant Physiology at the Department of Soil Science, Faculty of Natural Sciences, Comenius University in Bratislava, Slovakia.

Abstract: Medicinal and aromatic plants have been used by mankind since ancient times. This is primarily due to their healing effects associated with their specific secondary metabolites (some of which are also used as drugs in modern medicine), or their structures, served as a basis for the development of new effective synthetic drugs. One way to increase the production of these secondary metabolites is to use nanoparticles that act as elicitors. However, depending on the specific particle size, composition, concentration, and route of application, nanoparticles may have several other benefits on medicinal and aromatic plants (e.g., increased plant growth, improved photosynthesis, and overall performance). On the other hand, particularly at applications of high concentrations, they are able to damage plants mechanically, adversely affect morphological and biochemical characteristics of plants, and show cytotoxic and genotoxic effects. This paper provides a comprehensive overview of the beneficial and adverse effects of metal-, metalloid-, and carbon-based nanoparticles on the germination, growth, and biochemical characteristics of a wide range of medicinal and aromatic plants, including the corresponding mechanisms of action. The positive impact of nanopriming and application of nanosized fertilizers on medicinal and aromatic plants is emphasized. Special attention is paid to the effects of various nanoparticles on the production of valuable secondary metabolites in these plants cultivated in hydroponic systems, soil, hairy root, or in vitro cultures. The beneficial impact of nanoparticles on the alleviation of abiotic stresses in medicinal and aromatic plants is also discussed.

Keywords: bioactive agents; carbons; elicitors; metals; secondary metabolites; metalloids; nanoparticle; plants



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1. Introduction

The 20th century was characterized by a rapid increase in the use of synthetic (often toxic) substances in various sectors of the economy, including agriculture, food, and in the pharmaceutical industry. Moreover, huge amounts of harmful solvents were often used to prepare required drugs. Due to the growing environmental contamination, which is also reflected in adverse effects on human health, “green” solutions are indispensable today. However, unlike the “Green Revolution” of the mid-20th century, which significantly increased the amounts of synthetic pesticides and fertilizers to achieve high yields [1], increased attention is now being paid to the widest possible use of biologically/pharmacologically active compounds of natural origins [2–4]. Medicinal plants, and in particular their essential oils (EOs), have been used in folk medicine since prehistoric times. For example, the use of medicinal plants is mentioned in the Bible. Moreover, recipes with medicinal plants can

be found on a Sumerian tablet dating back to 3000 BC as well as Ebers papyrus (1500 BC). Several important works dealing with medicinal plants and corresponding medicines prepared from these plants, which arose during antiquity and the Middle Ages, were also preserved. *The Herball, or Generall Historie of Plantes*, published by the English botanist John Gerarde in 1597, includes approximately 600 medicinal plants [5–12]. Some fragrant medicinal plants, such as *Myrtus communis* L., *Ocimum basilicum* L., *Rosmarinus officinalis* L., and *Salvia fruticosa* Mill, are used as ritual plants in the main monotheistic religion [13].

Medicinal plants provide valuable sources of compounds that contain healing effects [5,6]. The phytotherapeutic effects of medicinal plants are caused by specific secondary metabolites, i.e., biologically active compounds formed in the processes of secondary metabolism. Unlike primary metabolism, which covers the growth and development of an individual, and can be characterized as indispensable, universal, uniform, and conservative, secondary metabolism covers the interaction of an individual with the environment, and although it is dispensable for growth and development, it is indispensable for survival in the environment and is considered unique, diverse, and adaptive [14]. For the pharmaceutical industry, secondary metabolites of medicinal plants that exhibit healing effects are particularly useful as lead compounds for the design of effective drugs [15–17]. Recently, there has been growing interest in obtaining increased amounts of valuable secondary metabolites of medicinal plants through hairy root cell suspension cultures. The advantage of these “green methods” compared to synthetic methods is the elimination of harmful solvents.

On the other hand, aromatic plants produce and secrete aromatic substances, and some of which exhibit therapeutic properties, such as antimicrobial and antioxidant activities, which are often used for culinary purposes, as well as in the food and liqueur industries [15–24]. Similar to medicinal plants, several culinary herbs and spices have been used as medicines over the centuries. For example, in Egypt, under the pharaohs, garlic was consumed by workers and slaves who built large pyramids “in order to increase their stamina and strength and protect them from disease” [25]. The use of spices can, to some extent, prevent food spoilage, especially in hot climates [26,27]. Today, it is possible to produce herbal-enriched dairy products, and functional dairy products with improved nutritional quality and medicinal values [28]. Laws and regulations on medicinal and aromatic plants in Europe, including the European Union, were summarized by Steinhoff [29] and Barbieri [30].

Over the last 20 years, we have experienced an unprecedented boom in nanotechnology associated with the application of nanosized particles/formulations in agriculture, food, and medicine. According to the U.S. National Nanotechnology Initiative [31], nanotechnology represents “the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications”. The European Commission in 2011 defined the term “nanomaterial” as “a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm” [32]. The uniqueness of nanomaterials is related to the fact that, despite the same chemical composition as the corresponding bulk materials, they may not only have different physical and chemical properties, but also different effects on living organisms [3,33–42].

Nanoparticles (NPs) can generally be prepared by mechanical division from top to bottom (physical method) or by “growth” from bottom to top (chemical method). Top-down methods, most often grinding using stabilizing agents, were the first to be used to prepare NPs. They usually lead to particles with diameters > 10 nm and relatively large variability, which is also reflected in problematic reproducibility. The bottom-up methods are much more elegant and, nowadays, a more widespread option for preparing NPs, which allows better control over the size of the NPs. A large number of different stabilizers (donor ligands, polymers, and detergents) are used to control the growth of NPs and to protect them from aggregation. Electrochemical reduction of metal salts and controlled

decomposition of metastable organometallic compounds are often used to prepare metal-based NPs. In the initial state of nucleation, the metal salt is reduced to form metal atoms that collide with other ions, metal atoms, or clusters, and irreversibly form “nuclei” of a stable metal core. The diameter of the cores should be below 1 nm depending on the strength of the metal bonds, the magnitude of the redox potential of the metal salt, and on the reducing agent used. Nowadays, when green synthesis of NPs is preferred, it refers to various plant or microbial extracts containing numerous biologically active compounds for the reduction of metal ions, acting as capping and stabilizing agents (increasingly being used for the synthesis of metal-based NPs). These bioactive compounds that are bound to the surface of NPs significantly improve the interaction of NPs with living cells and improve their biological efficiency [43–46].

Controlled release of active substances, the need for lower doses to achieve the same effect, and lower toxicity to non-target organisms are the main advantages of nanomaterials compared to their bulk counterparts, which contributes to reducing environmental pollution and costs [3,37,47–51].

The impact of nanoparticles (NPs) on plants can be different and depends on the chemical composition of NPs, the applied concentration, environmental conditions (e.g., pH, temperature, soil acidity, etc.), as well as on the treated plant species [52–57]. NPs used as fertilizers stimulate plant growth and yield and can positively affect the nutritional quality of crops [50,52,54–56], while nanosized herbicides suppress the unwanted weeds [48,49,53,56,58–60] and NPs used in plant protection contribute to healthy development and growth of plants by killing harmful insects, fungi, and other pathogens [3,34,35,48,49,53]. NP-induced oxidative stress can be used to produce valuable secondary metabolites, not only in field culture, but also in vitro using tissue or hairy root (HR) culture [51,61–67]. Reducing the adverse effects of abiotic stresses on plants using NPs offers an effective way to achieve higher yields and crops [50,51,68–71].

The increasing use of NPs in industry and agriculture is associated with their gradual accumulation in environmental matrices, where they could migrate, persist, or be transformed, accumulate in algae and plants, and enter the food chain. As a result, some toxic NPs can adversely affect non-target organisms and pose a serious threat to human health. To eliminate these risks, environmental monitoring is required for NPs, providing research on their fate in environmental matrices and contents in edible parts of plants. This is especially important in terms of medicinal plants that are consumed for their medicinal properties [36,49,52,53,72–75].

This review article summarizes the current findings on the effects of metal-, carbon-, and silicon-based NPs as well as NPs derived from organic materials on medicinal and aromatic plants. Increased attention is paid to the production of important secondary metabolites exhibiting medicinal properties under in vitro conditions suitable for use in the mass production of these biologically active compounds, to be an alternative to synthetically produced ones. The beneficial effects of NP on medicinal plants exposed to some abiotic stresses are also discussed.

2. Effects of Metal-, Metalloid-, and Carbon-Based NPs on Vascular Plants

Metal-, carbon-, silicon-, and selenium-based compounds, applied in bulk or in nanoform, affect growth and development of vascular plants. In general, metal ions and metal NPs, including some essential metals (e.g., Cu, Zn, Fe, Ni, etc.) applied at higher concentrations, are phytotoxic, generate oxidative stress, adversely affect germination, photosynthetic processes, inhibit activities of enzymes and biosynthesis of photosynthetic pigments and non-enzymatic antioxidants, and accumulate high metal amounts in their plant organs, which is reflected in impaired plant growth and development [55–57,76–83]. On the other hand, some medicinal plants (e.g., *Hypericum perforatum* L. or *Matricaria recutita* L.) were found to be tolerant metal excess and accumulate in their shoots/leaves high concentrations of toxic metal, such as cadmium [83,84]. Therefore, to ensure food safety,

cultivation of medicinal plants for commercial purposes under natural conditions must be performed on soils that are not contaminated with toxic metals [85].

Moreover, bulk and nanoscale metals and metal oxides can also be cytotoxic and genotoxic, cause cell-cycle arrest and apoptotic induction, as well as serious damage to DNA [57,86–90]. On the other hand, their low doses may stimulate plant growth and can be used as effective fertilizers for achieving higher yields [55,56,91–96]. Therefore, for individual plant species, it is necessary to know which concentrations have plant growth stimulating effects and those with plant growth inhibiting impact.

Carbon-based nanomaterials, such as multi-walled carbon nanotubes (MWCNTs), can penetrate seed coats and, when used in low concentrations, improve water absorption, water transport, seed germination, nitrogenase, photosystem and antioxidant activities, activate water channel proteins, and stimulate nutritional absorption [97,98]. The entry of carbon-based nanomaterials into roots in an apoplastic way is thought to cause elongation of cell membrane pores [99] and the increased ability of plants to absorb water and essential nutrients when exposed to carbon nanotubes leads to stimulation of plant growth [98,100,101]. They can also affect the plant phenotype and composition of soil microbiota [102]. On the other hand, at higher concentrations, CNTs may have an adverse effect on plants due to the reactive oxygen species (ROS) generation, leading to cell death [103].

Silicon is a metalloid, which is beneficial for plant growth and development, particularly under abiotic stress conditions (e.g., high salinity, water deficit, high temperature, presence of toxic metals) because it can alleviate damages in stressed plants; it can activate some defense mechanisms and regulate some physiological processes related to defense mechanisms in plants [50,54,104,105]. Savvas and Ntatsi [106] stated that mitigation of abiotic stresses in vascular plants by Si is associated with SiO₂ deposition inside the plant tissues. Si acts as antioxidant and protects plants from oxidative damages and, depending on applied concentration; it can have both beneficial and adverse impact on plants, and modulate negative effects of abiotic stresses on plants, e.g., [107,108].

NPs affecting medicinal and aromatic plants discussed in this review are presented in Figure 1. Beneficial and adverse effects of NPs on medicinal and aromatic plants are shown in Figure 2.

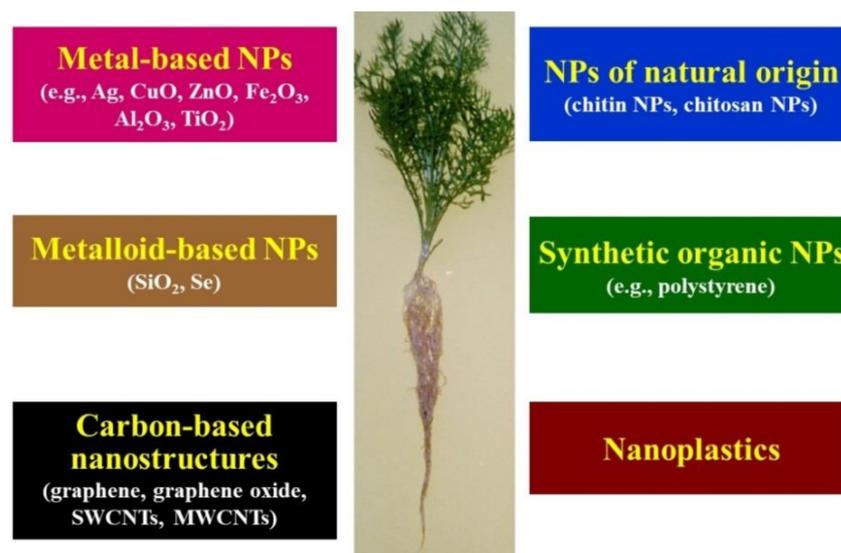


Figure 1. Types of nanoparticles (NPs) affecting medicinal and aromatic plants discussed in this paper.

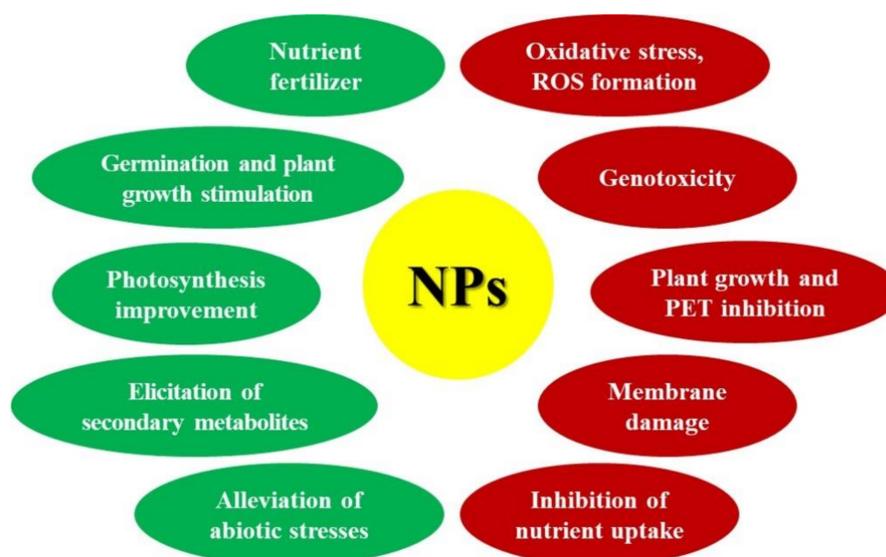


Figure 2. Beneficial and adverse effects of NPs on medicinal and aromatic plants.

3. Improved Production of Secondary Metabolites in Presence of NPs

As mentioned above, NPs exhibit similar effects to their bulk counterparts; however due to their specific properties connected with their nanoscale sizes, their ultimate effects on plants can be amplified or attenuated [80,109–114]. By green production of valuable secondary metabolites of medicinal plants elicited by various NPs, using in vitro cultures (Table 1) or HRs (Table 2), higher amounts of these pharmacologically important compounds can be achieved exceeding those observed with corresponding bulk elicitors. These secondary metabolites can be subsequently utilized by the pharmaceutical industry [115–120].

Table 1. Enhanced production of secondary metabolites (SM) of medicinal plants elicited by various NPs using in vitro cultures and plants grown in soil or hydroponic solutions compared to corresponding bulk elicitors. (CSC = cell suspension culture, TPC = total phenolic content, TFC = total flavonoid content, MS = Murashige and Skoog medium, EO = essential oil)

NPs of Elicitor	Plant	Cultivation Mode	Elicitor Dose	SM	Multiple of SM Content in Control	Refs.
Ag	<i>Momordica charantia</i> L.	CSC	5 mg/L	TPC TFC flavonoids hydroxybenzoic acid hydroxycinnamic acid	1.40 1.56 1.52 1.23 1.15	[121]
Ag	<i>Echinacea purpurea</i> L.	CSC, root derived callus (48 h) CSC, leaf derived callus (72 h)	2 mg/L	cichoric acid cichoric acid	≈2.22 ≈1.80	[122]
Ag	<i>Isatis constricta</i> L.	leaves of shoots regenerated in MS (5 days)	2 mg/L	tryptanthrin	1.71	[123]
Ag	<i>Caralluma tuberculata</i> L.	callus culture	90 µg/L	TPC TFC	≈3.75 ≈3.60	[124]
Ag	<i>Trigonella foenum-graecum</i> L.	2% agar (5 days) and then cultivation in sterile soil	200 µg/plant	diosgenin	1.30	[115]
Ag	<i>Linum usitatissimum</i> L.	cell suspension culture, 20 days	30 µg/L	secoisolariciresinol diglucoside lariciresinol diglucoside dehydrodiconiferyl alcohol glucoside guaiaacylglycerol-coniferyl alcohol ether glucoside	10.0 2.8 5.0 1.75	[125]
Ag	<i>Stevia rebaudiana</i> L.	callus culture	45 mg/L, after 2 d 30 mg/L, 45 mg/L, after 6 d	stevioside stevioside rebaudioside A	≈4.32 ≈3.26 ≈1.70	[126]

Table 1. Cont.

NPs of Elicitor	Plant	Cultivation Mode	Elicitor Dose	SM	Multiple of SM Content in Control	Refs.
Ag	<i>Vanilla planifolia</i> L.	in vitro cultivation in MS	25 mg/L 50 mg/L	TPC	≈1.83 ≈1.83	[127]
Ag	<i>Salvia officinalis</i> L.	foliar spaying	100 mg/L	rosmarinic acid	≈11.0	[128]
AgAu (1:3)	<i>Prunella vulgaris</i> L.	cell culture (+ 2 mg/L NAA), 14 days	30 µg/L	TPC TFC	1.54 1.39	[129]
Au	<i>Lavandula angustifolia</i> L.	in vitro culture	50 mg/L 10 mg/L	(<i>E,E</i>)-farnesol bisabolol oxide A cadale necaryophyllene oxide	1.91 1.15 1.76 1.23	[130]
Cu	<i>Artemisia absinthium</i> L.	seeds inoculated on MS medium	30 µg/mL	TPC TFC	≈1.66 ≈1.07	[131]
Zn	<i>Momordica charantia</i> L.	foliar spraying	20 ppm	carotenoids anthocyanins TPC TFC	2.55 1.11 1.19 1.45	[132]
Zn-Ag (0.95:0.05) (0.75:0.25)	<i>Withania somnifera</i> L. Dunal	in vitro culture (MS medium; 1 month)	20 mg/L	withanolide	≈14.08 ≈5.60	[63]
Ni	<i>Withania somnifera</i> L. Dunal	in vitro culture (MS medium; 1 month)	20 mg/L	withanolide	≈7.90	[63]
Fe	<i>Mentha piperita</i> L.	foliar application, 3 times	0.5 g/L 0.5 g/L 1.5 g/L	menthone menthol menthofuran	1.65 1.30 2.50	[133]
Co	<i>Artemisia annua</i> L.	cell suspension culture (24 h)	5 mg/L	artemisinin	2.25	[134]
CdSe QDs	<i>Withania somnifera</i> L. Dunal	in vitro culture (MS medium; 1 month)	20 mg/L	withanolide	≈3.75	[63]
CuO	<i>Stevia rebaudiana</i>	leaf regenerants tissue culture	20 mg/L	rebaudioside A stevioside	1.50 1.94	[135]
CuO	<i>Gymnema sylvestre</i> (Retz.) R. Br	cell suspension culture	3 mg/L	gymnemic acid II TPC TFC	9.0 ≈2.56 ≈1.79	[136]
ZnO	<i>Stevia rebaudiana</i> L. Bertoni	tissue culture grown shoots	0.1 mg/L 1.0 mg/L	rebaudioside A stevioside TPC stevioside TPC	1.35 1.53 1.42 1.60 1.63	[137]
ZnO	<i>Stevia rebaudiana</i> L.	leaf regenerants tissue culture	2 mg/L	rebaudioside A stevioside	1.49 1.27	[135]
ZnO	<i>Linum usitatissimum</i> L.	in vitro culture (MS medium)	500 mg/L	secoisolaricresinol diglucoside laricresinol diglucoside dehydrodiconiferyl alcohol glucoside guaiacylglycerol-β-coniferyl alcohol ether glucoside	1.28 1.35 1.60 1.54	[138]
ZnO	<i>Stevia rebaudiana</i> L.	hydroponic cultivation	75 mg/L	TPC TFC	1.61 1.88	[139]
ZnO	<i>Linum usitatissimum</i> L.	cell suspension culture	60 mg/L	total lignan	≈1.59	[140]
ZnO	<i>Hypericum perforatum</i> L.	cell suspension culture	100 ppb	hypericin hyperforin	3.8013.36	[141]
Fe ₂ O ₃	<i>Melissa officinalis</i> L.	plant irrigation at 60% FC	30 µM	EO per plant	≈1.60	[142]
Fe ₂ O ₃	<i>Hypericum perforatum</i> L.	cell suspension culture	100 ppb	hypericin hyperforin	5.40 12.02	[141]
Fe ₃ O ₄	<i>Dracocephalum polychaetum</i> Bornm.	cell suspension culture	100 ppm	naringin rutin quercetin apigenin rosmarinic acid hymol carvacrol	2.02 3.15 6.29 4.81 3.18 5.07 3.22	[143]
TiO ₂	<i>Linum usitatissimum</i> L.	cell suspension culture	150 mg/L	total lignan	1.50	[140]
TiO ₂	<i>Mentha piperita</i> L.	foliar spraying	150 mg/L	menthol menthone menthyl acetate	1.09 1.32 1.11	[144]
TiO ₂	<i>Vetiveria zizanioides</i> L.	foliar spraying	90 mg/L measurement 300 DAT)	khusimol	1.24	[145]

Table 1. Cont.

NPs of Elicitor	Plant	Cultivation Mode	Elicitor Dose	SM	Multiple of SM Content in Control	Refs.
TiO ₂	<i>Salvia officinalis</i> L.	spraying of the 4-month old plants	200 mg/L	TPC TFC <i>p</i> -cymene 1,8-cineol <i>cis</i> -thujonecamphor	1.63 1.72 1.61 2.23 1.88 1.31	[146]
TiO ₂	<i>Stevia rebaudiana</i> L. Bertoni	cultivation in soil, spraying 3-fold in 3 weeks	60 mg/L 200 mg/L	stevioside	≈1.67 ≈1.77	[147]
TiO ₂	<i>Nigella arvensis</i> L.	hydroponic cultivation, 21 d	2500 mg/L 50 mg/L 50 mg/L 2500 mg/L 1000 mg/L	glaucine (shoots) glaucine (roots) quercetin (shoots) quercetin (roots) TPC	2.4 1.7 1.5 1.3 2.2	[148]
TiO ₂	<i>Dracocephalum moldavica</i> L.	irrigation of hydroponically grown plants	100 mg/L	geraniol geranial (E-citral)Z-citral	1.41 1.05 1.07	[149]
TiO ₂	<i>Dracocephalum moldavica</i> L.	spraying of plants grown in pots	30 ppm 30 ppm 100 ppm	rosmarinic acid ellagitan ninchlorogenic acid caffeic acid	1.23 1.40 1.22 1.41	[150]
NiO	<i>Nigella arvensis</i> L.	hydroponic cultivation, 21 d	1000 mg/L 2500 mg/L 50 mg/L 50 mg/L 100 mg/L	glaucine (shoots) glaucine (roots) quercetin (shoots) quercetin (roots) TFC	3.20 2.60 2.2 1.2 2.5	[148]
Al ₂ O ₃	<i>Nigella arvensis</i> L.	hydroponic cultivation, 21 d	2500 mg/L 2500 mg/L 2500 mg/L 1000 mg/L	glaucine (shoots) glaucine (roots) quercetin(shoots) quercetin(roots)	1.37 1.60 1.22 1.43	[148]
Mn ₂ O ₃	<i>Atropa belladonna</i> L.	in vitro culture on MS medium	100 mg/L 25 mg/L	TPC TFC	3.05 4.49 2.92	[151]
Si	<i>Mentha piperita</i> L.	foliar spraying	100 mg/L	menthol/per plant menthone/per plant menthyl-acetate/per plant	1.811.751.83	[152]
SiO ₂	<i>Matricaria recutita</i> L.	seed treatment (1 h), then in vitro culture on MS	4 g/L 6 g/L 6 g/L	TPC TPC TFC	2.50 * 4.40 * 10.58 *	[153]
perlite	<i>Hypericum perforatum</i> L.	callus cultures from in vitro grown plants field grown plants	25 mg/L 50 mg/L 50 mg/L	alkaloids	14.24 12.69 1.75	[154]
perlite-TiO ₂	<i>Hypericum perforatum</i> L.	callus cultures from in vitro grown plants field grown plants	25 mg/L 50 mg/L 25 mg/L	alkaloids	12.35 11.80 1.34	[154]
MWCNTs	<i>Salvia verticillata</i> L.	spraying of plants	50 mg/L 50 mg/L 1000 mg/L 250 mg/L	TPC rosmarinic acid rosmarinic acid caffeic acid	1.20 3.40 3.99 2.88	[155]
MWCNTs	<i>Catharanthus roseus</i> L.	in vitro cultivation (MS medium)	50 mg/L 100 mg/L 150 mg/L 50 mg/L	alkaloids TPC	≈1.86 ≈1.63 ≈1.86 ≈1.36	[156]
MWCNTs	<i>Thymus daenensis</i> Celak.	in vitro culture (MS medium)	250 mg/L	TPC TFC	2.10 1.09	[157]
MWCNTs	<i>Satureja khuzistanica</i>	Leaf segments cultured in B5 basal medium	100 µg/mL	TPC TFC rosmarinic acid caffeic acid	1.96 2.61 2.60 1.76	[158]
MWCNT-COOH	<i>Salvia nemorosa</i> L.	cell suspension culture + 70 Gy γ -irradiation	100 mg/L	rosmarinic acid salvianolic acid B ferulic acid cinnamic acid	13.0 * 14.2 * 20.0 * 3.0 *	[159]
C60 fullerene	<i>Tanacetum parthenium</i> L., Pharmasaat genotype	foliar spraying (harvest at full flowering stage)	250 mg/L	parthenolide	≈8.2	[160]
fullerenol [C60(OH)20]	<i>Momordica charantia</i>	seed treatment	10.88 nM	cucurbitacin-B lycopene charantin insulin	1.74 1.09 1.05 1.91	[161]

* compared to wild plant, ≈ evaluated from graphs.

Table 2. Enhanced production of secondary metabolites (SM) of medicinal plants elicited by various NPs using hairy root cultures compared to corresponding bulk elicitors.

NPs	Medicinal Plant	Dose (Length of Treatment)	SM	Multiple of Control SM Content	Refs.
ZnO	<i>Hyoscyamus reticulatus</i> L.	100 mg/L (48 h) 100 mg/L (72 h)	hyoscyamine scopolamine	4.61 3.20	[67]
Fe ₂ O ₃	<i>Hyoscyamus reticulatus</i> L.	900 mg/L (24 h) 450 mg/L (48 h)	hyoscyamine scopolamine	≈5.0 ≈5.0	[65]
Fe ₂ O ₃	<i>Dracocephalum kotschy</i> Boiss	75 mg/L (24 h)	rosmarinic acid xanthomicrol cirsimaritin isokaempferide	9.7 11.87 3.85 2.27	[162]
SiO ₂	<i>Dracocephalum kotschy</i>	100 mg/L	rosmarinic acid xanthomicrol cirsimaritin isokaempferide	8.26 13.00 13.42 10.00	[163]
Ag-SiO ₂	<i>Artemisia annua</i> L.	900 mg/L (3 days)	artemisinin	3.90	[164]
Ag	<i>Datura metel</i> L.	20 ppm (12 h) (24 h) (48 h)	atropine	1.147 1.117 2.420	[165]
CuO	<i>Brassica rapa</i> L. spp. <i>pekinensis</i>	50, 100, 250 mg/L for 24, 48, 72 h	gluconapin glucobrassicinapin 4-methoxyglucobrassicin neoglucobrassicin 4-hydroxyglucobrassicin	≈1.38 ≈1.34 ≈1.51 ≈1.54 ≈1.82	[166]

Elicitors are compounds that are capable of causing stress to the plant, leading to increased synthesis and accumulation of secondary metabolites, or to the induction of new secondary metabolites [116,167]. In general, secondary metabolites of plants play a role in their communication and adaptation. Plant secondary metabolism utilizes building blocks and biosynthetic enzymes derived from primary metabolic processes, and it produces large number of specialized compounds that are essential for plant survival in its environment [168–170]. Many of the secondary metabolites are also biologically active compounds, which are therefore desirable to produce in large quantities directly from medicinal plants [115,117,119,171]. It has been found that many NPs can be used as effective elicitors, the use of which makes it possible to avoid various other, mostly harmful/ecotoxic chemicals [115,117,118,172]. Stress often induces the production of secondary metabolites in the plant tissue culture system [116]. The accumulation of valuable secondary metabolites in micropropagated medicinal plants induced by abiotic/biotic stress using NPs is studied intensively [113,115,117,172,173]. Hairy roots are also important for the large-scale production of industrially important secondary metabolites. These are differentiated cultures of the roots of higher plants that have been injured and subsequently infected with *Agrobacterium rhizogenes*. Such transformed roots are capable to grow rapidly on the basal medium, show genetic and biosynthetic stability, and can produce increased amounts of secondary metabolites [119,120,171,173–177].

4. Effect of Metal-Based NPs on Medicinal and Aromatic Plants

4.1. Silver-Based NPs

A comprehensive overview focused on phytotoxicity assessment of AgNPs and their interaction with plants, including whole plant and organs, as well as interactions on the cellular and molecular levels, was presented by Tkalec et al. [178]. Coating of AgNPs can affect their toxicity.

4.1.1. Impact on Plant Growth

Beneficial effect of AgNP seed germination characteristics of *Thymus kotschyanus* was reported by Khalaki et al. [179]. Moreover, treatment with 40 mg/kg AgNPs during the germination process effectively improved germination and growth of *Ocimum basilicum* L. plants and their resistance to salinity stress [180]. By application of 0.2 mg AgNPs (8–21 nm) per fenugreek seedling, the root and shoot length of seedlings was approximately doubled and wet weight of treated plants was even 3-fold higher compared to the control [115]. Increasing concentrations of AgNPs (27.5 ± 4.8 nm) up to 10 mg/L showed beneficial impact on growth and development of *Lavandula angustifolia* propagated in vitro, which was reflected in improved formation of shoots, increased plant weight, and longer roots compared to control. Increasing AgNPs concentrations reduced the number of secretory trichomes; the greatest diameter of trichomes on the adaxial surface of the leaf blade was observed at exposure to 2 mg/L AgNPs and the smallest one at 5 mg/L AgNPs. The largest trichome diameter on the abaxial surface was formed at treatment with 1 mg/L and the lowest one using 5 mg/L AgNPs [181].

Spraying of borago (*Borago officinalis* L.) plants at the seed growth stage with AgNPs using doses 20, 40, and 60 ppm resulted in improved seed yield compared to the control; this beneficial impact increased with increasing AgNPs concentration, although content of polyphenols in treated plants showed a decrease [182]. Spraying of shoots of borago plants at the onset of the flowering stage (65 days after cultivation) and maintained until flowering (98 days after cultivation) with solutions containing 0.2, 0.4, and 0.6 mM AgNPs resulted in considerable increase of leaf numbers, plant, and inflorescence dry weights, and petal abscission [183].

For vanilla (*Vanilla planifolia*) micropropagated in a semi-solid Murashige and Skoog (MS) medium treatment, 25 mg/L and 50 mg/L AgNPs with a mean diameter of 35 ± 15 nm was found to be the most favorable for shoot multiplication. The greatest lengths, number of shoots, and number of leaves were obtained with 25 mg/L and 50 mg/L AgNPs, and such treatment effectively reduced the contamination during micropropagation of *V. planifolia* [184].

Ag-SiO₂ core-shell NPs (101.8 ± 8.9 nm) applied at 900 mg/L for 3 d to the HR cultures of *Artemisia annua* promoted their dry weight, which was 71% higher than that of the control [164]. AgNPs and AgNO₃ did not affect the in vitro multiplication of *Campomanesia rufa* at doses 0.385 and 0.77 mg/L, respectively, while treatments with 15.4 mg/L showed toxic effects reflected in the reduced number of shoots [185].

4.1.2. Elicitor Effect

AgNPs also acted as elicitor in HR cultures of *Brassica rapa*, causing a pronounced increase in the contents of glucosinolates and their transcripts, as well as in total phenolic and flavonoid concentrations and transcripts, compared to non-elicited HRs [186]. After treatment of in vitro grown shoots of *Isatis constricta* with 2 mg/L AgNPs, lasting 5 days, the indigo and tryptanthrin content were higher by 15 and 71% than in the control; however, at prolonged treatment (10 or 15 days), their content showed a decrease. On the other hand, treatments with AgNPs were found to decrease indirubin production [123].

Foliar treatment of 40 mg/L AgNPs, besides stimulating growth of fenugreek (*Trigonella foenum-graecum*), plants increased the total content of photosynthetic pigments by 25%, while content of indole acetic acid was even doubled compared to the control. Moreover, seeds yielded from treated plants showed pronouncedly higher content of phenolics, flavonoids, and tannins, as well as a higher percentage of proteins and carbohydrates than those of control plants [187]. Diosgenin content in fenugreek seedlings treated with 0.2 mg AgNPs (8–21 nm) per seedling considerably increased compared to the control (214.06 ± 17.07 vs. 164.49 ± 7.67 µg/mL) [115]. Pronounced enhancement of secondary metabolites, including phenols, tannins, and alkaloids, was found in borago plants sprayed with solutions containing 0.2, 0.4, and 0.6 mM AgNPs [183].

Salvia officinalis plants foliarly treated with AgNPs contained enhanced levels of phenolic compounds; the content of rosmarinic acid (RA) and salvianolic acid A and B was positively correlated with the activity of phenylalanine ammonia-lyase (PAL) and RA synthase, but not with tyrosine aminotransferase. After treatment of plants with 100 mg/L AgNPs, even 8-fold higher RA content was observed than in control plants [128]. *Rosmarinus officinalis* L. plants sprayed with solution containing 25, 50, 100 ppm AgNPs showed beneficial impact on the contents of secondary metabolites. Application of 200 ppm AgNPs for 12 days resulted in enhanced carnosic acid (CA) content by <11% compared to the control. In AgNP-treated plants, positive correlation was observed between TFC and CA content. Translocation of AgNPs to rosemary roots was confirmed as well [188]. The composition of EO extracted from *Lavandula angustifolia* propagated on MS medium containing AgNPs (27.5 ± 4.8 nm; 10 and 50 mg/L) was considerably altered, showing a decrease in compounds of lower molecular weight, which were replaced by those with higher molecular weight [130].

AgNPs more effectively elicited production of cichoric acid in cell suspension cultures of *Echinacea purpurea* than AgNO₃, which reached even 9.54 mg/g dry weight (d.w.) in cell suspension culture after 48 h of treatment with 2 mg/L AgNPs and 8 mg/g d.w. in leaf suspension culture after 72 h of treatment [122]. Moreover, enhanced production of secondary metabolites, TPC, TFC, and protein content, and improved antioxidant and superoxide dismutase (SOD) activities were observed in *Artemisia absinthium* grown in vitro on MS medium treated with AgNPs [131]. Due to oxidative stress generated by AgNPs, artemisinin content in HRs increased and its production in 20-day-old HR cultures achieved up to 13.3 mg/L, being 3.9-fold higher than that of the control [164]. By application of 45 mg/L AgNPs to callus culture of *Stevia rebaudiana*, the amount of stevioside was enhanced, up to 32.34 mg/g d.w. of callus, suggesting that by using appropriate concentrations of AgNPs as an elicitor enhanced production of this secondary metabolite can be obtained [126]. AgNPs effectively elicited production of both lignans and neolignans in cell suspension culture of *Linum usitatissimum* [125].

Cell suspension cultures (CSC) of *Momordica charantia* elicited with AgNPs showed pronouncedly higher levels of Ag, malondialdehyde (MDA), and H₂O₂ compared to non-elicited ones, and in their extracts, considerably enhanced total phenolic content (TPC) and total flavonoid content (TFC) compared to the control were observed. In CSC elicited by 5 mg/L AgNPs, the amounts of flavonols, hydroxybenzoic, and hydroxycinnamic acids greatly exceeded the amounts observed in the control [121].

4.1.3. Effect on Antioxidant Enzymes

Significantly enhanced callus induction of *Citrus reticulata* L., as well as high TPC, TFC, and antioxidant activity were observed using co-treatment with 20 ppm AgNPs and 1 mg/L thidiazuron; considerable increase of SOD, peroxidase (POD), and catalase (CAT) levels were recorded on MS medium supplemented with 30 ppm AgNPs and thidiazuron [189]. Hormetic effects of Argovit on in vitro regeneration of vanilla using a temporary immersion bioreactor system were reported by Spinoso-Castillo et al. [127]. Whereas doses 25 and 50 mg/L of Argovit increased *Vanilla planifolia* growth, application of 100 and 200 mg/L showed strong inhibitory effect; a dose-dependent effect on generation of ROS formation, and increasing TPC, antioxidant capacity, and lipid peroxidation was observed. AgNPs in combination with plant growth regulators added to MS medium pronouncedly enhanced callus biomass of *Caralluma tuberculata*. Stimulated production of phenolics, flavonoids, and increased PAL, SOD, POD, CAT, ascorbate peroxidase (APX) activities, as well as antioxidant activity were observed in the callus cultures treated with 90 µg/L AgNPs [124]. AgNPs green synthesized from leaf extracts of *Swertia chirata* applied on regenerating shoot cultures of *S. chirata* were found to generate ROS. However, due to induced antioxidant defense by antioxidant enzymes, ROS content was balanced and shoot regeneration increased, suggesting that AgNPs applied to plant tissue cultures can act as growth stimulant for improved shoot regeneration [190].

Calendula officinalis L. plants exposed to 50 ppm AgNPs and magnetic fields (3 mT), either alone or in combination, pronouncedly increased phenolic content, activities of several enzymes, such as PAL, polyphenol oxidase (PPO), ascorbate peroxidase (APX), guaiacol peroxidase (GPX), glutathione reductase (GR), and radical scavenging in plants, suggesting positive effect of AgNPs on the defense mechanism of *C. officinalis* plants, combined treatment being the most effective [191]. Treatment of *Calendula officinalis* with AgNPs also reduced its DPPH (2,2-diphenyl-1-picrylhydrazyl) scavenging activity and increased formation of ROS and membrane peroxidation [192]. In the extracts of *Calendula officinalis* plants cultivated in hydroponic solution containing 0.4 mM AgNPs (30–50 nm), the extracts contained lower contents of chlorophyll (Chl), carotenoids, and anthocyanins than the control. Only content of flavonoids showed an increase by 14.6%; however, at higher AgNP concentrations, their content decreased as well, and saponin content increased by ca. 77% [192].

It was reported that AgNPs pronouncedly suppressed oxidative stress triggered by naphthalene toxicity in *Moringa oleifera* called the “Miracle Tree” [193]. AgNPs applied foliarly to the *Salvia officinalis* plants, penetrated via the leaf epidermis into the parenchyma cells, and after application of 50 and 1000 mg/L AgNPs, reduced levels of assimilation pigments and increased activities of antioxidants (enzymatic and non-enzymatic) were able to cope with the oxidation stress, compared to the control plants [128]. The cetyltrimethylammonium bromide (CTAB) coated AgNPs were found to be toxic to *A. cepa* roots, causing robust inhibition of roots and pronounced oxidative damage, whereas much bigger negatively charged citrate coated AgNPs aggregating to larger particles were least toxic. However, it could be mentioned that the toxicity of Ag⁺ ions was higher than that of both coated AgNPs [194].

4.1.4. Attenuation of Abiotic Stress

AgNPs enhanced the tolerance to drought stress in germination and early growth stages of *Thymus daenensis* Celak and *Thymus vulgaris* L.; they improved germination characteristics and root length up to 200 mM salinity, although they exhibited positive impact on vigor and shoot length only up to 100 mM salinity as compared to the control [195].

4.1.5. Cytotoxic and Genotoxic Effects of AgNPs

AgNPs with particle sizes >100 nm were found to penetrate the root tip cells of *Allium cepa* and adversely affected stages of cell division resulting in formation chromatin bridge, stickiness, disturbed metaphase, multiple chromosomal breaks, and cell disintegration, whereby at application of 100 ppm AgNPs mitotic index (MI) decreased from 60.30% (control) to 27.62% [196]. Mitigation of genotoxic and cytotoxic effects of AgNPs in onion root tips reflected by a decrease of MI, elevated chromosome aberrations, and tail DNA caused by oxidative stress can be attenuated by using antioxidants (e.g., vitamin E), pretreatment being more effective than combined treatment with AgNPs [197]. Cytotoxic and genotoxic impact of Ag nanorods on *A. cepa* roots depended on their concentration, a dose of 15 µM being more toxic than doses of 5 and 10 µM, respectively [198]. Although polyvinylpyrrolidone (PVP)-coated as well as uncoated AgNPs were found to be genotoxic, cytotoxic, and induce oxidative stress in *A. cepa* roots, even at low concentrations; under exposure to visible-light, their aggregation state will be altered, resulting in reduced toxicity [199]. Due to application of 25 and 50 mg/L AgNPs to *V. planifolia*, only a small MI decrease was observed and genotoxic effects were minimal, with < 5% of the total chromatic aberrations and 3 micronuclei in 3000 cells, despite the long-time exposure to AgNPs [200].

In general, considering the beneficial impact of AgNPs on enhanced production of secondary metabolites, they could be recommended to be used, particularly for production of stevioside in callus culture of *Stevia rebaudiana* L. [126] and for enhanced production of rosmarinic acid by foliar spraying of *Salvia officinalis* L. plants [128] (Table 1).

4.2. Copper-Based NPs

4.2.1. Impact on Plant Growth and Photosynthesis

Capsicum annuum plants grown in soil amended with 500 mg/kg CuNPs, which were evaluated at the vegetative stage, i.e., 45 days post transplantation, showed pronouncedly increased length and dry weight of roots, while plant tissues accumulated lower Cu amounts compared to treatment with bulk Cu particles. On the other hand, when treated plants were evaluated in the reproductive stage, i.e., 90 days post transplantation corresponding to a full life cycle, treatment with 500 mg/kg CuNPs resulted in increased photosynthesis, stomatal conductance, and Cu leaf content compared to that observed with application of bulk Cu particles. Treatment with 62.5 mg/kg CuNPs was found to increase transpiration, but total sugar, carotenoid, Chl, and vitamin C contents in the fruit, and the root and leaf enzyme activity, were not affected 90 days post transplantation in plants exposed to 62.5, 125, or 500 mg/kg CuNPs. The results of this experiment suggested that a dose of 500 mg /kg CuNPs, ensuring higher Cu bioaccumulation in the root, and leaf tissue over long-term exposure, is suitable to be used as a nanofertilizer [201]. CuO NPs phytosynthesized using *Punica granatum* peel extract foliarly sprayed on *Capsicum annuum* plants increased the height of plants, as well as growth and the Chl content of leaves; the fruit practically did not contain residues of sprayed NPs [202]. Application of 125 mg/kg CuO NPs to *Capsicum annuum* plants significantly reduced leaf P content by 41%, while exposure to 500 mg/kg CuO NPs decreased Zn content in leaves and fruits by 55% and 47%, respectively, compared to the control, thereby affecting the nutritional quality of bell pepper [203].

Foliar spraying of *Mentha piperita* L plants performed three times of the interval of 15 days up to flowering stages with 1.0 g/L CuNPs was found to enhance Chl content and EO percentage of 35% and 20%, respectively, as compared to control [133]. Investigation of the clonal microreproduction of *Mentha longifolia* plant showed that addition of colloidal solutions of CuNPs (0.5 mg/L) and CoNPs (0.8 mg/L) to MS nutrient medium resulted in an increase of microplant height and growth index on 45–48.4%, the quantity of internodes on 29.4–33.9%, quantity of shoots on 55.6–66.2%, and reproduction coefficient on 30–40% [204]. Application of 5 µM CuNPs (20–40 nm) for plant regeneration of *Ocimum basilicum* via somatic embryogenesis resulted in 5.6-fold higher percentage of explants produced somatic embryos (84 vs. 15%) and 4.35-fold higher average number of regenerated plantlets/explant (18.7 vs. 4.3) as compared to treatment with 0.1 µM CuSO₄ 5 H₂O [205]. Exposure of *Origanum vulgare* plants for 60 days to CuNPs at doses 0–200 mg Cu/kg increased root and shoot growth, and water content, but reduced shoot biomass, as well as starch, total sugar, and reducing sugar in leaves; whereas shoot length, MDA, and Chl levels were not affected. However, CuNPs affected root and shoot contents of Ca, Fe, Mg, and Mn, suggesting that nutrition value of oregano could be modified [206]. Phytotoxic effect of 200, 400, and 800 mg/L CuNPs on hydroponically cultivated coriander (*Coriandrum sativum*) plants was reflected in reduced biomass and root length, lower levels of Chls (Chla and Chlb) compared to control plants, and increased levels of H₂O₂ compared to untreated plants [207].

4.2.2. Elicitor Effect

Foliar application of 0.5 g/L CuNPs effectively enhanced the levels of camphene, α-phellandrene and limonene in *Mentha piperita* L. plants, while a dose of 1.0 g/L increased the concentrations of menthol, menthone, and menthofuran [133]. *Allium fistulosum* plants grown 80 days at greenhouse conditions in soil spiked with 150 mg/kg CuO NPs showed higher contents of Cu, Ca, and Fe in roots, and higher Ca and Mg content in bulb than plants exposed to bulk CuO or CuSO₄. Moreover, plants of Chinese scallion plants cultivated in soil supplemented with 75–600 mg/kg CuO NPs showed higher levels of allicin in leaves (56–187%) than the control, suggesting that CuO NPs have potential to be used as nanofertilizer for onion production [208].

Crystalline monoclinic cubic CuO NPs with mean size 47 nm applied to MS media for direct organogenesis of *S. rebaudiana* from nodal segments at a dose of 10 mg/L pronouncedly increased shoot organogenesis (88.5%), shoot length, mean number of shoots per explant, and fresh weight, as well as the content of glycosides, rebaudioside A, and stevioside [209]. The NPs of bimetallic alloys of Cu and Au (Cu:Au = 3:1) applied at a dose of 30 µg/L together with 0.5 mg/L naphthalene acetic acid were found to stimulate biomass accumulation on the 27th day of log phases, increased the radical scavenging activity, and enhanced TPC and TFC in submerge adventitious root cultures of *S. rebaudiana* (Bert.) [210]. Uncapped and polyethylene glycol (PEG) or PVP capped CuO NPs applied to the growth medium of in vitro cultured *S. rebaudiana* plants were able to increase the production of commercially important secondary metabolites. Regarding shoot organogenesis, increased growth parameters and higher content of steviol glycosides and non-enzymatic antioxidants (TPC, TFC) in shoots were observed at treatment with polymer-capped CuO NPs compared to uncapped ones [211].

Using cell suspension cultures of *Gymnema sylvestre* (Retz.) R. Br and CuO NPs as elicitor (3 mg/L for 48 h), the yields of gymnemic acid II, TPC, and TFC were considerably enhanced, and the cultures exhibited significant antioxidant, antidiabetic, anti-inflammatory, and anticancer activities [136]. *Bacopa monnieri* (L.) Pennell herb treated in vivo with Cu-based NPs (CuNP/CuO NPs) applied at doses 0–100 mg/L showed biphasic dependence of total contents of saponins, alkaloids, phenolics, and flavonoids on the concentration of used NPs. While at lower Cu/CuO NPs concentrations, the content of secondary metabolites increased; at higher concentrations, their strong reduction was observed. Besides enhancement of secondary metabolism, the CuNPs applied at sub-toxic doses also improved the antioxidant capacity in *Bacopa monnieri* herb via ROS-mediated defense response [212].

4.2.3. Genotoxicity

CdS and CuO NPs induced growth inhibition and caused cytological aberrations in both mitotic and meiotic cells in *Coriandrum sativum* L, the effect being like that of conventional mutagen, ethyl methanesulfonate, which was used as control [213]. Damaged root plasma membrane and altered genome of hydroponically cultivated coriander plants exposed to higher CuNP concentrations suggested that genotoxic impact of CuNPs was observed as well [207].

Considering the beneficial impact CuO NPs on the production of gymnemic acid II in *Gymnema sylvestre* (Retz.) R. Br cell suspension, which is 9.0-fold higher than that of the control [136] (Table 1), this method can be recommended for recovery of this anti-sweet compound.

4.3. Iron-Based NPs

4.3.1. Impact on Plant Growth and Assimilation Pigments

Chitosan-coated Fe₃O₄ NPs with sizes 3–22 nm applied at doses 200 and 400 mg/kg showed beneficial impacts on seed germination and growth of *Capsicum annuum* L. seedlings, whereby their efficiency was better than that of bare Fe₃O₄ NPs [214]. Priming of roots of 28-day-old chilli and marigold plants for 3 h in the suspension of FeS₂ NPs (100 µg/mL) prior to transplantation had beneficial impact on chilli yields and mean flower number of marigold, which was approximately doubled as compared to control (27 vs. 13) [215]. Introduction of 0.3 mg/L FeNPs (27.0 ± 0.51 nm) instead of FeSO₄ into a MS nutrient medium increased root length, root activity (evaluated as the reduction of triphenyltetrazolium), and leaf Chl in *Capsicum annuum* plants by 118, 58 and 5% related to control. A 10-fold higher FeNPs concentration increased Chl content even by 27% and beneficial impact on the above-mentioned characteristics were observed also at a combination of FeNPs with CuNPs or ZnNPs. It could be mentioned that the applied FeNPs concentration of 0.3 mg/L was 18.7-fold lower than that contained in standard MS medium [216].

Treatment with Fe₂O₃ NPs and a chelated Fe-EDTA fertilizer increased Fe content of *Arachis hypogaea* plants cultivated in pots compared to control; Fe₂O₃ NPs increased root

length, plant height, and biomass of peanut plants. The Fe₂O₃ NPs promoted the plant growth via regulating contents of phytohormones and antioxidant enzyme activities. Adsorption of Fe₂O₃ NPs onto sandy soil improved availability of Fe to the plants suggesting that Fe₂O₃ NPs can be used as fertilizer instead of traditional Fe fertilizers [91]. *Zingiber officinale* Rosc. plants cultivated hydroponically in Hoagland solution containing 100 ppm Fe₂O₃ NPs exhibited higher protein levels (1.699 µg/mL) compared to plants treated with Fe-EDTA (1.108 µg/mL) and plants cultivated without Fe³⁺ addition to nutrient solution (0.208 µg/mL). Similarly, in plants exposed to Fe₂O₃ NPs, the total Chl and carotenoid content was 1.18- and 1.28-fold higher than in plants treated with Fe-EDTA, and 2.23- and 2.25-fold higher than in control plants. Fe content in rhizome of Fe₂O₃ NPs-treated plants increased as well, suggesting that these NPs can be used to mitigate chlorosis [217].

Comparison of yield, growth, and Fe uptake of *Cuminum cyminum* L. plants grown on the calcareous soils and sprayed twice during the season, before and after flowering (with a 10 day interval), using three various Fe-containing fertilizers, showed that the highest weight of 1000 grains and plant growth was observed at application of Fe-nano-chelate using a dose 1 g/L, while treatment with Fe-siderophore was found to be the most suitable for seed fortification with Fe [218].

4.3.2. Elicitor Effect

Treatment of cell suspension cultures of *Dracocephalum polychaetum* Bornm with 100 ppm Fe₂O₃ NPs, static magnetic field (SMF) of 30 mT, as well as combined treatment with Fe₂O₃ NPs and SMF pronouncedly increased intracellular content of secondary metabolites, such as RA, naringin, apigenin, thymol, carvacrol, quercetin, and rutin; secretion of these secondary metabolites from cells exposed to the double stress (SMF and NPs) to the culture media was observed as well. Moreover, the applied treatments resulted in increased TPC, TFC, anthocyanins, lignin, and MDA contents and increased activity of PPO and PAL [143]. Exposures of HRs derived from 4-week-old leaves of *Dracocephalum kotschyi* Boiss and inoculated with *Agrobacterium rhizogenes* strain ATCC15834 to 75 mg/L Fe₂O₃ NPs for 24 h resulted in improved biomass accumulation and activities of antioxidant enzymes, enhanced TPC and TFC, and contents of some valuable secondary metabolites, such as RA and xanthomicrol, which reached 9.7- and 11.87-fold higher values than in the control [162].

Moreover, inoculation with *Agrobacterium rhizogenes* of HRs derived from cotyledon explants of *Hyoscyamus reticulatus* L, which were elicited with 900 and 450 mg/L FeNPs using exposure time of 24 and 48 h, respectively, achieved approximately fivefold higher content of tropane alkaloids, hyoscyamine, and scopolamine, and considerably higher activities of antioxidant enzymes compared to control [64]. Fe₂O₃ NPs acted as highly effective elicitor, increasing the growth and production of secondary metabolites of *Cichorium intybus* L. in HR culture induced by *Agrobacterium rhizogenes* strain 15834 [219]. Treatment of *S. rebaudiana* cultivated in vitro with 45 µg/L FeNPs resulted in beneficial impact on plant growth characteristics and production of stevioside, and rebaudioside A reached 4.2 ± 0.058 and 4.9 ± 0.068 mg/g (d.w.). At exposure to 135 µg/L FeNPs, the levels of TPC and TFC reached 3.2 ± 0.042 and 1.6 ± 0.022 mg/g (d.w.), respectively, although adverse effect on growth characteristics was observed. Exposure to 90 µg/L FeNPs resulted in increased activities of SOD, POD, CAT, and APX [220].

In cell suspension culture of *Hypericum perforatum* L. elicited with 100 ppb Fe₂O₃ NPs for 72 h, enhanced concentrations of hypericin (195.62 ± 10.00 vs. 16.272 ± 4.62 µg/g (d.w.)) and hyperforin (11.181 ± 0.17 vs. 2.072 ± 0.77 µg/g (d.w.)) compared to the control were observed, whereas the dry weight was comparable with control. It could be assumed that the Fe₂O₃ NPs may induce jasmonate production, playing a role in hypericin and hyperforin production, or can be involved in signal transduction process regulating jasmonate production genes in cells [141]. Simultaneous foliar application of 0.01% MgO NPs and 0.03% Fe₂O₃ NPs on *Hibiscus sabdariffa* plants exhibited synergistic and beneficial impact on the activity of antioxidant enzymes and anthocyanin and flavonoids levels, and

reduced H₂O₂ concentration in plants. On the other hand, at combined application of 0.03% MgO NPs and 0.03% Fe₂O₃, ROS production increased, and the antioxidant defense system was not able to attenuate toxic effects of produced H₂O₂ and, therefore, the observed characteristics were comparable to those of control plants [221].

Foliar treatment of *Ocimum basilicum* L plants grown in soil with Fe nanocomplexes Fe(His)₃ and Fe(Arg)₃ resulted in an increase of sesquiterpenes and a decrease of the content of oxygenated monoterpenes in the composition of secondary metabolites of EO, and enhanced antioxidant and antimicrobial activities of plants [222]. FeNPs applied foliarly to *Mentha piperita* L. at a dose of 1.5 g/L, three times of the interval of 15 days up to flowering stages, considerably enhanced contents of Chl and EO. Application of 0.5 g/L NPs increased the EO content and oil production by 60 and 50%, and menthone and menthol contents by 65% and 30%, respectively, compared to the control. On the other hand, at a threefold higher dose of FeNPs, menthofuran concentration was 2.5-fold higher than in the control [133].

Spraying of basil plants with 0.2% Fe-urea nanocomplex increased the content of epi- α -cadinol and *trans*- α -bergamotene to $27.09 \pm 2.5\%$ and $14.93 \pm 1.77\%$, respectively, although n-decane content was reduced strongly even by 99.1% and the concentration of RA achieved 5.81 ± 0.18 mg/g [223].

4.3.3. Attenuation of Abiotic Stress

Spraying of salt-stressed (100 mM of NaCl) *Dracocephalum moldavica* L. plants with Fe₂O₃ NPs considerably increased the leaf area, content of secondary metabolites (TPC, TFC, anthocyanins), as well as activities of antioxidant enzymes (GPX, APX, CAT, GR), suggesting improved antioxidant defense. Moreover, under salinity stress, the Fe₂O₃ NPs can serve as a source of Fe for this medicinal plant [224]. Application of Fe₃O₄ NPs was also able to greatly attenuate Cd and Pb induced toxicity in coriander plants grown in soil artificially contaminated with these toxic metals [225]. Treatment of *Mentha piperita* plants under salt stress with 10–30 μ M Fe₂O₃NPs improved the fresh and dry biomass of leaves, contents of essential elements such as P, K, Fe, Zn, and Ca, although did not affect Na content. Moreover, Fe₂O₃ NPs pronouncedly reduced lipid peroxidation and proline contents and decreased activities of CAT, SOD and GPX in salt-stressed plants [226]. In *Melissa officinalis* L. plants exposed to drought stress (80%, 60%, and 40% field capacity (FC)) considerable increase in MDA, H₂O₂, as well as proline content and electrolyte leakage was observed with decreasing FC, while TPC, activities of antioxidant enzymes, Chl content and relative water content were reduced. Although increasing of water deficit from 80% to 60% FC resulted in improved yield of EO, further reduction to 40% already showed an opposite effect. However, application of FeNPs (5–20 μ M) had beneficial impact on drought-stressed plants, which was reflected in further increase of EO yield, increased proline levels and mitigation of oxidative stress by activation of antioxidant defense system of plants and, thus, FeNPs protected the plants against oxidative stress damages [142].

4.3.4. Genotoxicity

Ghosh et al. [227] investigated the impact of FeNPs with different surface chemistries on the uptake, root morphology, DNA damage, oxidative stress, and cell death in *Allium cepa* roots after 24 h exposure. It was shown that FeNPs with low zeta potential, conductivity, and high polydispersity index, which were adsorbed on root surfaces, damaged the root tip, epidermal, and root hairs due to their colloidal destabilization and smaller size. High uptake of NPs was responsible for considerable DNA damage, chromosome/nuclear aberrations, and micronuclei formation. On the other hand, FeNPs, which were characterized with higher dissolution and substantial uptake, induced genotoxicity. Both types of FeNPs generated strong oxidation stress and in treated *A. cepa* roots ROS-mediated apoptotic and necrotic cell death was observed.

Elicitation of the production of hyoscyamine and scopolamine in HR of *Hyoscyamus reticulatus* L. by Fe₂O₃ NPs allows achieving ca. 5-fold higher amounts than in the con-

trol. This is a promising method that can be considered to produce tropane alkaloids [65] (Table 2). Moreover, 5.4- and 12-fold higher amounts of hypericin and hyperforin, compared to the control observed in cell suspension culture of *Hypericum perforatum* L., using 100 mg/L Fe₂O₃ NPs as an elicitor, suggest this method is very encouraging [141] (Table 1).

4.4. Zinc-Based NPs

4.4.1. Impact on Germination and Plant Growth

ZnO nanorods with a mean aspect ratio of 7, coated in gel and mixed with the seeds of *Solanum melongena* L. and *Capsicum annum* L., applied at doses 50, 100, and 150 mg/L, accelerated germination, which was reflected in reduced germination time and improved mean germination rate compared to control plants; application of 100 mg/L ZnO NPs ensured maximal transplant length as well as fresh and dry weight [228]. Amelioration of the seed germination rate and seedling vigor of *Capsicum annum* L. was observed at treatment with ZnO NPs suspensions at 100, 200, and 500 ppm, respectively. On the other hand, application of these ZnO NPs concentrations resulted in the inhibition of radical growth and stimulated accumulation of phenolic compounds [229]. Spraying of *Capsicum chinense* Jacq. plants during the main stages of phenological development with 1000 ZnO NPs stimulated plant height, stem diameter, and Chl content, and increased fruit yield and biomass accumulation in treated plants compared to control and treatment with ZnSO₄, whereas the double dose of ZnO NPs adversely affected plant growth [230].

Germination of seeds of *Abelmoschus esculentus* (L.) Moench was positively affected by treatment with ZnNPs (50–500 ppm), and in 30-day-old treated plants, an increase in Chl, protein, proline, and carbohydrate contents were observed, along with pronounced reduction of the carbohydrate content of leaves [231]. Spraying of leaves of 10-day old chickpea (*Cicer arietinum* L. var. HC-1) seedlings, with solution containing 1.5 ppm ZnO NPs, stimulated shoot dry weight, but when a dose of 10 ppm was applied, root inhibition was observed. Positive impact of ZnO NPs on plant biomass related to reduced ROS generation caused less lipid peroxidation, which also resulted in lower activity of antioxidant enzymes, such as SOD and POD, compared to the control [232]. Phytotoxic effects of the ZnO NPs and Zn microparticles (MPs) (10–2000 mg/L) on *Fagopyrum esculentum* was reflected in biomass reduction, increased Zn bioaccumulation in plants, and higher translocation factor of Zn being observed for treatment with ZnO NPs. Moreover, reduced glutathione level and CAT estimated at application of ZnO NPs indicated oxidative stress due to ROS generation [233]. In 6-week-old callus produced from leaf explants of *S. rebaudiana* Bertoni grown in MS medium supplemented with plant growth regulators addition of 0.1 mg/L ZnO NPs significantly enhanced fresh and dry weight of callus [117].

ZnO NPs (40 nm) positively affected growth of the *Echinacea leaf* callus and showed beneficial impact on the anticancer activity of plant extracts, in contrast to the control treatment with ZnO MPs. Moreover, application of ZnO NPs increased flavonoid contents of *Echinacea purpurea* [234]. A dose of 2000 ppm ZnO NPs increased dry weight of *Tanacetum parthenium* (L.) Schultz Bip plants from 28.09 g/day (control) to 32.54 g/day, while using 1000 ppm ZnO NPs, the EO content achieved 0.9% *v/w* compared to 0.56% *v/w* observed in the control plants; an increase in Zn absorption at application of ZnO NPs was observed as well, while Fe absorption was reduced [235].

ZnO NPs at doses 0.5–2.5 mg/L applied to hormone-free MS medium inhibited root growth of ginseng root culture, deceased the lateral root number, and decreased percentage of lateral root formation was observed at exposure to 2.5 mg/L ZnO NPs. In treated plants thinner vascular tissue or cortex area and more black points in root cap area were observed compared to control. On the other hand, exposure to ZnO NPs resulted in thicker endodermis [236].

Foliar application of ZnO NPs at doses 20, 60, and 100 ppm to *Momordica charantia* L. plants grown in pots did not considerably affect shoot weight and anthocyanin content, but pronouncedly increased Chl_a content, as well as contents of secondary metabolites (phenols, flavonoids, and carotenoids), along with carbohydrate and proline content in a

dose-dependent manner [132]. Growth characteristics in the callus of *Punica granatum* cv. Hegazy were adversely affected by 200 µg/mL ZnO NPs reflected in a stronger decrease in callus dry weight than at application of bulk ZnO (57.53% vs. 37.78%) and more elevated increment in Zn concentration over the control compared with that of ZnO bulk (335.24% vs. 247%) [237].

4.4.2. Elicitor Effect

Improved production of tropane alkaloids was observed using HRs obtained from two-week-old cotyledon explants of *Hyoscyamus reticulatus* treated with 100 mg/L of ZnO NPs after 48 and 72 h, when the levels of hyoscyamine and scopolamine reached 37.63% and 37%, respectively. The highest expression of h6h gene in HRs was observed at treatment with 100 mg/L of ZnO NPs after 24 h [67]. Zn-Ag NPs (molar ratio of 19:1) exhibiting photocatalytic and elicitor activity were able to improve the light absorption and increase oxidative stress in *Withania somnifera* plants, resulting in increased photosynthesis and transpiration rates along with an increase in some carbohydrates and enhanced content of withanolide, which was associated with upregulation of genes involved in photosynthesis, Calvin cycle, carbohydrate metabolism, and withanolide biosynthesis. Moreover, cyclic electron flux managing the electron flow around photosystem (PS) I was observed [63].

Spraying of *Capsicum chinense* Jacq. plants with 1000 ZnO NPs pronouncedly increased TPC, TFC, and content of secondary metabolites, such as dihydrocapsaicin in fruits, suggesting ameliorated nutraceutical quality of fruits [230]. *Hypericum perforatum* cell suspension cultures elicited with 100 ppm ZnO NPs stimulated production of hypericin and hyperforin, up to 7.87 and 217.45 µg/g d.w., providing 3 and 13-fold higher amounts compared to the control [141].

ZnO NPs capped with PEG and PVP enhanced TPC, TFC, content of steviol glycosides in shoots of *S. rebaudiana* Bertoni cultured in vitro more than uncapped ones [211]. By application of 2 mg/L ZnO NPs, 91% induction of in vitro roots formation in regenerants of *S. rebaudiana*, and increased contents of secondary metabolites of rebaudioside A (2.96% vs. 4.42%) and stevioside (1.01% vs. 1.28%) in leaves, compared to the control, were observed. With application of increasing ZnO NPs, the content of secondary metabolites gradually decreased to 1.22% and 0.21% for rebaudioside A and stevioside, respectively, corresponding to the values observed under stress induced by 2000 mg/L ZnO NPs [135]. In contrast to the beneficial impact of 1 mg/L ZnO NPs on shoot formation of micropropagated *S. rebaudiana* and steviol glycosides levels, which were practically doubled compared to control, further increase of ZnO NPs was accompanied with a decrease in formation of secondary metabolites and antioxidant activities, and at application of 1000 mg/L ZnO NPs, a strong phytotoxic effect was observed [137]. Toxic impact of ZnNPs (<100 nm) applied at concentrations 400–1000 mg/L accompanied with pronounced reduction of stevioside was also observed in the nodal explants of *Stevia* cultured in vitro on MS medium [238]. Fertilization of *Stevia rebaudiana* with 75 mg/L of green synthesized ZnO NPs through roots enhanced the concentrations of TPC and TFC and Zn content up to 406.8% with respect to the control, although the biosynthetic pathway of steviol glycosides was not affected; treatment did not show adverse impact on plant growth [139].

Seedlings of flax (*Linum usitatissimum*) cultivated on MS in the presence of 10 mg/L ZnO NPs showed improved growth compared to control, while application of 500 mg/L ZnO NPs increased the production of secoisolariciresinol diglucoside, lariciresinol diglucoside, dehydroniciferyl alcohol glucoside and guaiacylglycerol-β-coniferyl alcohol ether glucoside. In another experiment, in which the stem explants were cultured on MS media supplemented with plant growth regulator and 25 mg/L ZnO NPs, enhanced rooting effect and effective accumulation of metabolites was observed [138].

In *Thymus kotschyanus* and *T. daenensis* micropropagated in the presence of 150 mg/L ZnO NPs thymol and carvacrol contents of 22.8 mg/L and 0.68 mg/L, respectively, were reported by [172]. Treatment of *Glycyrrhiza glabra* L. seedlings with 1 and 10 µM ZnO NPs

increased the contents of glycyrrhizin, TPC, TFC, anthocyanins and proline, whereas by application of bulk ZnO at a dose of 10 μ M content of tannins was enhanced [239].

4.4.3. Impact on Antioxidant Enzymes

Growth of fresh and dry weight of HRs treated with 100 mg/L ZnO NPs showed a decrease compared to the control, whereas activities of CAT, GPX, and APX were considerably higher than in the control [67]. Significant increase of CAT activity was observed at application 60 and 100 ppm of ZnO NPs to *Momordica charantia* L. plants grown in pots, but the activities of GPX and AXP were not affected [132].

In cell suspension cultures of *Linum usitatissimum* L. exposed to ZnO NPs, the highest PAL activity was observed at treatment with 30 mg/L for 48 h, whereas at application of 60 mg/L ZnO NPs, the highest activity of cinnamyl alcohol dehydrogenase was achieved. On the other hand, using both above-mentioned ZnO NP concentrations, the highest TPC and lignan amounts could be obtained [140]. In seedlings of flax (*Linum usitatissimum*) cultivated on MS medium and in stem-derived callus, the presence of ZnO NPs (1–1000 mg/L and 10–50 mg/L, respectively) caused the dose-dependent ROS generation. A differential induction of SOD (in seedlings) vs. POD (in vitro cultures) enzymes was observed. At concentrations > 500 mg/L (seedlings) and >25 mg/L ZnONPs (callus) oxidative damage was observed [138].

Spherical green synthesized ZnO NPs with mean size of 41 nm had positive impact on root and shoot length of *Borago officinalis* plants, but did not affect significantly soluble sugar and anthocyanin levels, and CAT activity in the plants. Due to enhanced ROS generation by ZnO NPs, the contents of proline and Chl decreased and oxidative stress in plants was accompanied with increased H₂O₂ content, lipid peroxidation, phenol content, and APX, GPX, PAL activities [240].

ZnO NPs capped with PEG and PVP enhanced total antioxidant capacity, total reducing power and DPPH free radical scavenging activity in shoots of *S. rebaudiana* Bertoni cultured in vitro more than uncapped ZnO NPs, concentration 1 mg/L being highly effective [211]. Addition of 100 mg/L ZnO NPs resulted in effective increase in TPC, TFC, total antioxidant capacity and DPPH free radical scavenging activity in 6-week-old callus produced from leaf explants of *S. rebaudiana* Bertoni grown in MS medium; the highest total reducing power was observed at application 50 mg/L ZnO NPs [117].

4.4.4. Cytotoxic and Genotoxic Effects

Cytotoxic and genotoxic impact of ZnO NPs (5 and 50 μ g/mL) causing oxidative stress in roots of *Allium cepa* was reflected in lack of membrane integrity, reduced metabolic activity, ROS generation, chromosome aberration, DNA damage, cell-cycle arrest, and cell death in onion roots; considerably higher Zn levels were estimated in the cytoplasmic and nuclear fractions of *A. cepa* roots. It was confirmed that, for the toxicity of ZnO NPs suspension beside Zn²⁺ ions, predominantly ZnO NPs were responsible [241]. Similar effects were observed by Ghosh et al. [242] who treated *A. cepa* roots with ZnO NPs having a size of 85 nm, which deregulated the components of ROS antioxidant machinery causing DNA strand breaks and cell-cycle arrest at the G₂/M checkpoint. Mitochondrial and chromosomal damage induced by oxidative stress in *A. cepa* roots treated with Zn²⁺ ions, bulk ZnO, and ZnO NPs (25 nm) was also reported by Ahmed et al. [243]. ZnO NPs attachment and internalization, and a considerable increase in levels of thiobarbituric acid reactive substances and antioxidant enzymes in treated roots, were observed as well. Summarizing the adverse effects of ZnO NPs on onion roots, they can be considered as a clastogenic/genotoxic and cytotoxic agent [244]. Treatment of *A. cepa* roots with 100 mg/L ZnO NPs reduced MI compared to the control (53.2% vs. 63.6%), which further decreased to 50% under UV irradiation. At application of 0.1 mg/L with ZnO NPs lagged metaphase and anaphase with multiple chromatin bridges in the root tip cells were recorded, although at doses 10 mg/L and 100 mg/L, respectively, both stickiness and diagonal anaphase were

predominant. It was observed that, following exposure to ZnO NPs, the generation of ROS and MDA was accelerated [245].

Elicitation of the production of hyoscyamine and scopolamine in HR of *Hyoscyamus reticulatus* L. by ZnO NPs allows achieving 4.61- and 3.20-fold higher amounts than in the control. This is a promising method that can be considered to produce tropane alkaloids [67] (Table 2). Moreover, 3.80- and 13.36-fold higher amounts of hypericin and hyperforin compared to the control observed in cell suspension culture of *Hypericum perforatum* L. using 100 mg/L ZnO NPs as an elicitor suggest this method as very encouraging [141] (Table 1).

4.5. TiO₂-Based NPs

TiO₂ NPs may have a positive effect on photosynthetic efficiency by increasing electron transport between the PSII and PSI, positively affecting Rubisco activity in the Calvin and Benson cycle [246].

4.5.1. Impact on Germination, Plant Growth and Assimilation Pigments

TiO₂ NPs (10–25 nm) applied at doses 20–40 mg/L were found to accelerate the germination characteristics of *Alyssum homolocarpum*, *Carum copticum*, and *Nigella sativa* seeds, and increase their vigor, while most effective stimulation of germination of *Salvia mirzayanii* seeds was obtained with 80 mg/L TiO₂ NPs [247]. TiO₂ NPs (43 nm) coated in gel, which were mixed with the seeds of pepper using doses 50, 100, and 150 mg/L, accelerated germination and enhanced lengths, fresh and dry weights of seedlings compared to control, concentration of 100 mg/L TiO₂ NPs being the most effective [228]. Nanopriming of seeds with TiO₂ NPs (anatase) (10–40 mg/mL) considerably enhanced germination as well as morphological characteristics and Chl content of *Petroselinum crispum* seedlings grown in vitro in MS medium, the dose of 30 mg/L being the most effective [248]. Exposure to 40 ppm TiO₂ NPs improved fennel seed germination time by 31.8% in comparison to the untreated control, while treatment with 40 ppm TiO₂ NPs improved dry weight compared to the untreated control [249]. On the other hand, Khater and Osman [250] reported that spraying of fennel plant with 6 ppm TiO₂ NPs enhanced Chl synthesis, which was reflected in improved photosynthesis.

Foliar treatment of *Mentha piperita* plants with TiO₂ NPs using a dose of 150 mg/L increased fresh and dry weights by 48% and 62.6%, and nitrate reductase and carbonic anhydrase activities 150 days after planting by 17.7% and 19.1%, respectively, compared to control plants; an increase of nitrogen content, stomatal conductance, and net photosynthetic rate by 12.6%, 8.5% and 23.8%, respectively, compared to the control plants, was observed as well. Diameter and density of peltate glandular trichomes, which are important from the aspect of EO production, were increased by 77.8% and 62.5%, respectively, at treatment with 100 mg/mL TiO₂ NPs [144]. *Mentha piperita* L. and *Salvia officinalis* L. plants exposed to TiO₂ NPs either via the leaves (using TiO₂ NPs suspension) or via the root system (in soil) resulted in reduced Chl contents in *M. piperita* and *S. officinalis* plants treated through root system, but not after application of NPs suspension on leaves of sage plants, likely due to the abundance of trichomes, providing a natural barrier for the NP accumulation to the symplast. In the soil-exposed plants translocation of uptaken TiO₂ NPs from roots to shoots resulted in reduced Chl levels. The reduction of Chl correlated mainly with the loss of Mg (sage) and Mn (peppermint) in treated plants [251].

Foliar application of 0.04% TiO₂ NPs improved the contents of total Chl, carotenoids, and soluble proteins, as well as grain yield of safflower plants to greater extent than application of 0.02% TiO₂ NPs and bulk TiO₂ [252].

In contrast to smaller TiO₂ NPs of 50 nm, larger TiO₂ NPs of size 68 nm had beneficial effect on germination of *Abelmoschus esculentus* seeds. However, the small-sized TiO₂ NPs applied at a dose of 200 mg/kg pronouncedly increased Chl_a and total Chl content compared to the control; a dose of 800 mg/kg considerably increased fresh weight of plants compared to the control. On the other hand, both types of NPs reduced APX in roots and leaves, whereas GR activity in roots decreased, but increased in the leaves. A considerable

raise of SOD activity in roots and leaves of plants exposed to TiO₂ NPs signaled their phytotoxic impact. Moreover, treatment with TiO₂ NPs caused a size-dependent and dose-dependent decrease in essential minerals Ca, Mg, and Fe contents in fruits, as well as adversely altered the proximate compositions (except carbohydrate) of fruits [253].

Treatment with TiO₂ NPs at 50–200 mg/L (83.7 nm) moderately increased the root and shoot fresh biomass of *Coriandrum sativum* L. plants cultivated in hydroponic solution. At application of 100–400 mg/L TiO₂ NPs, enhanced activities of SOD, CAT, and APX mitigated the oxidative stress; pronouncedly reduced root fresh biomass and water content was observed using a dose of 400 mg/L. At exposure to 50 mg/L TiO₂ NPs stimulated accumulation of Ca, Mg, Fe, Mn, Zn, and B in shoots, resulting in improved nutrient quality of edible plant parts was observed; internalization or translocation of TiO₂ NPs to shoots was not detected [254]. At studying of the transgenerational effects TiO₂ NPs in *Ocimum basilicum* plants, it was found that hydrophobic or hydrophilic TiO₂ NPs exhibited beneficial impact on plants growth, but more negative effects on photosynthesis compared to pristine TiO₂ NPs. Treatments with hydrophobic and hydrophilic TiO₂ NPs resulted in the reduction of Chl_b and total Chl by 52% and 30%, respectively, while total sugar and reducing sugar contents achieved 186% and 145% of contents observed in unexposed plants in both cycles [255].

Spraying of *Vetiveria zizanioides* plants with 90 mg/L TiO₂ NPs, which was performed 300 d after transplantation, increased the Chl content and maximum photochemical efficiency of PS II and yield of EO by 27.2%, 23.5%, and 55.1%, respectively, compared to the control [145].

4.5.2. Elicitor Effect

Spraying of *S. rebaudiana* Bertoni plants with 400 ppm TiO₂ NPs showed pronounced beneficial effect on fresh and dry weights of shoots, while application of 200 ppm mostly enhanced stevioside glycoside and reduced MDA levels [147]. In addition, application of 100 mg/L TiO₂ NPs also increased EO content and contents of important secondary metabolites. Moreover, TiO₂ NPs ameliorated agronomic traits and increased antioxidant enzyme activities in *D. moldavica* L. plants grown under salt stress, and considerably reduced H₂O₂ levels [149].

The beneficial impact of 150 mg/L TiO₂ NPs on foliarly treated *M. piperita* plants was reflected in an increase of EO yield up to 105.1% and application of 150 mg/L TiO₂ NPs increased the yields of menthol, menthone, and menthyl acetate by 124.1%, 169.4%, and 130.5%, respectively, over the control, whereby contents of these secondary metabolites were enhanced as well [144]. Concentration of 0.06% TiO₂ NPs was reported as most favorable for foliar spraying of *Cuminum cyminum* L. to achieve the highest EO yield of cumin [256]. Treatment of black cumin plants in the early flowering stage with 100 mg/L TiO₂ NPs promoted the geranyl diphosphate synthase (GPPS) expression 24 h after treatment more than application of a half dose, which resulted in improved production of thymoquinone [257]. TiO₂ NPs applied foliarly at a dose 100 mg/L acted as an elicitor by improving secondary metabolism in *S. officinalis* plants resulting in enhanced biosynthesis of natural antioxidants and at application of 100 mg/L TiO₂ NPs highest dry weights of roots and shoots were observed as well [146]. Spraying of rosemary leaves with TiO₂ NPs (7-times, using doses 20–400 ppm) pronouncedly affected quantity of EO, mostly increasing the content of secondary metabolites, although at concentrations >200 ppm some of these compounds (e.g., β -pinene, 3-pinanol, myrcene, 1,8-cineol) showed a decrease [258].

Ebadollahi et al. [154] compared the effect of TiO₂/perlite nanocomposites (15.50–24.61 nm) applied at doses 25–200 mg/L on production of secondary metabolites in the calli obtained from in vitro, as well as from field grown plants of *Hypericum perforatum*. They found that, at application of 25 mg/L TiO₂/perlite NCs, the enhancement of alkaloids production in the calli obtained from in vitro grown plants related to control was almost by one order higher than in calli obtained from field grown plants. Exposure of *Tanacetum parthenium* L. grown in greenhouse to TiO₂ NPs affected the expression of genes involved in

biosynthesis pathway of parthenolide and β -caryophyllene; TiO₂ NPs upregulated the costunolide synthase (COST) and feverfew (*T. parthenium*) germacrene A synthase (TpGAS) but downregulated the feverfew (*T. parthenium*) (E)- β -caryophyllene synthase (TpCarS) with increasing time from 6 to 24 h. Exposure to salinity increased the expression of these three genes with increasing time, suggesting that TiO₂ NPs and salinity can be used as elicitors for achieving more effective production of secondary metabolites [259].

Khusimol content and yield of *Vetiveria zizanioides* plants sprayed with 90 mg/L TiO₂ NPs 300 d after transplantation increased by 24.5% and 93.2%, respectively, compared to control [145]. In hydroponically cultivated *Nigella arvensis* plants treated for 21 days with TiO₂ NPs increased amounts of secondary metabolites, such as glaucine and quercetin, as well as higher TPC levels were observed compared to the control, although the concentrations of the elicitor providing the highest levels of individual bioactive components differed each from other [148].

4.5.3. Attenuation of Abiotic Stress

Treatment of *Verbascum sinuatum* plants exposed to artificial drought conditions (−0.6 MPa) with 20 ppm TiO₂ was found to mitigate negative impact of water deficit on growth characteristics and contents of assimilation pigments by stimulation of antioxidant defense systems, resulting in improved drought tolerance [260]. Foliar application of 10 ppm TiO₂ NPs increased shoot dry mass and EO content of *Dracocephalum moldavica* L. plants and in plants exposed to drought stress. Plants grown under water deficit, which were treated with 10 ppm TiO₂ NPs, had more proline and considerably lower content of H₂O₂ and MDA compared to untreated plants, suggesting that TiO₂ NPs can mitigate water deficit-induced oxidative damages. On the other hand, assimilation pigments in leaves were pronouncedly reduced in *Dracocephalum moldavica* plants treated with 10 ppm TiO₂ NPs [261]. Whereas spraying with TiO₂ NPs positively affected growth of *Thymus vulgaris* cultivated under drought stress, it did not affect the components of EO [262].

TiO₂ NPs (2 and 5 ppm) increased tolerance of *Glycyrrhiza glabra* L. plants to cold stress, reduced MDA and H₂O₂ levels in cold-stressed (4 °C) plants, resulting in lesser oxidative damage, and increased the contents of phenolics, total protein, and osmolytes [263]. Treatments of sensitive and tolerant chickpea genotypes with TiO₂ NPs did not induce oxidative damage in plants, which were able to mitigate membrane damage and electrolyte leaching, and pronouncedly reduce MDA content also under cold stress conditions via improved redox status of the genotypes, with a concentration of 5 ppm TiO₂ NPs being the most effective [264].

Everyday spraying with TiO₂ NPs at doses 25 and 50 mg/L was found to prevent *Crocus sativus* L. plants cultivated hydroponically against harmful effects on morphological characteristics of plants caused by UV irradiation (30 and 45 min daily for one month). Combined treatment reduction of dissolved sugars, increased levels of total anthocyanins and MDA in leaves, as well as higher radical scavenging activity were observed; a raise in TPC and TFC in saffron stigmas was estimated as well, which could contribute to enhanced nutritive value of saffron [265].

TiO₂ NPs (anatase; 10–25 nm) were able to increase concentrations of assimilation pigment in leaves of flax under normal and water deficit conditions, reduce the levels of H₂O₂ and MDA, resulting in lower degree of lipid peroxidation, particularly at a dose of 10 mg/L, and enhance seed oil and protein contents in treated plants [266]. In cell suspension cultures of flax exposed to 50, 100, and 150 mg/L TiO₂ NPs, increased activity of cinnamyl alcohol dehydrogenase and maximum TPC content was observed at application of 150 mg/L TiO₂ NPs; TiO₂ NPs at tested concentrations increased the total lignan content as well [140].

4.5.4. Genotoxicity

Using *A. cepa* root tip test, it was shown that TiO₂ NPs (>50 nm) applied at 0.1 and 100 g/L reduced the MI from 63.6% (control) to 59.5% and 53.5%, respectively, and at

additional UV stress further decrease to 58.0% and 51.4%, respectively, was observed. Whereas at treatment with 0.1 mg/L TiO₂ NPs (anaphase) multiple chromatin bridges, at exposure to 10 mg/L and 100 mg/L TiO₂ NPs distributed and fragmented chromosomes can be observed. The chromosomal aberration of *A. cepa* root cells can be associated with accelerated generation of ROS and higher MDA levels at the presence of TiO₂ NPs [245]. Similar results were observed also by Pakrashi et al. [267] or Ahmed et al. [268] who reported that due to oxidative stress induced by of TiO₂ NPs the ROS levels as well as SOD and CAT activities of *A. cepa* roots increased by 10%, 20.8%, and 12.4%, respectively, and the levels of O₂⁻ in roots showed a dose-dependent increase. TiO₂ applied at a dose 1000 mg/L caused DNA damage in *A. cepa* root meristem cells, which, expressed as %DNA tail, achieved 56.54 ± 3.82% and 37.57 ± 3.60% for TiO₂ NPs of 50 and 21 nm, respectively [269].

Considering 2.4-fold enhancement of glaucine in *Nigella arvensis* L. plants cultivated in hydroponic system in the presence of 2500 mg/L TiO₂ NPs, this method seems to be suitable to achieve enhanced levels of this aporphine alkaloid in *N. arvensis* plants [147] (Table 1).

4.6. NPs of Other Metals

4.6.1. MgO NPs and Mn₂O₃ NPs

Elicitor Effect

MgO NPs immobilized on the surface of nanoperlite using *Melissa officinalis* extract as a capping agent applied at doses 25, 50, and 150 mg/L of MgO/perlite NCs, showing the size 30 nm elicited in vitro biosynthesis of RA in *M. officinalis* plant organ cultures [270]. Mn₂O₃ NPs (ca. 30 nm) supplemented to MS culture medium with tissue culture of *Atropa belladonna* at doses 25–200 mg/L affected growth characteristics, leaf relative water content, Chl levels, H₂O₂, and MDA contents, and electrolyte leakage by altering the protein content and activation of antioxidant and defense enzymes. Mn₂O₃ NPs also affected biosynthesis of secondary metabolites, including TPC, TFC, and alkaloids in a dose-dependent manner. Application of 25 mg/L Mn₂O₃ NPs was found to promote not only plant growth, but also the production of alkaloids in shoot tip cultures of *Atropa belladonna*, which reached 1.84- and 2.92-times greater levels as that of positive (22.3 mg/L MnSO₄ · 4H₂O) and negative (medium without Mn) controls, respectively. Extracts prepared from plantlets showed antioxidant properties [151].

Attenuation of Abiotic Stress

Mn compounds are able to stimulate crop growth and mitigate abiotic stress, whereby at application of nanosized Mn particles, higher efficiency in attenuation of abiotic stresses and less toxic effects can be achieved compared to bulk Mn particles. In addition, plant Mn deficiency can be overcome by additional supply of Mn, resulting in induction of manganese superoxide dismutase at the transcriptional level, to suppress ROS production and promote Mn-dependent proteins for preservation of cell integrity [271].

Genotoxicity

Chromosomal aberrations and a decrease in MI compared to the control, with a pronounced raise in H₂O₂ and O₂⁻ production and lipid peroxidation, was observed in *Allium cepa* roots treated with 12.5–100 µg/mL MgO MPs and MgO NPs, the toxicity of NPs being higher [272].

4.6.2. CoNPs

Elicitor Effect

Artemisia annua cell suspension culture exposed to 5 mg/L CoNPs for 24 h achieved artemisinin content of 113.35 mg/g (d.w.), being 2.25-fold higher than that of the control. Increased artemisinin production was assumed to be associated with decreased expression levels of SQS and DBR2 genes playing essential roles in the regulation of artemisinin pathway [134].

4.6.3. NiNPs and NiO NPs

Impact on Plant Growth

Exposure of *Coriandrum sativum* L. plants to NiNPs with mean particle size 20 nm, applied at doses 20, 40, and 80 ppm for 22 days, resulted in reduced water content, root, and shoot growth, decreased levels of photosynthetic pigments, lower antioxidant activity and increased NiNPs content in plants, suggesting toxic effect of NiNPs on this medicinal plant [273]. In vitro grown seedlings of *Abelmoschus esculentus* treated with NiO NPs (100–1000 mg/L) showed impaired plant growth, lower Chl content, pronouncedly altered levels of anthocyanin contents, TPC, and TFC and increased ROS and MDA levels, suggesting phytotoxicity of NiO NPs [274].

Elicitor Effect

Nigella arvensis plants treated with 50 mg/L NiO NPs resulted in 2.2- and 1.8-fold higher quercetin content in the shoots and roots compared to the control plants. On the other hand, following exposure of black cumin plants to 1000 mg/L NiO NPs up to 3.2-fold higher glaucine content in shoots, 2.9-fold higher kaempferol content in roots, and considerably higher levels of TPC and TFC were observed compared to the control plants, suggesting that NiO NPs can be used as an elicitor for effective in vitro production of secondary metabolites [148].

Genotoxicity

Treatment of *Allium sativum* L., *Allium schoenoprasum* L., *Allium porrum* L., and *Allium fistulosum* L. growing root tips with NiO NPs, even at a dose of 10 mg/L induced genotoxicity in plants. NiO NPs caused perturbation of biochemical homeostasis and disrupted normal physiology of the cells, which was reflected in enhanced lipid peroxidation, MDA levels, and activities of antioxidant enzymes (CAT, SOD, and GPX) [275].

4.6.4. Cr₂O₃ NPs

Genotoxicity

Chromosomal aberrations and cytogenetic effects in root tip cells of *A. cepa* due to exposure to Cr₂O₃ NPs (0.01–100 µg/mL) were reported by Kumar et al. [276] and in *A. cepa* roots treated with 25–100 ppm Bi₂O₃ stickiness chromosome laggards, disturbed anaphase-telophase, and anaphase bridges were observed in anaphase-telophase cells, pro-metaphase, and c-metaphase in other cells, as well as a pronounced rise in DNA damage [277].

4.6.5. CeO₂ NPs

Coriandrum sativum L. plants germinated and cultivated for 30 days in soil amended with 125 mg/kg CeO₂ NPs were characterized with longer roots, pronouncedly increased CAT activity in shoots, and APX activity in roots, and changed the chemical environment of carbohydrates in shoots, suggesting impact of CeO₂ NPs on the nutritional properties of cilantro [278]. Green synthesized organometallic CeO₂ nanostructures with mean size 38 ± 5 nm applied at a dose of 4 mg/L increased callus induction of *Berberis lycium* Royle to 90%, whereas using a dose of 20 mg/L direct shoot regeneration was improved to 79% [279]. On the other hand, CeO₂ NPs (≈20.28 nm) and bulk CeO₂ (≈4.24 µm) particles applied at doses 12.5–100 ppm for 4 h exhibited cytotoxic and genotoxic effects on the root meristem cells of *A. cepa* reflected in decreased MI values, considerably increased chromosomal aberrations including chromosome laggards, disturbed anaphase-telophase, stickiness, bridges, and caused DNA damage [280].

4.6.6. Al₂O₃ NPs

Due to oxidative stress induced in roots of *A. cepa*, which were exposed to Al₂O₃ NPs—ROS, SOD, and CAT activities were enhanced by 30%, 17.1%, and 13.2%, respectively, as compared to the control and the levels of O₂[−], which showed a dose dependent increase [268].

Genotoxicity

Exposure of *A. cepa* roots to Al₂O₃ NPs showed chromosomal aberration, whereby application of low Al₂O₃ NPs concentration (0.1 mg/L) disturbed metaphase. At treatment with 10 and 100 mg/L Al₂O₃ NPs—abnormal anaphase and sticky metaphase were observed; reduction of MI and generation of ROS was observed as well [245]. Genotoxic effects and oxidative damage on *A. cepa* caused by Al₂O₃ NPs were pronouncedly higher than those of bulk Al₂O₃, and a considerable raise of GPX accompanied with the depletion in CAT activity was observed in plants treated with both Al₂O₃ NPs and bulk Al₂O₃, respectively [281].

4.6.7. AuNPs

Elicitor Effect

AuNPs (24.2 ± 2.4 nm) applied at concentrations of 50 and 10 mg/L, respectively, elicited biosynthesis of secondary metabolites in *Lavandula angustifolia* in vitro cultures, whereby lower molecular weight compounds of EO (e.g., α- and β-pinene, camphene, δ-3-carene, *p*-cymene, 1,8-cineole) were replaced by compounds showing higher molecular weight, e.g., cadalene, α-bisabolol, and (*E,E*)-farnesol [130]. Spraying of shoots of 6-year-old ginseng plants with AuNPs, performed 3-fold, increased the content of ginsenosides Rg1, Re, Rf, and Rb1; using the steaming process only, the levels of Rd and Rg3 were enhanced [282].

Considering 3.2-fold enhancement of glaucine in *Nigella arvensis* L. plants cultivated in hydroponics in the presence of 1000 mg/L NiO NPs, this method seems to be suitable to achieve enhanced levels of this aporphine alkaloid in *N. arvensis* plants [136] (Table 1).

5. Effect of Metalloid-Based NPs on Medicinal Plants

5.1. Silicon and Silica NPs

Silicon has beneficial impact on plants, particularly under stress conditions, and is considered a non-essential beneficial plant nutrient. It ameliorates not only the vigor of plants, but also their resistance to exogenous stresses [50,283,284].

5.1.1. Impact on Germination and Plant Growth

SiO₂ NPs applied at a dose of 400 mg/L pronouncedly improved seed germination, enhanced the length and fresh/dry weight of plant organs of *Nigella sativa* L., and increased levels of photosynthetic pigments, total protein, total amino acid, and proline [285]. Irrigation of hawthorn (*Crataegus aronia* L.) seedlings with SiO₂ NPs at doses 10, 50, and 100 mg/L for 45 days before exposure to drought stress resulted in improved plant biomass, xylem water potential, and MDA content, especially under drought conditions, and had positive influence on photosynthetic pigments; relative water content and membrane electrolyte leakage were not affected and carbohydrate and proline content showed a decrease under all water regimes, especially under water stress [286]. Plants grown on MS medium from *Matricaria recutita* seeds treated for 1 h with SiO₂ NPs (4 or 6 g/L) were characterized with improved growth characteristics, higher relative water content, TPC, and TFC, but reduced levels of H₂O₂ and MDA [153].

5.1.2. Elicitor Effect

Pretreatment of *Calendula officinalis* L. seeds with 200 mg/L SiNPs resulted in maximal increase of quercetin content in plants grown under 50% FC [287]. Treatment of *Tanacetum parthenium* L. plants with 25 mM SiO₂ NPs increased the expression of TpGAS, COST, and TpCarS genes, which are involved in the biosynthesis pathway of the secondary metabolites, parthenolide, and β-caryophyllene, when the time increased from 6 to 24 h, and a similar effect on the expression of genes exhibited salinity stress [259]. *Mentha piperita* L. plants treated with 50 and 100 mg/L SiNPs considerably enhanced the density and diameter of the peltate glandular trichomes, Chl content, net photosynthetic rate, TPC, and EO content, as well as content of secondary metabolites at 150 days after plantation [152].

Dracocephalum kotschyi HRs elicited by 100 mg/L SiO₂ NPs after 48 h exposure time showed considerable increase in biomass compared to the control and pronounced enhancement of the expression of *pal* and *ras* genes, as well as a strong increase in several secondary metabolites was observed as well [163]. SiO₂ NPs and TiO₂ promoted the expression of GPPS, a key gene involved in thymoquinone biosynthesis pathway in *Nigella sativa* L. plants, TiO₂ NPs being more effective, and a dose of 100 mg/L raised the gene expression more than that of 50 mg/L. The tested NPs acting as elicitors increased the biosynthesis of thymoquinone in plants via upregulation of related metabolic pathway genes [257]. Continuous production of metabolites from plant cultures using nanoharvesting, in which NPs are designed to bind and carry biomolecules out of living cells, was described by Khan et al. [288] who treated *Solidago nemoralis* HR cultures in MS medium with mesoporous SiO₂NPs (165 nm diameter) functionalized with both TiO₂ (425 mg/g particles) for coordination binding sites, and NH₂ (145 mg/g particles) to stimulate cellular internalization in order to obtain increased production of polyphenolic flavonoids. Moreover, observed post-nanoharvesting growth indicating the viability of the roots after nanoharvesting, and thus their ability to synthesize henceforward the flavonoids, suggested that application of NPs can facilitate continuous isolation of many biologically active compounds from living and functioning plant cultures.

5.1.3. Attenuation of Abiotic Stress

SiNPs effectively reduced adverse effect of saline stress on leaf dry and fresh weight and Chl content in *Ocimum basilicum* plants and increased proline levels at exposure to SiNPs suggested induction of the tolerance in basil plants [289]. Exposure of *Allium cepa* roots to non-irradiated suspensions of SiO₂ NPs and those irradiated with UV-A light did not lead to the adsorption of SiO₂ NPs on the root surface and no considerable adverse impact was observed even at high exposure concentrations. Consequently, it can be supposed that cell wall shielded the cell membrane from direct contact with NPs. It could be mentioned that similar results were obtained also with application of TiO₂ NPs showing photocatalytic potential [290]. Priming of *Calendula officinalis* L. seeds with 200 mg/L SiNPs greatly enhanced antioxidant activity and TFC of plants exposed to drought stress of 25% FC [287].

Production of rosmarinic acid elicited by SiO₂ NPs in HR of *Dracocephalum kotschyi* achieving up to 8.26-fold higher yield compared to control can be considered as very promising [163]. However, also beneficial impact of foliar treatment of *Mentha piperita* plants with 100 mg/L SiNPs resulting in nearly double enhancement of menthol, menthone and menthyl-acetate in plants seems to be convenient for application also in the field [152] (Table 1).

5.2. Selenium NPs

Selenium is a member of the chalcogen family. It is classified by some researchers as metalloid showing intermediate properties between metals and nonmetals [291,292]. It resembles chemically to sulfur and shares a similar pathway for uptake and translocation in plants.

5.2.1. Impact on Plant Growth and Elicitor Effect

Impact of SeNPs and nitric oxide on growth, metabolism, antioxidant machinery, gene expression, and flowering *Cichorium intybus* L. plants was discussed by Abedi et al. [293]. Stimulating effect on *Capsicum annuum* grown in vitro in MS medium was observed after addition of 0.5 and 1.0 mg/L SeNPs; considerable induction in nitrate reductase activity was observed as well [294]. The low doses of 0.5 and 1 mg/L of SeNPs showed growth-stimulating effects of growth of *Capsicum annuum* grown in vitro in MS medium, while higher SeNPs concentrations (10 and 30 mg/L) were found to be phytotoxic due to DNA hypermethylation, upregulation of the bZIP1 transcription factor as well as upregulation of the expression of the WRKY1 transcription factor and inhibition in the differentiation of

xylem tissues [294]. Exposure of *Ocimum basilicum* plants to CdSSe quantum dots (QDs) and Cd²⁺ ions resulted in an initial adverse impact on plant growth, but after 3 and 6 weeks, the roots of treated plants were comparable with those of the control group. Although the *Ocimum basilicum* plants exposed to CdSSe QDs accumulated Cd predominantly in roots, when they were applied at doses 25 and 50 mg/kg of plant material, higher translocation of Cd to shoots was observed compared with application of Cd²⁺ ions during 3 and 6 weeks. This can be related to the functional groups on the surface of QDs, which make easier their movement by the cationic transporters or permit free movement of QDs through the cells, whereas due to interaction of Cd²⁺ ions with CO₃²⁻ and PO₄³⁻ species inside the plant, insoluble salts are formed, which can be immobilized in the apoplastic or symplastic compartments [295].

5.2.2. Elicitor Effect

Treatment of *Capsicum annuum* grown in vitro in MS medium with SeNPs enhanced the activity of phenylalanine ammonia-lyase and concentrations of soluble phenols as well [294]. Similar results were obtained at in vitro treatment of *Momordica charantia* with SeNPs [296].

6. Effects of Carbon-Based NPs on Medicinal and Aromatic Plants

In addition to biochar, which is widely used to improve soil quality, nanoscale carbonaceous materials, such as carbon dots (CDs), graphene (GR), graphene quantum dots (GR QDs), graphene oxide (GO), reduced GO (rGO), fullerenes, single-walled (SWCNTs), and multi-walled carbon nanotubes (MWCNTs) on plants are also increasingly used in agriculture [40,297–299]. CDs are quasi-spherical carbon-based NPs (>10 nm) with a core that can be either amorphous or nanocrystalline. GR is a two-dimensional allotropic form of carbon, formed by individual layers of sp²-bonded carbon atoms arranged in a hexagonal lattice with a distance of 0.142 nm between adjacent carbon hexagon atoms. GO is achieved by introducing carbonyl, hydroxy, and epoxide groups on planar surfaces and edges of graphene sheets, while rGO is obtained by oxidation of GR, followed by reduction and exfoliation. Carbon nanotubes (CNTs) are cylindrical structures with open or closed ends and, depending on the number of concentric layers of rolled graphene sheets, are classified as SWCNTs (outer diameter 0.8–2 nm) and MWCNTs (outer diameter 5–20 nm) with a length ranging from 100 nm to several centimeters. Fullerenes are composed entirely of carbon and exist in the form of hollow balls (buckyballs), ellipsoids, or tubes (buckytubes or CNTs), e.g., [40,300,301].

6.1. Carbon Dots

Impact on Photosynthesis

Li et al. [81] comprehensively overviewed the interactions of CDs on plant growth, internal physiological processes, and further external factors affecting plant growth. Amine functionalized CDs, effectively conjugated over the surface of the chloroplast after absorbing light or photons can transfer electrons towards chloroplasts, thereby positively affecting photosynthetic electron transport resulting in faster conversion of light energy to the electrical energy and finally to the chemical energy [302]. Li et al. [303] prepared far-red (FR) CDs that are able to efficiently convert UV-A light to 625–800 nm FR emission, i.e., wave lengths suitable to be directly absorbed by photosynthesizing organisms. In an in vitro experiment, coating of chloroplasts of *Lactuca sativa* L. var. *longifolia* with FR CDs resulted in a hybrid photosynthetic system, ensuring improved efficiency of electron transport between photosystem PSII and PSI, leading to increased ATP production. Moreover, in an in vivo experiment, the FR CDs-treated lettuce achieved higher electron transfer rate by 28.00% compared to the control, resulting in increased fresh and dry weights by 51.14% and 24.60%, respectively, suggesting that FR CDs could be used for improved conversion efficiency from solar energy to chemical energy.

6.2. Graphene Quantum Dots and Graphene Nanosheets

Treatment of coriander and garlic seeds with 0.2 mg/mL of GR QDs for 3 h before planting resulted in improved growth rate of plant organs of both plants, including fruits, suggesting that GR QDs could be used as plant growth regulators [304]. Spraying of graphene nanosheets (GNS) on *Capsicum annuum* L. and *Solanum melongena* L. plants during two seasons at doses 0.1, 0.2 and 0.3 GNS/g induced metabolic regulation of the leaves physiological status and resulted in an increased number of branches and number of fruits per plant, as well as fruit yield. GNS were localized on plastids, cell walls, and intercellular spaces of both plants, and GNS situated inside chloroplasts were found to activate assimilation pigments resulting in promotion of fructose, sucrose, and starch. Application of GNS triggered activity of antioxidant enzymes CAT, APX, GPX, and glutathione-S-transferase, and induced SOD and antioxidant molecules, reducing the levels of OH and O₂⁻ radicals and, thus, prevented the lipid peroxidation and electrolyte leaching. Moreover, increased PAL activity due to GNS treatment stimulated the formation of valuable secondary metabolites [305].

6.3. Graphene Oxide

6.3.1. Impact on Germination and Plant Growth

Exposure of *Salvia mirzayanii* seed to GO retarded and reduced the germination as well as growth characteristics of plants due to lower water uptake and oxidative stress, the effects being greater in demucilaged compared to intact (mucilaginous) seeds. On the other hand, the dependence of growth characteristics on the applied concentration of GO/polyaniline (PANI) NC was bi-phasic, showing growth stimulation at low composite doses and growth inhibition at high composite doses. In shoots of *S. mirzayanii* plants exposed to GO, and high concentration of GO/PANI, elevated H₂O₂ levels were estimated. GO/PANI NC also showed beneficial impact on germination and ensured a regular porosity pattern in roots resulting in ameliorated water uptake and, therefore, they could be utilized in drought-prone ecosystems [306].

6.3.2. Attenuation of Abiotic Stress

The addition of 800 µg/L nanosized GO to *Plantago major* L. leaf-derived calli grown on the 1/2 MS medium, in which drought stress conditions were induced by PEG, caused a 78.5% decrease in relative growth rate and 48.2% reduction of osmotic potential value, while dry matter and H₂O₂ contents increased by 35.1% and 54.2%, respectively. Under normal water availability in the presence of 800 µg/L nanosized GO, a pronounced increase of phenolic and flavonoid contents by 40.9% and 35.3%, respectively, compared to the control, was observed, while proline content showed a considerable decrease by 26.9% [307].

6.4. SWCNTs

Attenuation of Abiotic Stress

Exposure of *Hyoscyamus niger* seeds under drought stress (0.5–1.5 MPa) to low concentrations of SWCNTs for 14 days resulted in improved water uptake and upregulation of mechanisms involved in starch hydrolysis, while oxidative stress and electrolyte leakage were suppressed. In the presence of SWCNTs, plant defense system was activated, resulting in increased activities of antioxidant enzymes, such as APX, CAT, POD, and SOD as well as improved biosynthesis of phenolics and proline, which finally contributed to the mitigation of drought stress [308].

6.5. MWCNTs

6.5.1. Impact on Germination and Plant Growth

Beneficial impact of MWCNTs on growth rate, germination, and morphological characteristics of *Salvia sclarea* and *Salvia macrosiphon* was also reported by Mehrjardi et al. [309].

6.5.2. Elicitor Effect

In vitro cultivation of *Thymus daenensis* seeds in MS medium containing MWCNTs, which were found to pass across the plant cell wall and enter the cellular cytoplasm, affected early germination of plants, and stimulated the production of plant biomass up to a dose of 250 µg/mL, while further increasing of MWCNTs concentration reduced the biomass. Moreover, MWCNTs upregulated the activities of enzymes and antioxidants and elicited biosynthesis of some secondary metabolites and antioxidants, the optimum dose of MWCNTs being 250 µg/mL [157]. Treatment of *Satureja khuzistanica* Jamzad plants grown in vitro with 250 mg/L MWCNTs resulted in RA content of 140.49 mg/g (d.w.), while at in vivo exposure of *S. khuzistanica* to MWCNTs for 24 h, the RA content of 7.13 mg RA/g (d.w.) was achieved [310]. Stimulation of callus induction, biosynthesis of secondary metabolites, and improved antioxidant capacity in medicinal plant *S. khuzestanica* grown in vitro by MWCNTs was also reported previously by Ghorbanpour and Hadian [158].

Spraying of the leaves of two-month-old *Salvia verticillata* L with MWCNTs (0–1000 mg/L) resulted in their absorption via the epidermal cells layer into the parenchymal cells of the exposed leaves; the treatment reduced levels of assimilation pigments and caused oxidative stress in a dose-dependent manner. However, at application of 50 and 1000 mg/L MWCNTs, an (approximate) 4-fold increase of RA compared to the control was observed, whereby the activity and gene expression patterns of RA synthase correlated with the RA accumulation. While lower ROS levels at application of lower MWCNT concentrations contributed to improved production of secondary metabolites, treatment with higher concentrations was phytotoxic due to increased oxidative stress [155]. The γ -irradiation of *Salvia nemorosa* callus, using a dose 70 Gy, resulted in a high yielding cell line able to produce up to 18.53, 5.21, 1.9, and 7.59 mg/g d.w. of RA, salvianolic acid B, ferulic acid, and cinnamic acid, respectively. The cell suspension culture prepared of irradiated callus and elicited with 100 mg/L MWCNT-COOH (outer diameter of 20–30 nm) achieved fresh and dry biomass of 268.47 g/L and 22.17 g/L, respectively. Both treatment with γ -irradiation and elicitation using MWCNT-COOH pronouncedly improved the antioxidant activity of cultures. These findings showed that improved production of secondary metabolites in *S. nemorosa* achieved by combination of cell line selection via γ -irradiation with elicitation with MWCNT-COOH could be utilized for large-scale production of phenolic compounds [159].

MWCNTs increased the production of biomass production in callus culture of *Catharanthus roseus* cultivated in the dark, promoted the biosynthesis of total produced alkaloids, whereby strong improvement in the production of vinblastine and vincristine alkaloids was observed, not only with callus cultivation at dark, but also in light conditions [311].

6.5.3. Attenuation of Abiotic Stress

The addition of 50 mg/L of MWCNTs functionalized with carboxylic acid groups (MWCNT-COOH) in hydroponic solution was able to improve the adverse impact of salt stress (50 and 100 mM NaCl) on hydroponically cultivated *O. basilicum* L. plants, resulting in increased contents of assimilation pigments and the levels of non-enzymatic antioxidants and enhanced activities of antioxidant enzymes, including APX, CAT, and GPX. Whereas application of 25 mg/L MWCNT-COOH was found to be beneficial for plant growth and EO content and compound profile; treatment with a 4-fold higher dose was found to be phytotoxic. Hence, MWCNT-COOH could be considered as plant growth promoting and stress protecting agents, which have potential to be used in agriculture [312].

6.5.4. Genotoxicity

Uptake of MWCNTs in *Allium cepa* root cells modified cellular morphology, adversely affected membrane integrity and mitochondrial function, and caused considerable DNA damage, micronucleus formation, and chromosome aberration, as well as formation of internucleosomal fragments, which is indicative of apoptotic cell death. Accumulation of

cells in the sub-G₀ phase of the cell cycle, pronounced increases in CpG methylation, and in the levels of 5-methyl-deoxycytidine verified the cyto-genotoxic effect of MWCNT [313].

The use of MWCNT-COOH as an elicitor of rosmarinic acid and salvianolic acid B in a cell suspension culture prepared from γ -irradiated (70 Gy) *Salvia nemorosa* L callus, which allows to reach >13- and 14-fold higher concentrations of these secondary metabolites than in the control, can be recommended for obtaining these bioactive acids on a larger scale [159] (Table 1).

7. Effects of Organic Material-Derived NPs on Medicinal and Aromatic Plants

Chitosan/tripolyphosphate NPs supplemented to culture media modified the root architecture and differentiation in micropropagated *Capsicum annuum*, and at toxic doses 5–20 mg/L caused interruption of plant growth and development. On the other hand, at a dose of 1 mg/L, it acted as an effective elicitor to trigger organogenesis via micropropagation, causing considerable increases in contents of secondary metabolites, including soluble phenols, proline, and alkaloid [314]. Exposure of seeds of *Capsicum annuum* to aqueous suspensions of nanoscale chitin (0.001–0.05% *w/v*) or hydropriming reduced mean germination time at 25 °C on blotter paper to 4.9–5.3 days compared to 5.4–6.7 days observed with untreated seeds, seeds treated with 1% acetic acid, or 1% Captan fungicide. Application of 0.05% chitin NPs or hydropriming ameliorated seedling emergence at 19 to 30 °C and chitin NPs was able to reduce fungal growth as well [315].

Root meristems of *A. cepa* obtained from seeds exposed to nanoplastics (50 nm) at doses 0.01–1 g/L showed reduction of MI and caused induction and of cytogenetic anomalies and micronuclei suggesting their cytotoxicity and genotoxicity. This adverse impact of nanoplastics is caused by the mechanical surface contact of nanoplastics with root external layers and the internalization of nanoplastics in different cellular compartments. Consequently, nanoplastics internalized into crop plants could enter in different trophic levels of the food chain and, so, they represent a hazard for the health of the human population [316]. Polystyrene NPs applied at doses 25–400 mg/L considerably inhibited growth of *A. cepa* roots, induced the production of OH and O₂⁻ radicals, and increased DPPH scavenging activity and lipid peroxidation, causing a decrease in MI compared to the control. They also caused various chromosomal and nuclear aberrations and downregulated the expression of the plant cyclin-dependent kinase (CDKA) encoding gene: *cdc2*, an important cell cycle regulator. The above results suggest the cytotoxic and genotoxic potential of polystyrene NPs [317].

8. Conclusions

Aromatic and medicinal plants grown in the field require low energy input for cultivation, can contribute to increasing biodiversity in agroecosystems, and their cultivation can also be used to restore degraded areas. Secondary metabolites of aromatic and medicinal plants represent a rich source of phytochemicals that can be used not only for medicinal purposes or as nutraceuticals, but also as “lead compounds” for the design of new drugs. Medicinal plants should generally not be grown in contaminated soil, and chemicals used in the growth or protection of crops should be kept to a minimum. On the other hand, it is desirable to ensure favorable conditions for their germination and plant growth. In this context, the use of nanoparticles, which allow a controlled release of the active ingredient and the use of a smaller amount of active ingredient to achieve the same (or even better) biological effect than in the case of bulk, has a great perspective. The use of seed nanopriming can significantly improve plant germination and growth and can be considered a suitable approach for the revegetation of medicinal plants in harsh environmental conditions. In agricultural soils with low nitrogen content, mesoporous SiO₂ NPs loaded with urea can contribute to achieving the desired levels of this macronutrient. On the other hand, in calcareous soils characterized by a lack of micronutrients (especially Zn and Fe), mineral fertilization of medicinal and aromatic plants using nanoscale particles of these essential nutrients or their oxides can be favorable. In particular, foliar spraying with nanosized

metal fertilizers allows maximum use of plant nutrients and contributes to the fortification of plants with essential micronutrients. In general, low-concentration nanoparticles applied in such treatment do not contribute to environmental contamination and do not pose a risk to non-target organisms. Medicinal plants, especially their essential oils containing secondary metabolites, show many biological activities, e.g., anti-inflammatory, antimicrobial, antiviral, antidiabetic, anticancer, etc. Oxidative stress induced by NPs stimulates the production of these valuable compounds, not only in medicinal and aromatic plants grown in the field, but also with higher efficiency in tissue and hair root cultures of these plants. Therefore, these “green” in vitro methods, which do not use harmful solvents, can be promising for the efficient production of these beneficial bioactive metabolites. Utilizing the ability of nanoparticles to mitigate the adverse impact of abiotic stresses on medicinal and aromatic plants can be particularly useful in changing climatic conditions, where longer periods of drought and elevated temperatures can be expected in the near future. Increased plant tolerance to salts due to the application of nanoparticles will facilitate the cultivation of medicinal and aromatic plants in soil with higher salinity without adversely affecting their performance. Medicinal and aromatic plants have been associated with the human population since ancient times; their popularity as alternatives to synthetic drugs is currently growing, and the use of appropriate nanoparticles can significantly contribute to their better yield, production of higher concentrations of valuable metabolites, and better nutritional value.

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Abbreviations

APX (ascorbate peroxidase); CA (carnosic acid); CAT (catalase); CDKA (cyclin-dependent kinase); CDs (carbon dots); Chl (chlorophyll); CNTs (carbon nanotubes); CSC (cell suspension culture); CTAB (cetyltrimethylammonium bromide); DPPH (2,2-diphenyl-1-picrylhydrazyl); EDTA (ethylenediaminetetraacetic acid); EO (essential oil); FC (field capacity); FITC (fluorescein isothiocyanate); GNS (graphene nanosheets); GO (graphene oxide); GPPS (geranyl diphosphate synthase); GPX (guaiacol peroxidase); GR (glutathione reductase); GR QDs (graphene quantum dots); HR (hairy root); MDA (malondialdehyde); MI (mitotic index); MIC (minimum inhibitory concentration); MP (microparticle); MS (Murashige and Skoog); MWCNTs (multi-walled carbon nanotubes); NC (nanocomposite); NP (nanoparticle); PAL (phenylalanine ammonia-lyase); PANI (polyaniline); PEG (polyethylene glycol); POD (peroxidase); PPO (polyphenol oxidase); PS (photosystem); PVP (polyvinylpyrrolidone); RA (rosmarinic acid); rGO (reduced GO); ROS (reactive oxygen species); QDs (quantum dots); SMF (static magnetic field); SM (secondary metabolite); SOD (superoxide dismutase); SWCNTs (single-walled carbon nanotubes); TFC (total flavonoid content); TPC (total phenolic content).

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