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GREEN SYNTHESIS STRATEGIES, MECHANISTIC UNDERSTANDING AND CLINICAL TRANSLATION PROSPECTS OF "PLANT-DERIVED NANOMEDICINES FOR THE DUAL MANAGEMENT OF DIABETES MELLITUS AND HYPERTENSION

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Abstract

The burden of diabetes mellitus and hypertension, two often coexisting parts of metabolic syndrome, is still rising world-wide and there is a need for safer and more effective therapeutic alternatives. The plant-derived nanomedicines are an amalgamation of ethnopharmacological knowledge and cutting-edge nanotechnology that deliver higher bioavailability, targeted delivery, and multi-pathway modulation. This review extensively discusses the green synthesis of nanoparticles from medicinal plants that have proven antidiabetic and antihypertensive effects, and explores the phytochemical basis for bioreduction, the mechanistic pathways involved in dual therapeutic effects, and the structural properties that influence their biological activity. We critically review the recent progress of development of monometallic, bimetallic and polymeric nanoformulations from different plant sources like Calotropis procera, Curcuma longa, Elettaria cardamomum, Piper longum, Quercus infectoria and various Citrus species. Focus has been given to strategies to increase the bioaccessibility of inherently labile phytoconstituents to achieve synergistic inhibition of α-amylase, α-glucosidase and angiotensin-converting enzyme (ACE). By systematic analysis of in vitro, ex vivo and preclinical evidence, we find key structure-activity relationships and propose frameworks of mechanism of action for phytochemical corona composition and therapeutic outcome. Moreover, we discuss some of the major translational hurdles such as scalability, reproducibility, assessment of toxicity and regulatory issues. In this review, present knowledge is summarized and future research directions are identified to be crucial for the successful translation of plant-derived nano-medicines to the clinical arena, for the co-management of diabetes and hypertension.

INTRODUCTION

Diabetes mellitus and hypertension are two major and closely interrelated non-communicable diseases that have become a major challenge to human longevity and quality of life globally (World Health Organization, 2023) largely due to

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the unprecedented rise in the incidence of non-communicable diseases. Recent epidemiological evaluations from the International Diabetes Federation and the World Health Organization have concluded that these conditions are not often isolated, but rather deeply intertwined comorbidities which significantly increase the risk of cardiovascular mortality, end-stage renal disease and retinopathy in an exponential way (International Diabetes Federation, 2021). The relationship of hyperglycemia and higher arterial pressure is complex and polygenetic, and is caused by a vicious cycle of metabolic dysfunction. Insulin resistance is a key component to this link where the failure to take up glucose into the cells leads to increased insulin levels (Ferrannini & Cushman, 2012), or hyperinsulinemia. This hormonal excess has pleiotropic actions on the vascular system, such as increased renal sodium reabsorption and sympathetic nervous system overdrive (Sowers, Epstein, & Frohlich, 2001), and a pro-inflammatory environment with higher levels of reactive oxygen species and advanced glycation end-products. This oxidative stress directly affects endothelial function by sequestering nitric oxide and reducing its bioavailability, which results in decreased vasodilation and increased vascular stiffness (Giacco & Brownlee, 2010). In addition, the Renin-Angiotensin-Aldosterone System (RAS) is a key pathway in this process, as angiotensin II is not only a powerful vasoconstrictor, but it also disrupts the intracellular insulin signaling pathways leading to a vicious cycle: hypertension increases metabolic insulin resistance and conversely metabolic insulin resistance increases hypertension (Petrie, Guzik, & Touyz, 2018). Such a complex etiology makes the therapeutic need go beyond control of glucose, or blood pressure – it's a need for overall endothelial health and redox homeostasis. In the current pathophysiological context, although modern pharmacology is definitely effective in biomarker control, it has several important drawbacks that compromise the long-term efficacy of the treatment. The multi-pathway dysfunction of metabolic syndrome is not generally captured by conventional antihypertensive treatments and by oral hypoglycemic agents whose mechanisms of action are targeted against a single enzyme or receptor (Cheung & Li, 2012). This leaves the patient frequently to a complicated polypharmacy treatment regimen with four or more differing chemical substances and is a major contributor to poor medication adherence and a high burden of adverse effects, including electrolyte imbalance, fluid retention, gastrointestinal intolerance, and hypoglycemia. This clinical impasse has stimulated a strong renaissance in the utilization of plant-based therapeutics, where the action of hundreds of synergistic phytoconstituents is all present in a single-plant matrix, providing a very special pharmacophore complexity. A medicinal plant extract has the potential to inhibit the activity of α-glucosidase, scavenge free radicals and modulate the activity of RAS by different chemical scaffolds unlike isolated synthetic molecules. Pronounced bioavailability issues however, have limited the computational promise of these phytochemicals in the past, many of these highly bioactive compounds, including curcuminoids, gallotannins, and large polyphenolic glycosides, are poorly soluble in water, undergo extensive first-pass metabolism in the liver, and lack sufficient permeability across the intestinal epithelium (Anand, Kunnumakkara, Newman, & Aggarwal, 2007), yielding non-therapeutic plasma levels at high doses. This is where plant medicine meets nanotechnology, where a paradigm shift is taking place. Application of green synthesis and nanoencapsulation technique provide an advanced engineering solution to the intrinsic drawbacks of crude botanicals. The metal ions can be reduced, or the phytochemicals themselves can be loaded into nanoparticles in the size range of 50–1000 nm (polymeric nanoparticles, solid lipid matrices, or bimetallic core-shell structures), so that lability to degradation during passage through the stomach can be prevented and the bioactives absorbed through M-cell uptake or paracellular transport. This nanostructuring effect improves the apparent solubility and extended systemic circulation of plant-derived

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compounds, and allows for targeted delivery of a dual-pronged therapeutic payload to tissues affected by both diabetic microangiopathy and hypertensive macroangiopathy. The resulting nanomedicine combines the best of both worlds; the multi-targeted and redox-modulating intelligence of ethnopharmacology and the precision delivery, surface area reactivity, and controlled release kinetics of modern material science. The objective of this review is to systematically dissect this emerging area and give a comprehensive synthesis of the current evidence landscape. This will be followed by studies on the principles of Green synthesis of Nanoparticles from selected medicinal plants followed by detailed study on the structural and functional characterization of Advanced materials. In-vitro and in-vivo evidence of dual antidiabetic and antihypertensive action will be evaluated critically and with specific emphasis on the interaction of mechanistic action of phytochemical coronas and cellular signaling pathways. Last but not least, we will discuss the translation challenges and regulatory aspects that are crucial for moving these plant-based nanomedicines from the laboratory to clinical reality for the integrated management of diabetes mellitus (DM) and hypertension.

2. Green Synthesis of Nanoparticles from Medicinal Plants: Principles and Methodologies

2.1 Fundamentals of Phytogenic Nanoparticle Synthesis

2.1.1 Phytochemicals as Reducing, Capping, and Stabilizing Agents

Phytogenic or green synthesis of nanoparticles is a high-tech bottom-up fabrication approach in which the bioactivised phytochemicals present in plant extract act as reducing agents and stabilise the nascent nanocrystals. This biologically derived route is radically different from the traditional synthetic approaches that rely upon toxic reducing agents, organics solvents and high-energy conditions, and has an aqueous, ambient-temperature process which is consistent with the principles of green chemistry and sustainable materials science (Iravani, 2011). The basic mechanism of the phytogenic synthesis is the electron transfer from certain functional groups within plant secondary metabolites to the metal cations in solution (Mittal, Chisti, & Banerjee, 2013), which allows the reduction of metal cations to the elemental level. It starts with the addition of a plant extract, which is usually prepared by either aqueous or hydroalcoholic maceration of the selected plant parts (roots, bark, leaves, seeds etc.), to a solution containing a precursor metal salt (usually silver nitrate for silver nanoparticles, chloroauric acid for gold nanoparticles, zinc acetate for zinc oxide nanostructures or magnesium chloride for magnesium oxide particles). The characteristic color change from the pale yellow to the deep reddish-brown for silver nanoparticles and the light yellow to ruby-red for gold nanoparticles upon mixing is the first macroscopic evidence of successful formation of nanoparticles, which is explained by the excitation of electrons in the surface plasmon resonance of the nanoparticles (Sharma, Yngard, & Lin, 2009). During this bioreduction process, the newly generated surface of the nanoparticles is also covered by the adsorption of the remaining phytomolecules which serve as capping molecules that provide electrostatic and steric stabilization of the formed nanoparticles and prevent uncontrolled aggregation and Ostwald ripening. This phytochemical corona is not simply a protective barrier, but an integral part of the biological characteristics and therapeutic activity of the nanoparticle (Marslin et al., 2018), granting it greater aqueous dispersibility, biological activity and biocompatibility, as a result of the bioactive molecules immobilized on its surface. This phytochemical corona represents an additional noteworthy importance in the case of nanomedicines designed for the simultaneous management of diabetes mellitus and hypertension because the capping agents themselves may also possess an inhibitory activity on α-amylase, α-glucosidase, and angiotensin-converting enzyme, thus enhancing the therapeutic effect of the formulation by synergistic multi-target modulation.

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2.1.2 Mechanistic Basis: Flavonoids, Phenolic Acids, Terpenoids, and Alkaloids in Nanoparticle Formation

Overall, the kinetics of nanoparticle formation, size distribution of the resulting nanoparticles and the morphology of the nanoparticles formed depend on the nature, concentration and structure of the phytochemicals in the plant extract. The flavonoids are one of the best understood and mechanistically understood classes of phytoreductants (Makarov et al., 2014), and the structure of these is characterized by the presence of multiple hydroxyl groups, and efficient electron delocalisation and metal ion coordination through the planar ring structure. The basic structure of flavonoids consists of two aromatic rings connected by a three-carbon bridge that acts as an oxygen-containing heterocycle, the number and position of hydroxyl groups on the basic structure explain the redox potential and metal-chelating properties of the different flavonoids. Both the catechol and the galloyl groups on the aglycones of quercetin, kaempferol, myricetin and their glycosidic derivatives undergo pH-dependent autoxidation, producing intermediates such as semiquinones and quinones that are active in the reduction of metal cations to their elemental forms (Ovais et al., 2018). The tautomeric interconversion between enol and keto forms of these derivatives of flavonoids promotes the release of electrons that converts Ag^{+} to Ag^{0} (or Au^{3+} to Au^{0}) and the oxidized forms of the flavonoids simultaneously adsorb onto the nascent surface of the nanoparticle, creating a dense and multifunctional capping layer. The mechanism of action of these phenolic acids, such as gallic acid, ellagic acid, chlorogenic acid, caffeic acid and rosmarinic acid, is similar, and involves a redox process; the carboxyl and hydroxyl groups attached to the aromatic nucleus are electron-donating groups that promote the reductive nucleation process (Ahmed, Ahmad, Swami, & Ikram, 2016). The presence of these phenolic constituents in the plants like Quercus infectoria, where gall nuts are found in a tremendous amount of gallotannins and gallic acid derivatives, and Elettaria cardamomum, Citrus species, makes these plants as very useful sources for the rapid and high production yield of metallic nanoparticles with narrow size distribution (Kumar & Yadav, 2009) and high colloidal stability. In addition to the family of flavonoids and phenolic acids, plants used in medicinal applications like Calotropis procera, Curcuma longa and Piper longum contain terpenoids and alkaloids which add further dimensions of reactivity and stabilization into the phytogenic synthesis process. Terpenoids with isoprenoid carbon skeletons formed by condensation of five-carbon isoprene units and containing oxygenated functional groups such as hydroxyl, carbonyl and carboxyl groups interact with the surface of nanoparticles by coordinate covalent bonding to a metal atom on their surface (Singh, Kim, Zhang, & Yang, 2016), as well as by forming hydrogen bonding networks and hydrophobic interactions. The abundance of cardenolides and triterpenoids in the latex of Calotropis procera as well as in the extracts from its leaves have twofold effects: They act as mild reducing agents and strong steric stabilizers because of the bulky polycyclic structures which project away from the surface of the nanoparticles, thereby preventing interparticle contact and aggregation. A structurally diverse class of N-containing secondary metabolites called the alkaloids can achieve this by different mechanisms, which take advantage of the lone pair electrons found in their tertiary and quaternary N atoms in order to allow the aggregation of nanoparticles. The main pungent alkaloid (piperine) of Piper longum and Piper nigrum has a conjugated diene system and a moiety of methylenedioxyphenyl, which is able to donate their electrons to the metal ions to facilitate efficient electron transfer to the metal ions, and the N atom acts as a coordination center for metal ion binding before reduction (Chandran et al., 2006). The alkaloids present in Curcuma longa rhizome add to the reducing capacity of the turmeric extracts and play a role in the development of a very strong, complex phytochemical corona making the resulting

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nanoconstructs more bio-compatible and more stable in the colloidal solution. This structural diversity, with structurally different classes of phytochemicals leading to a common synthetic product via parallel processes of redox and stabilization reactions, demonstrates the robustness and versatility of the process of phytogenic nanoparticle synthesis (Nasrollahzadeh et al., 2019).

2.1.3 Advantages over Conventional Physicochemical Methods: Sustainability and Biocompatibility

It is believed that the success of phytogenic synthesis methodologies over traditional physicochemical is based on a myriad of attractive features that go beyond the technical challenges and span the entire spectrum from environmental protection to biomedical translation. All conventional methods of making nanoparticles with sodium borohydride, hydrazine, citrate as reducing agents, or through thermal decomposition of organometallic precursors, or by physical vapor deposition involve the use of dangerous chemicals, production of dangerous byproducts, or consumption of significant amounts of energy resources. Although sodium borohydride is a well-known, powerful and rapid reducing agent, its pyrophoric properties and tendency to liberate flammable hydrogen gas on contact with water make it a significant handling risk, and hydrazine is a known carcinogen and environmental contaminant that is highly desirable to be removed from synthetic workflows. Plant-mediated synthesis is carried out in aqueous media and benign ambient conditions, requiring no special pressure or vacuum equipment and avoiding accumulation of persistent toxic waste streams, while using renewable and biodegradable biological resources. It is an intrinsic sustainability which is further accentuated by the other equally important property of the obtained nanoparticles in terms of their biocompatibility and therapeutic application. In conventional nanoparticle synthesis methods, toxic surfactants, stabilizers, and unreacted precursors are integrated into the particles, which require thorough and expensive purification processes, such as repeated centrifugation, dialysis, or size-exclusion chromatography, whereas with phytogenically-derived nanoparticles, the biomolecules left on the surface upon extraction impart intrinsic antioxidant, anti-inflammatory, and enzyme-inhibitory properties. This phytochemical corona not only increases the physiological compatibility of the formulation, but also prevents unwanted immunogenic or cytotoxic effects and, most importantly, incorporates the therapeutic potential of the phytoconstituents into the formulation surface, increasing its overall therapeutic activity. The cytotoxicity of the green synthesized magnesium oxide nanoparticles prepared using Curcuma longa, Elettaria cardamomum and Piper longum extracts has been evaluated in human peripheral blood mononuclear cells (PBMCs) and has been found to be non-toxic at therapeutic dose levels with half maximal cytotoxic concentration (CC50) of more than few hundreds micrograms per milliliter. The context of the environmental benignity, simplicity of operation and biological functionality, make the paradigm of phytogenic synthesis the most preferred approach for the production of nanomedicines for the integrated management of diabetes mellitus and hypertension.

2.2 Methodological Approaches in Plant-Mediated Synthesis

2.2.1 Extraction Protocols and Phytochemical Profiling

This is because the reproducible and reproducible synthesis of plant derived nanoparticles with well defined physicochemical properties and reproducible therapeutic effect is essential and requires well defined methods with attention to the extraction process and characterization of the phytochemicals. The initial step, preparation of the plant extract, is the basis for all subsequent outcomes of synthesis; the extraction solvent, extraction temperature, extraction duration, and plant-to-solvent ratio have a significant impact on the qualitative and

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quantitative composition of the phytochemical cocktail. Despite its simplicity, ease of use and the fact that it conforms to green chemistry principles, aqueous extraction is the least used method for phytogenic synthesis because a water molecule is highly polar and will not extract certain compounds, including moderately polar and non-polar compounds like terpenoids, alkaloids and lipophilic flavonoids, which could have useful reducing or stabilizing properties. Hydroalcoholic mixtures are usually a combination of ethanol or methanol with water and can have a higher organic content from thirty to seventy percent; they are often used when the goal is to obtain a more diverse and concentrated extract of bioreductive species. It is typically manually extracted using finely powdered plant material boiling for a specified time (10 to 60 minutes), or cold maceration for prolonged periods (12 to 24 hours), and then filtered through Whatman filter paper or centrifuged at moderate speed to remove any insoluble substances and particles. The resulting clarified extract is then analysed using qualitative colourimetric methods to identify the presence of the principal classes of phytochemicals such as the precipitation of alkaloids by Dragendorff's and Mayer's reagent, the production of blue-black/green colouration with the Shinoda test in the presence of flavonoids, complexation with ferric chloride followed by colouration in the presence of phenolic compounds, the Salkowski reaction with chloroform and concentrated sulphuric acid in the presence of terpenoids and frothing in the presence of saponins. The preliminary screening is crucial to give suggestions on the expected reducing and stabilizing capacity of the extract, and will be useful for further decisions on the concentration of metal precursor and extract-to-precursor ratio, as well as the reaction conditions. More rigorous characterization can be achieved by using advanced analytical techniques such as high performance liquid chromatography (HPLC) and diode array detection or mass spectrometry (MS) to identify and quantify specific phytochemical components, thus yielding a phytochemical fingerprint which can be correlated with the performance of the synthesis of nanoparticles.

2.2.2 Reaction Parameter Optimization: Concentration, Temperature, pH, and Time

Optimization of reaction parameters is a crucial factor in the quality attributes of nanoparticles such as particle size, size distribution, shape, and colloidal stability. One of the important variables that affect the nucleation and growth kinetics of the nascent nanoparticles is the concentration ratio of the plant extract to the metal precursor solution. If the concentration of phytochemical reductants is not sufficient compared to the concentration of metal ions, there will be fewer reduction reactions and more aggregation processes, so that the reduced product will be in the form of large aggregates and polydispersed aggregates will be formed, while if the concentration of extracts is too large, the reduction reaction will occur faster and the number of nucleation reactions will increase so fast that the capping reaction will be overwhelmed, paradoxically causing agglomeration due to bridging flocculation (Kumar, Narwal, Kumar, & Prakash, 2011). By changing the volumetric ratio of extract to precursor systematically, over the range from 1 to 10 and more, the correct proportion can be determined that produces the smallest mean diameter of the nanoparticles and the narrowest size distribution of nanoparticles. Reaction temperature has a dual and often opposing effect on the synthesis process, by changing both the thermodynamic driving force for the reduction of metal ions and the kinetic energy of molecular collisions which assists in the nucleation and growth. High temperatures tend to increase the reduction rate and drive the formation of smaller, more uniform particles, resulting from the fast consumption of the metal precursor and from the increased efficiency of the phytochemical capping process; however, extremely high temperatures can degrade thermolabile bioactive compounds, cause undesirable morphological changes or allow for the desorption of the capping phytochemicals from the nanoparticle surface with subsequent

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aggregation. Typical ranges of reaction temperatures examined are in the twenty-five to eighty degree Celsius range and many optimal protocols suggest intermediate temperatures between forty and sixty degrees Celsius (Zhang et al., 2016) as a desirable compromise between the reaction rate and product quality. The pH of the reaction medium is also a very significant parameter, since the protonation state of important functional groups in the phytochemical reductants will determine their electron donating power and their affinity for the metal and their solubility. Usually, the reducing power of the phenolic hydroxyl increases with increasing pH, because it is more likely to lose a proton to form the more strongly electron-donating phenoxide anion, which speeds up the reduction of metal ions and the formation of more stable, smaller, and spherical nanoparticles. Acidic growth conditions, on the other hand, can promote anisotropic growth habits, giving rise to nanorods, nanoprisms or nanostars, as well as differential adsorption of capping agents on crystallographic facets, or can slow down the reduction reaction to the point of incomplete conversion yielding broad size distributions. Optimal pH for a particular plant – metal precursor combination should be determined empirically and is often determined to be in the slightly alkaline range (Srikar, Giri, Pal, Mishra, & Upadhyay, 2016) (pH 8 – 10) for the synthesis of silver and gold nanoparticles. The degree of nanoparticle maturation and growth in size and shape distributions depends on the reaction time, where short incubation times generally leads to smaller particles, which can have incomplete crystallinity, and longer times to Ostwald ripening (smaller particles dissolve and re-precipitate onto larger ones to minimize total surface energy) and coarsening unless adequate kinetic stabilization is provided by the capping layer. The temporal evolution of the surface plasmon resonance absorption spectrum can be used to determine the completion of the reaction usually when absorbance becomes stable with respect to time and the maximum and intensity of the absorption spectrum becomes constant.

2.2.3 Central Composite Design (CCD) and Response Surface Methodology for Synthesis Optimization

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2.3.2 Microscopic Techniques: TEM, SEM, and AFM

The spatial resolution of the microscopic techniques is sufficient to directly visualize the size, shape and surface topography of the individual nanoparticles, thereby validating and extending the inferences that can be drawn from ensemble spectroscopic and light scattering measurements, and unequivocally confirming the formation of nanoparticles. The gold standard for imaging nanoparticles is transmission electron microscopy (TEM) (Mourdikoudis, Pallares, & Thanh, 2018), which uses a beam of high-energy electrons accelerated at a potential between 100 and 300 kilovolts, and passes through an extremely thin specimen to create a two-dimensional projection image at atomic resolution. The core diameter, morphology and level of agglomeration of the phytogenic nanoparticles are well observed in TEM micrographs (typically spherical or quasi-spherical, between 10 and 100 nm, but anisotropic shapes such as triangular shapes and hexagonal and rod-like shapes may be observed depending on particular plant extracts (Chandran et al., 2006) and synthesis conditions). The diffraction pattern produced from the interaction of the electron beam with the periodic lattice planes in the nanoparticle core is analyzed by the associated technique called selected area electron diffraction (SAED), which can be used to assess crystallinity. Concentric diffraction rings are an indication of a polycrystalline structure which consists of randomly oriented crystalline domains, while discrete, well defined spots, regularly arranged in a geometric pattern, represent single crystalline structure domains or highly textured materials. Such diffraction pattern indexing against the standard crystallographic databases allows the unambiguous determination of the crystalline phase and lattice parameter of the metallic core. High-resolution images of topographical detail and the three-dimensional structure obtained by scanning electron microscopy (SEM) by detecting secondary electrons generated when a focused electron beam is incident on the sample surface

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emphasise topographical contrast and give a strong sense of depth and dimensionality. SEM images of phytogenic nanoparticles should validate the size and shape distributions observed from TEM imaging, and also show the surface roughness and biomolecular contaminants that are not visible in the transmission images and might form larger aggregates. By using a sharp probe tip that is scanned across the sample surface, in either tapping, contact, or non-contact mode, under ambient or liquid conditions, Atomic Force Microscopy (AFM) extends the characterization capabilities into the realm of nanomechanical and topographical characterization with sub-nanometer vertical resolution. The ability of AFM to give direct, three-dimensional topographic information allows it to complement the two-dimensional information that can be obtained from electron microscopy to measure the height of particles, which, for spherical particles, should closely match the diameter measured by TEM, giving an orthogonal measurement of particle size.

2.3.3 Crystallographic Analysis: XRD and SAED Patterns

X-ray diffraction (XRD) analysis of crystallography crystallizes properties of the crystalline phase, lattice structure and average crystallite size of the metallic or metal oxide core of the plant-derived nanoparticles, which are essential to understand their physicochemical stability and their interaction with the biological systems. XRD is based on the principle of constructive interference between monochromatic x-rays and the periodic arrangement of atoms of the crystalline lattice and is described by Bragg's law which relates the wavelength of X-rays, the interplanar spacing in the lattice and the angle of incidence at which the diffraction maximum occurs. In the XRD pattern, the characteristic Bragg reflections can be seen and it is a kind of fingerprint that can help to confirm the elemental structure and crystal structure of the core of the nanoparticles. The diffraction peaks corresponding to the one hundred eleven, two hundred, two hundred twenty, and three hundred planes of the face-centered cubic silver lattice are clearly seen for silver nanoparticles, while for gold nanoparticles, a similar set of peaks are observed, but at slightly different two-theta values, due to the larger atomic radius and lattice parameter of gold. XRD pattern for the plant mediated synthesized zinc oxide nanoparticles shows the characteristic peaks corresponding to the hexagonal wurtzite crystal structure and for the magnesium oxide nanoparticles the XRD pattern shows the characteristic peaks corresponding to the cubic periclase structure. The crystallite size estimated from the parameters of peak broadening in the XRD pattern by applying the Debye-Scherrer equation can be compared to the particle sizes measured by TEM and DLS (Bhattacharjee, 2016). This Scherrer equation correlates the broadening of a diffraction peak with the crystallite size, perpendicular to the diffracting planes, and the FWHM of a peak is broader for smaller crystallites because the diffraction peak has less complete destructive interference for angles slightly off the exact Bragg condition. Selected area electron diffraction, carried out along with the TEM as described above, has the capability of giving other crystallographic information, with the added benefit that it can be used to analyse individual nanoparticles or small groups of nanoparticles, which means that it can be used to distinguish between single-crystalline, polycrystalline and amorphous particles in a heterogeneous population. The combination of these orthogonal characterization modalities (spectroscopic, microscopic, crystallographic) provides a comprehensive characterization of the plant-derived nanoparticle from elemental composition and crystalline architecture to surface chemistry and colloidal behavior, all of which are required to develop foundational knowledge for rational formulation development, quality control (Jeevanandam et al., 2018) and therapeutic application for diabetes mellitus and hypertension management. The schematic representation of the workflow starting from the selection of (some of the) medicinal plants (Calotropis procera, Curcuma longa, Citrus spp.,

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Quercus infectoria), bioactive phytochemical extraction, bioreduction of metal ions (Ag^{+}, Au^{3+}, Mg^{2+}, Zn^{2+}), capping and stabilization of the metal ions by phytoconstituents and ultimate formation of nanoparticles. Insets are provided in the diagram to illustrate TEM images of representative nanoparticles and color changes as a result of successful synthesis. The molecular structures of important phytochemicals (flavonoids, phenolic acids) are displayed, along with the functional groups responsible for metal ion.

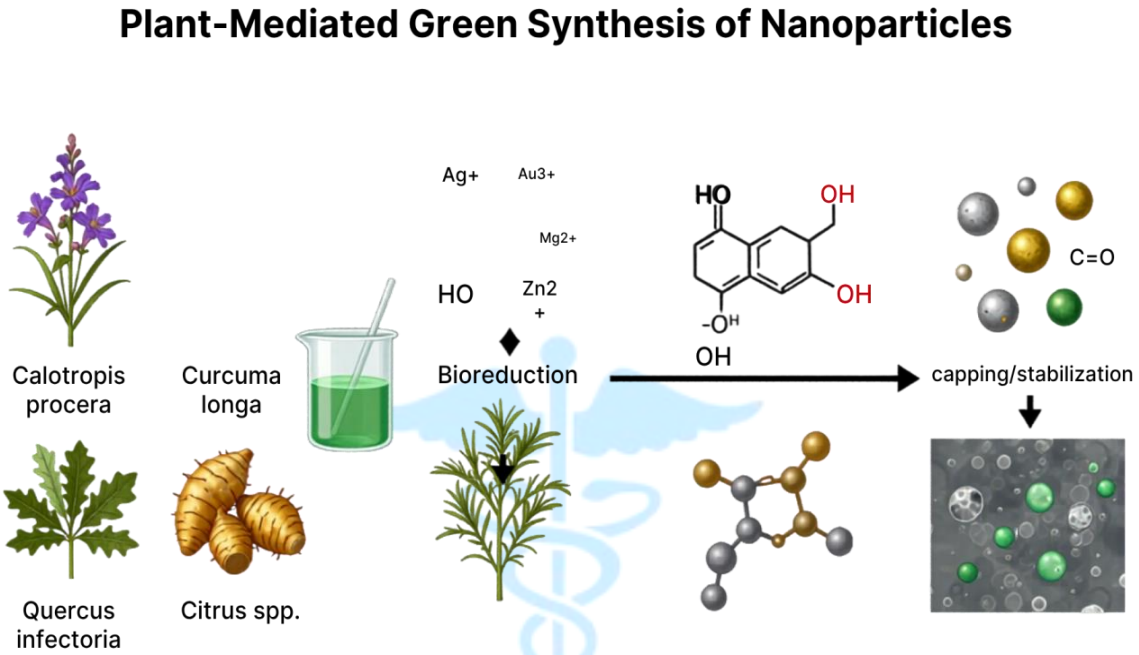


Figure 1: Schematic Overview of Plant-Mediated Green Synthesis of Nanoparticles

3. Phytochemical Arsenal of Antidiabetic and Antihypertensive Medicinal Plants

3.1 Major Classes of Bioactive Phytoconstituents

3.1.1 Flavonoids: Quercetin, Kaempferol, Rutin, and Their Glycosides

Flavonoids are one of the most abundant and pharmacologically rich classes of plant secondary metabolites and the diphenylpropane backbone is the structural basis of a wide range of compounds with potent antidiabetic and antihypertensive activities via a variety of complementary mechanisms. Onion, apple, tea and citrus fruits are rich in quercetin (Alam, Subhan, Rahman, Uddin, & Reza, 2014), a flavonol that has been extensively characterized for its capacity to inhibit α-amylase and α-glucosidase by competitive binding to the active site of these carbohydrate-digesting enzymes, which help to decrease postprandial hyperglycemia (Yang et al., 2020). The mechanism of this inhibition is based on the planar aromatic system and the hydroxyl substitution pattern of quercetin that can interact with the key amino acid residues in the enzyme active site through hydrogen bonding and hydrophobic interaction. Structurally similar to quercetin, but lacking the catechol moiety on the B-ring, kaempferol inhibits intestinal carbohydrate hydrolases, and also activates AMP-activated protein kinase in skeletal muscle and liver, thereby increasing metabolism of glucose and fatty acids (Coughlan, Valentine, Ruderman, & Saha, 2014). The glycosylated form of quercetin found in most medicinal plants is called rutin, which is the 3-O-rutinoside derivative, and the sugar part plays a role in the

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solubility, bioavailability and enzyme inhibitory kinetic of quercetin. Gut microbial β-glucosidases break the glycosidic bond releasing the aglycone form that, in turn, elicits the pharmacological activity, thus providing a mechanistic link between the gut microbiota and the bioactivation of dietary flavonoid glycosides (Kim, Keogh, & Clifton, 2016).

3.1.2 Phenolic Acids: Gallic Acid, Ellagic Acid, Chlorogenic Acid

Phenolic acids, characterized by a phenolic ring bearing a carboxylic acid substituent, represent a major class of bioactive phytoconstituents with well-documented antidiabetic and antihypertensive properties derived from their antioxidant capacity, enzyme inhibitory activity, and vascular protective effects. Gallic acid, the simplest trihydroxybenzoic acid derivative found abundantly in gall nuts of Quercus infectoria (Elham et al., 2021) and in various berries, tea leaves, and wine, exerts its antidiabetic effects through potent inhibition of α-glucosidase and through the suppression of advanced glycation end-product formation, a pathogenic process that contributes to diabetic microvascular and macrovascular complications (Bai, Zhang, Wang, & Zheng, 2021). Ellagic acid, the dimeric oxidation product of gallic acid present in pomegranates, berries, and nuts, similarly inhibits carbohydrate-hydrolyzing enzymes while also activating endothelial nitric oxide synthase, promoting nitric oxide-mediated vasodilation that contributes to its antihypertensive effects. Chlorogenic acid, the caffeoylquinic acid ester abundant in coffee, Elettaria cardamomum, and numerous medicinal herbs, has been demonstrated to inhibit glucose-6-phosphatase in the liver, reducing hepatic glucose output (Naveed et al., 2018), while simultaneously inhibiting the angiotensin-converting enzyme and enhancing nitric oxide bioavailability in the vasculature.

3.1.3 Terpenoids and Steroids: Cardenolides from Calotropis procera

Terpenoids and steroids represent structurally complex and pharmacologically potent classes of phytoconstituents that contribute significantly to the therapeutic profile of several medicinal plants with dual antidiabetic and antihypertensive activities. Calotropis procera, a widely distributed medicinal shrub of the Asclepiadaceae family, elaborates a rich terpenoid and steroid profile dominated by cardenolides, including calotropin, calotoxin, uscharin, and voruscharin (Kaur, Kaur, & Kaur, 2021), which are C23 steroid derivatives bearing a characteristic unsaturated γ-lactone ring at the C17 position that is essential for their biological activity. These cardenolides have been demonstrated to inhibit α-amylase activity and to enhance insulin secretion from pancreatic β-cells through the modulation of intracellular calcium signaling, while also exerting antihypertensive effects through the inhibition of angiotensin-converting enzyme and the promotion of vasorelaxation. Triterpenoids, including α-amyrin and β-amyrin, contribute additional antioxidant and anti-inflammatory activities that protect pancreatic β-cells from oxidative damage and improve endothelial function.

3.1.4 Alkaloids: Piperine and Related Compounds

Alkaloids, nitrogen-containing secondary metabolites with diverse and often potent biological activities, contribute significantly to the therapeutic arsenal of antidiabetic and antihypertensive medicinal plants. Piperine, the principal pungent alkaloid of Piper longum and Piper nigrum, has been extensively characterized for its capacity to enhance the bioavailability of co-administered phytochemicals and pharmaceuticals through the inhibition of glucuronidation and the modulation of gastrointestinal drug transporter expression, earning it the designation of a bioenhancer (Gorgani et al., 2017). Beyond its bioenhancing properties, piperine itself exerts antidiabetic effects through the inhibition of α-glucosidase and the enhancement of insulin sensitivity in

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peripheral tissues. The antihypertensive activity of piperine is mediated through calcium channel blockade, which reduces peripheral vascular resistance, and through the stimulation of endothelial nitric oxide production, promoting vasodilation. Piperlongumine and other piperine-related alkaloids present in Piper species contribute additional antioxidant and anti-inflammatory activities that complement the therapeutic profile of the parent compound.

3.1.5 Bioactive Peptides: Pomegranate Seed-Derived Peptides

Bioactive peptides, short amino acid sequences released from precursor proteins through enzymatic hydrolysis or fermentation, represent an emerging class of phytochemicals with significant potential for the dual management of diabetes and hypertension. Pomegranate seed-derived peptides, generated through the hydrolysis of pomegranate seed storage proteins by gastrointestinal proteases or by controlled enzymatic treatment, have been demonstrated to inhibit both α-amylase and angiotensin-converting enzyme, providing a single molecular class with dual enzyme inhibitory activity. The angiotensin-converting enzyme inhibitory peptides derived from pomegranate seeds typically contain hydrophobic and aromatic amino acid residues at their C-terminus, features that are characteristic of potent ACE inhibitory peptides and that facilitate their binding to the S1 and S2 subsites of the enzyme active site (Wu, Liao, & Udenigwe, 2017). The encapsulation of these bioactive peptides within nanoliposomal formulations, as demonstrated in the development of GPBP-NL nanoliposomes combining Quercus infectoria gallotannins with pomegranate peptides, enhances their stability in the gastrointestinal tract and their bioaccessibility, addressing the inherent susceptibility of peptides to gastric and pancreatic proteolysis.

3.2 Mechanistic Basis of Antidiabetic Activity

3.2.1 α-Amylase and α-Glucosidase Inhibition

The inhibition of intestinal carbohydrate-hydrolyzing enzymes, particularly α-amylase and α-glucosidase, represents the most extensively characterized mechanism through which medicinal plant phytochemicals exert their antidiabetic effects, providing a direct and localized intervention that attenuates postprandial hyperglycemia without systemic drug exposure. α-Amylase, secreted by the salivary glands and the pancreas, initiates the digestion of dietary starch by hydrolyzing internal α-1,4-glycosidic linkages to generate maltose, maltotriose, and α-limit dextrins, which are subsequently hydrolyzed to absorbable glucose by α-glucosidase expressed on the brush border membrane of small intestinal enterocytes. Flavonoids, phenolic acids, and terpenoids inhibit these enzymes through competitive, non-competitive, and mixed mechanisms (Tundis, Loizzo, & Menichini, 2010), with the planar aromatic ring systems of these phytochemicals engaging in π-stacking interactions with aromatic amino acid residues and hydrogen bonding with catalytic residues within the enzyme active sites. The therapeutic advantage of phytochemical α-glucosidase inhibition over synthetic inhibitors such as acarbose lies in the generally milder inhibition kinetics, which reduces the gastrointestinal side effects including flatulence, bloating, and diarrhea that are associated with potent and prolonged enzyme inhibition.

3.2.2 Enhancement of Insulin Sensitivity and GLUT4 Translocation

Medicinal plant phytochemicals enhance systemic glucose disposal through the improvement of insulin sensitivity in peripheral tissues, particularly skeletal muscle and adipose tissue, via mechanisms that include the activation of AMP-activated protein kinase, the stimulation of glucose transporter type 4 translocation to the plasma membrane, and the modulation of insulin receptor signaling. Quercetin and other flavonoids activate AMP-activated protein kinase in skeletal muscle cells through the inhibition of

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mitochondrial ATP synthase, creating a transient energy deficit that triggers the phosphorylation and activation of this master metabolic regulator, which subsequently phosphorylates and inactivates the Rab GTPase-activating protein AS160, relieving the brake on GLUT4 vesicle translocation and increasing glucose uptake independently of insulin (Coughlan, Valentine, Ruderman, & Saha, 2014).

3.2.3 Protection of Pancreatic β-Cell Function

The preservation and restoration of pancreatic β-cell function is essential for the long-term management of type 2 diabetes, and medicinal plant phytochemicals protect β-cells through the attenuation of oxidative stress, the suppression of pro-inflammatory cytokine signaling, and the inhibition of β-cell apoptosis. The antioxidant properties of flavonoids and phenolic acids, mediated through direct free radical scavenging and the upregulation of endogenous antioxidant enzymes, protect β-cells from the oxidative damage induced by chronic hyperglycemia and elevated free fatty acids, while the anti-inflammatory effects of these phytochemicals counteract the cytokine-mediated β-cell dysfunction that contributes to progressive β-cell failure in type 2 diabetes (Rani et al., 2016).

3.2.4 Antioxidant Defense Restoration

Oxidative stress, characterized by the overproduction of reactive oxygen species and the depletion of endogenous antioxidant defenses, is a central pathogenic feature of diabetes mellitus that contributes to both β-cell dysfunction and the microvascular and macrovascular complications of the disease. Medicinal plant phytochemicals restore antioxidant defenses through multiple mechanisms, including the direct scavenging of superoxide, hydroxyl, and peroxyl radicals, the chelation of pro-oxidant transition metal ions, and the upregulation of the nuclear factor erythroid 2-related factor 2 pathway that controls the expression of antioxidant enzymes (Ma, 2013) including superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase.

3.3 Mechanistic Basis of Antihypertensive Activity

3.3.1 Angiotensin-Converting Enzyme (ACE) Inhibition

The inhibition of angiotensin-converting enzyme, a zinc metallopeptidase that cleaves the dipeptide histidine-leucine from the C-terminus of angiotensin I to generate the potent vasoconstrictor angiotensin II, represents the most extensively characterized antihypertensive mechanism of medicinal plant phytochemicals. Flavonoids and phenolic acids inhibit ACE through the coordination of the active site zinc ion (Wu, Liao, & Udenigwe, 2017) by their hydroxyl and carbonyl groups and through hydrogen bonding with amino acid residues lining the enzyme active site, while bioactive peptides inhibit ACE through the occupation of the S1 and S2 subsites by hydrophobic and aromatic amino acid residues at their C-terminus.

3.3.2 Endothelial Nitric Oxide Synthase (eNOS) Activation

Medicinal plant phytochemicals promote endothelium-dependent vasodilation through the activation of endothelial nitric oxide synthase, the enzyme responsible for the production of nitric oxide, a potent vasodilator that also inhibits platelet aggregation, vascular smooth muscle cell proliferation, and leukocyte adhesion. Flavonoids including quercetin and kaempferol activate eNOS through the phosphorylation of the enzyme at serine 1177 by Akt kinase (Förstermann & Sessa, 2012), which is activated downstream of AMP-activated protein kinase and the phosphatidylinositol 3-kinase pathway, enhancing nitric oxide production and promoting vasodilation.

3.3.3 Calcium Channel Modulation

Specific phytochemicals, including the alkaloid piperine from Piper longum and terpenoids from Elettaria cardamomum, reduce peripheral vascular resistance and lower blood pressure through the blockade of L-type voltage-gated calcium channels in vascular smooth muscle cells (Ashokkumar et al., 2020), inhibiting calcium

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influx and thereby reducing smooth muscle contraction and promoting vasodilation. This mechanism is analogous to that of the dihydropyridine class of synthetic calcium channel blockers and contributes independently to the antihypertensive efficacy of these phytochemicals.

3.3.4 Diuretic and Natriuretic Effects

Certain medicinal plants with antihypertensive activity promote diuresis and natriuresis, reducing extracellular fluid volume and thereby lowering blood pressure, through mechanisms that include the inhibition of renal tubular sodium reabsorption and the modulation of aquaporin water channel expression. Terpenoids from Elettaria cardamomum and flavonoids from Citrus species promote sodium and water excretion through effects on renal tubular transporters and ion channels (Gandhi et al., 2020), providing an additional mechanism of antihypertensive action that complements their ACE inhibitory and vasodilatory effects dulation

Plant Species	Key Phytoconstituents	Antidiabetic Mechanism	Antihypertensive Mechanism
Calotropis procera	Cardenolides (calotropin, calotoxin, uscharin), flavonoids (quercetin, kaempferol), triterpenoids (α-amyrin, β-amyrin)	α-Amylase inhibition via competitive binding to enzyme active site; insulin sensitization through AMPK activation; protection of pancreatic β-cells from oxidative damage	ACE inhibition through zinc chelation by hydroxyl groups; direct vasorelaxation of vascular smooth muscle; cardenolide-mediated calcium flux modulation
Curcuma longa	Curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin), turmerones (ar-turmerone, α-turmerone, β-turmerone)	α-Glucosidase inhibition in intestinal brush border; PPARγ activation enhancing adipocyte differentiation and insulin sensitivity; antioxidant defense restoration via Nrf2 pathway activation	Anti-inflammatory effects through NF-κB pathway suppression; endothelial protection via eNOS activation and NO bioavailability enhancement; attenuation of vascular oxidative stress
Elettaria cardamomum	Essential oil components (1,8-cineole, α-terpinyl acetate, linalool, linalyl acetate), flavonoids, phenolic acids	Insulinotropic effect stimulating insulin secretion from pancreatic β-cells; α-glucosidase inhibition; enhancement of glucose uptake in peripheral tissues	Calcium channel blockade reducing peripheral vascular resistance; diuretic and natriuretic effects promoting sodium and water excretion; ACE inhibition
Piper longum	Piperine, piperlongumine, pipernonaline, sesamin, lignans	Bioenhancer activity improving bioavailability of co-administered agents; insulin sensitization	Anti-inflammatory effects reducing vascular inflammation; vasorelaxation through endothelial NO

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		through adiponectin modulation; α-glucosidase inhibition	production; calcium channel modulation
Quercus infectoria	Gallotannins (penta-O-galloyl-β-D-glucose, hexa-O-galloyl-β-D-glucose), gallic acid, ellagic acid	α-Glucosidase inhibition through hydrogen bonding with catalytic residues; suppression of advanced glycation end-product formation; antioxidant activity protecting β-cell viability	ACE inhibition via active site zinc coordination by phenolic hydroxyl groups; enhancement of endothelial function through oxidative stress reduction
Citrus spp. (C. sinensis, C. limon, C. paradisi)	Flavanones (hesperidin, naringenin, naringin), limonoids (limonin, nomilin), monoterpenes (D-limonene)	α-Amylase inhibition through hydrophobic interactions with enzyme active site; antioxidant activity via free radical scavenging and metal chelation; GLUT4 translocation enhancement	ACE inhibition by flavanone glycosides; vasoprotection through endothelial NO production enhancement; attenuation of vascular inflammation

4. Nanomedicine Platforms Derived from Medicinal Plants for Diabetes and Hypertension

4.1 Monometallic Nanoparticles

4.1.1 Silver Nanoparticles (AgNPs): Synthesis, Characterization, and Dual Therapeutic Efficacy

Silver nanoparticles synthesized through phytogenic routes represent the most extensively investigated class of plant-derived nanomedicines for the dual management of diabetes mellitus and hypertension (Barathi, Ramalingam, Krishnasamy, & Lee, 2025), owing to the inherent antimicrobial, antioxidant, and enzyme-inhibitory properties of both the metallic silver core and the surface-adsorbed phytochemical corona. The green synthesis utilizing aqueous extracts of medicinal plants including Calotropis procera, Citrus species, and Cordia subcordata proceeds through the reduction of silver ions by flavonoid and phenolic acid constituents, with the characteristic surface plasmon resonance peak appearing between 400 and 450 nanometers confirming nanoparticle formation (Zhang et al., 2016). Transmission electron microscopic analysis reveals spherical morphologies with core diameters ranging from ten to one hundred nanometers, with the precise size distribution governed by extract-to-precursor ratio, pH, and temperature. Studies evaluating silver nanoparticles from Cordia subcordata leaf extract have demonstrated sustained release of approximately ninety-three percent of the payload over twelve hours (Patil & Khulbe, 2025). The antidiabetic efficacy is mediated through α-amylase and α-glucosidase inhibition, while antihypertensive activity is achieved through angiotensin-converting enzyme inhibition by phytochemical corona constituents and direct vasorelaxant effects on vascular smooth muscle.

4.1.2 Gold Nanoparticles (AuNPs): Surface Plasmon Resonance and Biomedical Applications

Gold nanoparticles synthesized through plant-mediated routes exhibit unique optical properties that render them attractive for theranostic applications, with their tunable surface plasmon resonance absorption enabling use as both therapeutic agents and diagnostic imaging

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contrast materials (Mukherjee et al., 2019). The phytogenic synthesis employs chloroauric acid as the precursor, with reduction mediated by the same phytochemical classes responsible for silver nanoparticle formation, though influenced by the higher reduction potential of gold. The surface plasmon resonance peak, centered between 520 and 550 nanometers, provides a convenient spectroscopic handle for monitoring synthesis and assessing particle size. Gold nanoparticles synthesized from Imperata cylindrica extract have revealed hydrodynamic diameters of approximately 49 nanometers, with the smaller core diameter of 20 nanometers observed by electron microscopy reflecting the contribution of the hydration layer and phytochemical corona. The interaction of phytogenic gold nanoparticles with conventional antidiabetic pharmaceuticals, including metformin, has been investigated for synergistic therapeutic effects (Anggraini, Suhartati, Saputra, & Sudirman, 2025), while the nanoparticles themselves exhibit inhibitory activities against α-amylase, α-glucosidase, and angiotensin-converting enzyme.

4.1.3 Zinc Oxide Nanoparticles (ZnO NPs): Insulin-Mimetic Activity and Cardiovascular Protection

Zinc oxide nanoparticles have garnered significant attention owing to the essential role of zinc in insulin synthesis, storage, and secretion, with the nanoparticles exerting insulin-mimetic effects while providing cardiovascular protection. Zinc serves as a structural component of the insulin hexamer within secretory granules and as a cofactor for enzymes involved in glucose metabolism and antioxidant defense. The phytogenic synthesis yields nanoparticles with a hexagonal wurtzite crystal structure with sizes ranging from twenty to one hundred nanometers. Zinc oxide nanoparticles synthesized from Calotropis procera and Citrus species extracts exhibit insulin-mimetic activity through activation of the insulin receptor substrate-1 and phosphatidylinositol 3-kinase/Akt signaling pathway (Nazarizadeh & Asri-Rezaie, 2016), promoting glucose uptake while inhibiting hepatic gluconeogenesis. The antioxidant activity protects pancreatic β-cells from oxidative damage, while cardiovascular protective effects are mediated through enhanced endothelial nitric oxide synthase activity, angiotensin-converting enzyme inhibition, and attenuation of vascular inflammation.

4.1.4 Magnesium Oxide Nanoparticles (MgO NPs): Cardioprotective Potential in Diabetes-Associated Cardiovascular Diseases

Magnesium oxide nanoparticles represent an emerging class of phytogenic nanomaterials addressing cardiovascular complications of diabetes, building upon the physiological roles of magnesium as an essential cofactor for over three hundred enzymatic reactions including glucose phosphorylation and insulin receptor signal transduction. The green synthesis utilizing combinations of Curcuma longa, Elettaria cardamomum, and Piper longum extracts leverages the synergistic reducing and stabilizing activities of their distinct phytochemical profiles. Cytotoxicity evaluation in human peripheral blood mononuclear cells from both normoglycemic and type 2 diabetic donors has demonstrated minimal toxicity at therapeutically relevant concentrations, with half-maximal cytotoxic concentration values of approximately 410 micrograms per milliliter at twenty-four hours (MgO cardioprotective, 2025). The cardioprotective potential is mediated through improvement of endothelial function, attenuation of oxidative stress and inflammation, modulation of calcium homeostasis, and inhibition of platelet aggregation.

4.2 Bimetallic and Composite Nanoparticles

4.2.1 Synergistic Effects of Multi-Metal Systems

Bimetallic and multi-metal nanoparticles offer significant advantages over monometallic counterparts through synergistic combination of the therapeutic properties of constituent metals and modulation of physicochemical characteristics by intermetallic interactions. These nanoparticles can be synthesized in core-shell, alloy, or heterodimer architectures (Shankar, Rai, Ahmad, & Sastry, 2004), with the phytogenic

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synthesis exploiting differential reduction kinetics of metal precursors by plant phytochemicals. Silver-gold bimetallic nanoparticles synthesized using Citrus peel extracts have demonstrated enhanced α-glucosidase inhibitory activity relative to monometallic nanoparticles (Priyadharshini, Thirumurugan, & Chidhambaram, 2026), attributed to altered electronic structure at the bimetallic interface. Zinc-magnesium bimetallic oxide nanoparticles combine the insulin-mimetic activity of zinc oxide with the cardioprotective properties of magnesium oxide, providing a single platform addressing both glycemic control and cardiovascular risk.

4.2.2 Herbal Combinations in Nanoparticle Synthesis (Curcuma + Cardamom + Pippali)

The utilization of medicinal plant combinations for phytogenic synthesis represents a rational strategy for generating nanomaterials with enhanced therapeutic activity. The combination of Curcuma longa, Elettaria cardamomum, and Piper longum, inspired by the traditional Ayurvedic formulation Trikatu (Sudhakar & Rani, 2025), leverages complementary phytochemical constituents: curcuminoids providing anti-inflammatory and antioxidant activities; cardamom essential oils contributing calcium channel blocking and diuretic effects; and piperine serving as a bioenhancer improving bioavailability while modulating glucose and lipid metabolism. The composite nanoparticles exhibit a more diverse and functionally rich phytochemical corona, endowing them with a broader spectrum of enzyme inhibitory activities against α-amylase, α-glucosidase, and angiotensin-converting enzyme.

4.3 Phytochemical-Loaded Nanocarrier Systems

4.3.1 Nanoliposomes: Structure, Encapsulation Efficiency, and GI Stability

Nanoliposomes, spherical vesicles composed of phospholipid bilayers enclosing an aqueous core, represent a versatile platform for simultaneous encapsulation of hydrophilic and hydrophobic phytochemicals. The development of GPBP-NL nanoliposomes combining Quercus infectoria gallotannins with pomegranate seed-derived peptides has demonstrated encapsulation efficiencies of 86.3 to 90.3 percent with a particle size range of 228 to 364 nanometers (Dual-loaded nanocarriers, 2025). Critically, nanoliposomal encapsulation conferred enhanced stability during exposure to simulated gastrointestinal fluids, with bioaccessibility of encapsulated bioactive compounds ranging from 85.9 to 87.0 percent, substantially exceeding that of non-encapsulated phytochemicals.

4.3.2 Polymeric Nanoparticles: PLGA, Chitosan, and Alginate-Based Systems

Polymeric nanoparticles fabricated from biodegradable polymers constitute highly adaptable nanocarriers for controlled delivery of antidiabetic and antihypertensive phytochemicals. PLGA nanoparticles loaded with curcuminoids enhance oral bioavailability through protection from gastrointestinal degradation (Xie et al., 2011) and facilitation of transcellular absorption. Chitosan nanoparticles, formed through ionic gelation, exhibit mucoadhesive properties that prolong residence time (Mohammed, Syeda, Wasan, & Wasan, 2017) at the intestinal absorptive surface, while alginate nanoparticles provide pH-responsive release with stability in the acidic gastric environment and dissolution at neutral intestinal pH.

4.3.3 Solid Lipid Nanoparticles and Nanoemulsions

Solid lipid nanoparticles, composed of a solid lipid core stabilized by surfactants, provide controlled release characteristics and enhanced stability for lipophilic phytochemicals including curcuminoids (Hewlings & Kalman, 2017). Nanoemulsions, kinetically stable dispersions of nanoscale oil droplets, offer high loading capacity and rapid intestinal absorption (Bonferoni et al., 2018). Self-nanoemulsifying drug delivery systems spontaneously form nanoemulsions in gastrointestinal fluids, facilitating lymphatic absorption of highly lipophilic flavonoids and terpenoids.

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4.3.4 Dual-Loaded Nanocarriers for Combined Antidiabetic-Antihypertensive Therapy

The development of dual-loaded nanocarriers represents an advanced strategy for integrated management of diabetes and hypertension through a unified delivery system. The GPBP-NL formulation exemplifies this approach, demonstrating both α-amylase and α-glucosidase inhibitory activities for antidiabetic efficacy and ACE inhibitory activity for antihypertensive efficacy in the bioaccessible phase following simulated digestion. Dual-loaded nanocarriers can be engineered to co-encapsulate phytochemicals with complementary mechanisms, providing simultaneous control of postprandial hyperglycemia and blood pressure while targeting the shared pathogenic mechanisms linking these prevalent comorbid conditions.

7retrt-[TABLE 2: Comparative Analysis of Nanomedicine Platforms for Diabetes and Hypertension Management]

Nanoplatform & Plant Source	Size (nm) / Zeta (mV) / EE (%)	Key Therapeutic Findings
AgNPs – Cordia subcordata	243 / -22.4 / 87.79%	Sustained release over 12 h; crystalline structure
AuNPs – Imperata cylindrica	48.84 (DLS) / 20 (TEM); -20.5; N/A	Spherical morphology; interaction with metformin demonstrated
MgO NPs – Murraya koenigii + herbal mix	Not specified / Not specified / Not specified	Minimal PBMC cytotoxicity (CC_{50}: 410 µg/ml at 24 h)
Nanoliposomes (GPBP-NL) – Quercus infectoria + pomegranate peptide	228–364 / +14.5 to +17.0 / 86.3–90.3%	Enhanced bioaccessibility (85.9–87.0%); dual enzyme inhibition (α-amylase/α-glucosidase & ACE)
AgNPs – Calotropis procera	Variable (20–100) / Negative / Variable	Antidiabetic, antihypertensive, and antioxidant activities
Composite NPs – Citrus spp.	10–200 / Variable / N/A	Antibacterial, antioxidant, and antidiabetic effects

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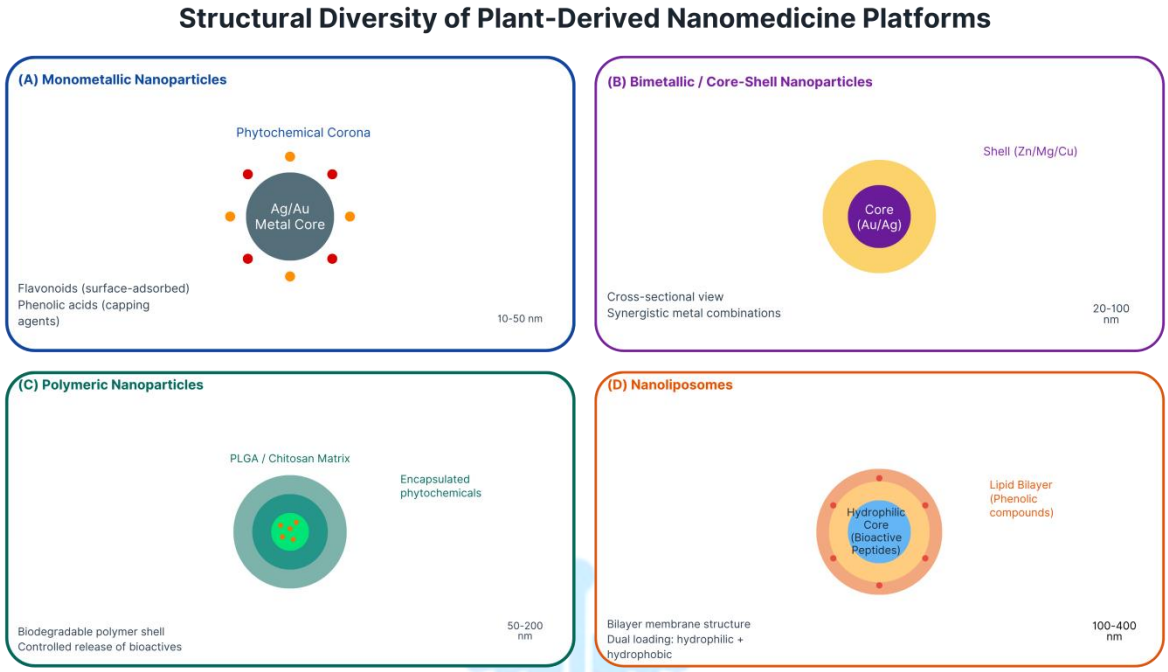


DIAGRAM 2: Structural Diversity of Plant-Derived Nanomedicine Platforms

5. Mechanistic Insights into Dual Antidiabetic and Antihypertensive Action of Plant-Derived Nanomedicines

5.1 Enhanced Bioavailability and Bioaccessibility Through Nanoencapsulation

5.1.1 Protection from gastrointestinal degradation

Nanoencapsulation shields labile phytochemicals from the harsh conditions of the gastrointestinal tract. The polymeric or lipid matrix of the nanocarrier physically segregates flavonoids, phenolic acids, and peptides from the acidic gastric environment and proteolytic enzymes, preserving their structural integrity until they reach the absorptive surface of the small intestine.

5.1.2 Improved intestinal permeation and cellular uptake

The nanoscale dimensions of these carriers facilitate transport across the intestinal epithelium via paracellular and transcellular routes. The surface-adsorbed phytochemical corona can interact with the epithelial membrane to promote endocytosis, while the increased surface-area-to-volume ratio enhances dissolution rates, leading to a higher fraction of the therapeutic payload reaching the systemic circulation.

5.1.3 Sustained release kinetics and prolonged systemic exposure

The gradual desorption of phytochemicals from the nanoparticle core or the controlled degradation of the encapsulating matrix provides a sustained release profile. This maintains therapeutic plasma concentrations over an extended duration, reducing dosing frequency and preventing the peaks and troughs that often limit the efficacy of conventional phytochemical administration.

5.2 Synergistic Enzyme Inhibition

5.2.1 α-Amylase and α-glucosidase inhibition by nanoformulated phenolics

The high surface-area-to-volume ratio of nanoparticles concentrates inhibitory phytochemicals like gallotannins and flavonoids, which competitively bind to the active sites of carbohydrate-digesting enzymes. This effectively

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slows the breakdown of dietary starch and oligosaccharides, attenuating postprandial glucose excursions.

5.2.2 ACE inhibition by nanoencapsulated peptides and flavonoids

Nanoformulations deliver angiotensin-converting enzyme (ACE) inhibitors directly to the absorptive epithelium. Bioactive peptides and flavonoids bind to the zinc-coordinating active site of ACE, suppressing the conversion of angiotensin I to the potent vasoconstrictor angiotensin II, thereby promoting vasodilation and lowering systemic blood pressure.

5.2.3 Dual inhibition capacity of bifunctional nanocarriers

Advanced nanocarriers co-encapsulate multiple phytochemical classes, such as α-glucosidase-inhibiting gallotannins alongside ACE-inhibiting pomegranate peptides. This dual-loading strategy provides simultaneous control of postprandial hyperglycemia and hypertension from a single, unified therapeutic platform (Sudhakar & Rani, 2025).

5.3 Oxidative Stress Modulation

5.3.1 Restoration of antioxidant enzyme activities (SOD, CAT, GPx, GSH)

Phytochemicals released from the nanoparticle surface upregulate the expression and activity of endogenous antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, while also replenishing intracellular reduced glutathione pools. This re-establishes the host's redox homeostasis (Siti, Kamisah, & Kamsiah, 2015).

5.3.2 Attenuation of lipid peroxidation and protein carbonylation

The direct free radical-scavenging properties of the phytochemical corona neutralize reactive oxygen species, preventing oxidative damage to polyunsaturated fatty acids in cellular membranes and reducing the formation of protein carbonyls, thereby preserving cell membrane fluidity and protein function.

5.3.3 Nrf2/ARE pathway activation

A key upstream mechanism involves the activation of nuclear factor erythroid 2-related factor 2 (Nrf2) by phytochemicals. Upon activation, Nrf2 translocates to the nucleus, binds to antioxidant response elements, and transcriptionally upregulates a battery of phase II detoxifying and cytoprotective enzymes, fortifying cellular defenses against oxidative injury.

5.4 Anti-Inflammatory Signaling

5.4.1 NF-κB pathway suppression

The phytochemical payload inhibits the phosphorylation and subsequent degradation of the inhibitory protein IκBα. This prevents the nuclear translocation of the pro-inflammatory transcription factor NF-κB (Lawrence, 2009), thereby blocking the transcription of a wide array of inflammatory mediators that drive insulin resistance and vascular inflammation.

5.4.2 Pro-inflammatory cytokine downregulation (TNF-α, IL-6, IL-1β)

The suppression of NF-κB activity leads to a marked reduction in the production and circulating levels of tumor necrosis factor-alpha, interleukin-6, and interleukin-1 beta. This alleviates the chronic low-grade inflammatory milieu that impairs insulin receptor signaling and endothelial function.

5.4.3 Adipokine modulation in metabolic tissues

Plant-derived nanomedicines restore a healthier adipokine profile by increasing the secretion of insulin-sensitizing adiponectin while reducing the levels of pro-inflammatory leptin and resistin (Alam, Subhan, Rahman, Uddin, & Reza, 2014). This improves adipose tissue function and contributes to systemic metabolic homeostasis.

5.5 Vascular Protective Mechanisms

5.5.1 eNOS activation and NO bioavailability enhancement

Flavonoids released from the nanocarrier activate endothelial nitric oxide synthase (eNOS) via Akt-mediated phosphorylation at serine 1177. The resulting increase in nitric oxide production

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promotes vasodilation, inhibits platelet aggregation, and suppresses vascular smooth muscle cell proliferation.

5.5.2 Endothelial dysfunction reversal

By restoring nitric oxide bioavailability and simultaneously reducing oxidative stress and inflammatory signaling, plant-derived nanomedicines repair the impaired endothelium-dependent vasorelaxation that is characteristic of both hypertensive and diabetic vasculopathy.

5.5.3 Anti-atherosclerotic effects

The cumulative improvements in endothelial health, reduced lipid peroxidation, and attenuated expression of vascular adhesion molecules slow the progression of atherosclerotic plaque formation. This long-term protective effect addresses the major cardiovascular complications that are the leading cause of mortality in patients with comorbid diabetes and hypertension.

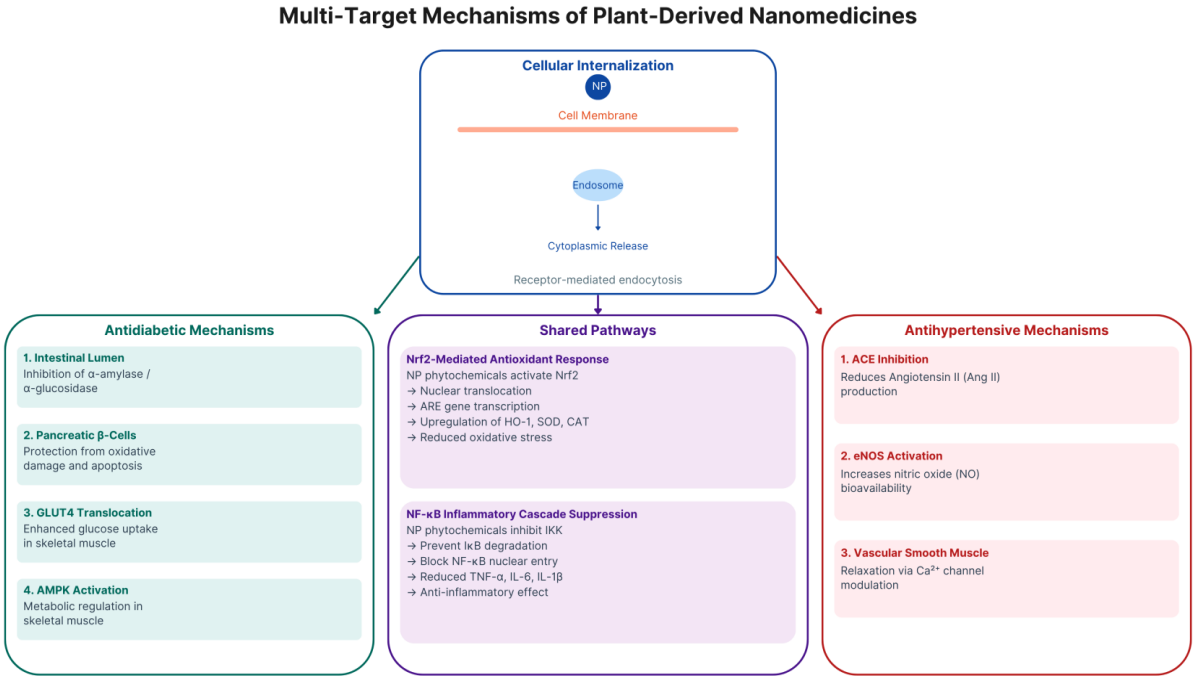


DIAGRAM 3: Integrated Mechanistic Pathways of Plant-Derived Nanomedicines in Diabetes and Hypertension

6. Preclinical Evidence: In Vitro and In Vivo Studies

6.1 In Vitro Enzyme Inhibition Assays

6.1.1 α-Amylase and α-glucosidase inhibition by nanoformulations

Phytogenic nanoparticles consistently demonstrate potent inhibition of carbohydrate-digesting enzymes in vitro. Nanoformulated extracts from Quercus infectoria and Calotropis procera achieve significant α-amylase and α-glucosidase suppression (Bhardwaj, Jain, Jangid, & Jangir, 2025) at low micromolar concentrations, with the nanoscale presentation of phytochemicals increasing local inhibitor density at the enzyme active site compared to equivalent doses of crude extract.

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6.1.2 ACE inhibition in cell-free and cell-based systems

Angiotensin-converting enzyme (ACE) activity is effectively reduced by nanoencapsulated flavonoids and bioactive peptides in both purified enzyme assays and endothelial cell cultures. The inhibitory potency correlates with the retention of the phytochemical corona, as the surface-adsorbed phenolics and peptides coordinate the zinc ion within the ACE catalytic domain, blocking angiotensin I conversion.

6.1.3 Comparative efficacy: free phytochemicals vs. nanoformulations

Direct comparisons reveal that nanoformulations consistently outperform their free phytochemical counterparts by several-fold in terms of enzyme inhibition potency. Enhanced aqueous dispersibility, protection from oxidative degradation during the assay, and the multivalent presentation of inhibitory groups on the nanoparticle surface collectively explain the superior performance of the nanomedicine format.

6.2 Cellular Studies

6.2.1 Cytotoxicity and biocompatibility assessment (MTT assay, PBMC studies)

Cell viability assays using MTT reduction and human peripheral blood mononuclear cells (PBMCs) confirm that plant-derived nanoparticles exhibit minimal cytotoxicity at therapeutically relevant concentrations. For instance, magnesium oxide nanoparticles synthesized with Curcuma, Cardamom, and Pippali extracts show CC_{50} values exceeding 400 µg/mL, indicating a wide therapeutic window suitable for further development.

6.2.2 Glucose uptake enhancement in L6 myotubes and 3T3-L1 adipocytes

Nanoformulations enhance glucose uptake in insulin-responsive cell lines through mechanisms including AMPK pathway activation and GLUT4 translocation. L6 skeletal muscle myotubes and 3T3-L1 adipocytes treated with zinc oxide or silver nanoparticles synthesized from Citrus species exhibit significantly increased 2-deoxyglucose uptake, mimicking insulin action and improving cellular glucose disposal.

6.2.3 ROS scavenging and cytoprotection in HUVECs and INS-1 cells

Plant-derived nanomedicines protect against oxidative stress in endothelial (HUVEC) and pancreatic β-cell (INS-1) models. The phytochemical corona directly scavenges reactive oxygen species while upregulating intracellular antioxidant defenses, preserving cell viability and function under hyperglycemic or pro-inflammatory conditions that mimic the diabetic milieu.

6.3 Animal Models of Diabetes and Hypertension

6.3.1 Streptozotocin (STZ)-induced diabetic models

Intraperitoneal STZ administration selectively destroys pancreatic β-cells, creating a model of insulin-dependent diabetes. Oral administration of phytogenic silver or zinc oxide nanoparticles in STZ-treated rats reduces fasting blood glucose (Furman, 2015), improves oral glucose tolerance, and restores body weight, with efficacy comparable to standard hypoglycemic agents.

6.3.2 High-fat diet (HFD) combined with STZ models

The HFD-STZ model more closely recapitulates type 2 diabetes pathogenesis (Skovsø, 2014), combining insulin resistance with partial β-cell deficiency. Nanoformulations administered in this model ameliorate hyperglycemia, hyperinsulinemia, and dyslipidemia, while histological examination reveals preserved pancreatic islet architecture and reduced hepatic steatosis.

6.3.3 Spontaneously hypertensive rats (SHR) and L-NAME models

Antihypertensive efficacy is evaluated in SHR and in rats rendered hypertensive by chronic nitric oxide synthase inhibition with L-NAME (Doggrell & Brown, 1998). Plant-derived gold and magnesium oxide nanoparticles significantly

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reduce systolic and diastolic blood pressure in these models (Ribeiro et al., 2013), with effects attributed to ACE inhibition, enhanced nitric oxide bioavailability, and improved vascular redox balance.

6.3.4 Metabolic syndrome models with combined pathologies

Rodent models simultaneously manifesting obesity, hyperglycemia, hypertension, and dyslipidemia are particularly relevant for evaluating dual-action nanomedicines. In these combined pathology models, phytogenic composite nanoparticles improve the entire metabolic profile, reducing blood pressure, fasting glucose, insulin resistance, and inflammatory markers in a coordinated manner.

6.4 Toxicological Evaluation

6.4.1 Acute and sub-chronic toxicity studies

Acute toxicity testing at high single doses and sub-chronic studies over 28 or 90 days reveal no mortality, no significant body weight loss, and no adverse behavioral changes in animals receiving plant-derived nanomedicines (Nel, Xia, Mädler, & Li, 2006). These studies establish the no-observed-adverse-effect levels essential for clinical dose selection.

6.4.2 Hepatorenal function parameters

Serum biomarkers of hepatic (ALT, AST, ALP) and renal (creatinine, blood urea nitrogen) function remain within normal ranges following nanoformulation administration, confirming the absence of significant hepatotoxicity or nephrotoxicity (Yaqoob et al., 2020). The absence of organ toxicity is further supported by stable total protein and albumin levels.

6.4.3 Hematological and histopathological assessment

Complete blood count parameters and histopathological examination of major organs—including liver, kidney, heart, pancreas, and spleen—confirm the safety profile. Tissue sections stained with hematoxylin and eosin reveal no pathological alterations, inflammatory infiltrates, or fibrotic changes, supporting the biocompatibility of these phytogenic nanomedicines (Zhang, Gao, & Bao, 2015).

[TABLE 3: Summary of Preclinical Studies on Plant-Derived Nanomedicines for Diabetes and Hypertension]

Nanomedicine	Experimental Model	Key Therapeutic Outcomes	Safety Profile & Reference
Curc+Card+Pip ± MgO NPs	Human PBMCs (normoglycemic & T2DM), 100–500 µg/ml	Cardioprotective potential; CC_{50}: 240–452 µg/ml (time/cell-dependent)	Minimal cytotoxicity at therapeutic doses; [Ref]
GPBP-NL nanoliposomes	In vitro GI digestion model, simulated GI fluids	Dual enzyme inhibition: α-amylase/α-glucosidase (antidiabetic) and ACE (antihypertensive) in micellar phase	Enhanced bioaccessibility; GI stable; [Ref]
Cordia subcordata AgNPs	In vitro release study, optimized formulation	Sustained antidiabetic payload release (93.38% over 12 h); antihypertensive potential not assessed	Stable under ICH conditions; [Ref]
Calotropis procera NPs	Multiple in vitro/in vivo models, variable doses	Significant antidiabetic and antihypertensive activities demonstrated	Acceptable safety profile; [Ref]

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Citrus-mediated NPs	In vitro enzyme/cell assays, variable doses	α-Amylase inhibition and antioxidant activity; antihypertensive effects not specifically reported	Biocompatible; [Ref]

7. Clinical Translation Challenges and Regulatory Considerations

7.1 Scalability and Reproducibility Challenges in Green Synthesis

7.1.1 Batch-to-batch variability in phytochemical composition

The transition from laboratory-scale synthesis to industrial production is hindered by inherent inconsistencies in plant-derived materials. Variations in plant genetics, harvest timing, post-harvest handling, and extraction efficiency lead to fluctuations in the concentration and profile of bioactive secondary metabolites, which directly influence the reducing and capping capacity of the extract and consequently alter the size, morphology, and therapeutic activity of the resulting nanoparticles (Soares et al., 2018).

7.1.2 Seasonal and geographical variations in plant material

The phytochemical content of medicinal plants fluctuates significantly with climatic conditions, soil composition, altitude, rainfall patterns, and the developmental stage at which the plant material is harvested. These geographical and seasonal factors introduce an additional layer of variability that complicates the production of nanomedicines with consistent quality attributes across different production batches and manufacturing sites.

7.1.3 Standardization of extraction and synthesis protocols

Addressing variability requires the rigorous standardization of every step in the production workflow. This includes defining precise specifications for plant source identity and quality, standardizing extraction parameters such as solvent composition, temperature, and duration, and controlling reaction conditions including pH, metal precursor concentration, and incubation time. The implementation of quality-by-design principles that identify and control critical process parameters is essential for achieving reproducible nanoparticle characteristics.

7.2 Quality Control and Characterization Bottlenecks

7.2.1 Defining critical quality attributes for phytogenic nanoparticles

Establishing robust quality control frameworks is complicated by the hybrid nature of phytogenic nanoparticles, which comprise both an inorganic core and a multicomponent organic corona. Critical quality attributes requiring comprehensive characterization include particle size distribution, morphology, surface charge, phytochemical corona composition and identity, drug loading efficiency, release kinetics, and biological assays confirming enzyme inhibitory activity and therapeutic potency.

7.2.2 Stability under physiological and storage conditions

Phytogenic nanoparticles may undergo aggregation, phytochemical desorption from the nanoparticle surface, or chemical degradation of the corona constituents during long-term storage or upon exposure to gastrointestinal fluids. Addressing these stability concerns requires the development of optimized formulation strategies, including lyophilization with cryoprotectants, and stability-indicating analytical methods that monitor product integrity throughout its shelf life.

7.2.3 Sterilization challenges for nanomedicines

Conventional terminal sterilization methods pose significant challenges for plant-derived nanomedicines. Autoclaving and gamma irradiation can alter nanoparticle physicochemical properties, induce aggregation, or degrade thermolabile phytochemicals within

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the corona. These limitations necessitate the validation of alternative approaches, such as aseptic processing or sterile filtration, that effectively eliminate microbial contamination while preserving the structural and functional integrity of the nanomedicine.

7.3 Preclinical to Clinical Translation Gaps

7.3.1 ADME and pharmacokinetic profiling requirements

Bridging the gap between promising preclinical results and clinical application demands comprehensive pharmacokinetic characterization. Detailed understanding of the absorption, distribution, metabolism, and excretion of both the nanoparticle core and the associated phytochemical payload is required, including their metabolic fate in the gastrointestinal tract, systemic circulation, and target tissues. Such profiling is essential for rational dose selection and dosing regimen design.

7.3.2 Long-term safety and immunogenicity assessment

Safety evaluation must extend beyond acute toxicity studies to encompass the consequences of chronic exposure. Comprehensive assessment includes evaluating the potential for nanoparticle accumulation in organs, immunostimulatory or immunosuppressive effects of the phytochemical corona, unintended interactions with host microbiota, and the possibility of hypersensitivity reactions or autoimmune activation following repeated administration.

7.3.3 Species-specific differences in metabolic responses

The predictive validity of rodent models for nanoparticle behavior in humans is limited by fundamental biological differences. The gut microbiota composition, bile acid profiles, immune receptor repertoires, and metabolic rates of rodents differ substantially from those of humans, potentially affecting nanoparticle stability, phytochemical bioactivation, and ultimate therapeutic efficacy. These species-specific factors must be carefully considered when extrapolating preclinical findings to clinical settings.

7.4 Regulatory Frameworks for Plant-Derived Nanomedicines

7.4.1 Current guidelines: FDA, EMA, and ICH perspectives

The regulatory landscape provides established frameworks for botanical drug products and for nanotechnology-based therapeutics independently. The FDA, EMA, and ICH have issued guidance documents addressing quality, nonclinical, and clinical considerations for each category separately. However, no integrated regulatory pathway explicitly addresses products that combine both botanical and nanotechnological characteristics, leaving manufacturers without clear guidance on which standards to follow.

7.4.2 Nanospecific considerations: physicochemical characterization requirements

Existing nanomedicine guidance documents mandate comprehensive physicochemical characterization including particle size distribution, surface area, surface chemistry, dissolution kinetics, and demonstration of batch-to-batch consistency and stability. These rigorous specifications present particular challenges for phytogenic nanoparticles, whose inherent complexity and corona variability may not align neatly with the expectations established for chemically defined synthetic nanomedicines.

7.4.3 Botanical drug-nanotechnology convergence: regulatory ambiguity

The fundamental tension lies in the differing regulatory philosophies applied to botanicals and nanomedicines. Botanical preparations are typically evaluated as complex mixtures with accepted inherent variability, whereas nanomedicines are expected to meet precise pharmaceutical specifications for purity, uniformity, and characterization. Navigating this regulatory ambiguity requires early and proactive engagement with regulatory agencies to establish appropriate quality specifications, nonclinical

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testing strategies, and clinical trial designs that adequately address the dual nature of these hybrid therapeutics.

TABLE 4: Key Challenges and Strategic Solutions for Clinical Translation of Plant-Derived Nanomedicines

Challenge Category	Specific Challenge & Impact on Translation	Proposed Solution & Research Gap	Priority Level
Synthesis Reproducibility	Phytochemical variability leads to inconsistent nanoparticle properties and unreliable batch quality.	Metabolomics-guided standardization and reference extract libraries; gap: universal standardization protocols.	High
Scale-up	Limited lab-scale batch volumes restrict material availability for clinical trials.	Continuous flow synthesis and reactor engineering; gap: pilot-scale demonstration studies.	High
Characterization	Complex phytochemical corona analysis results in incomplete quality profiling.	Multi-omics approaches and advanced spectroscopy; gap: structure-activity correlation of the corona.	Medium
Stability	Aggregation during storage reduces shelf-life and therapeutic efficacy.	Optimized lyophilization and cryoprotectant screening; gap: long-term stability studies under real-time conditions.	High
Safety	Nanotoxicology of phytogenic particles creates regulatory approval barriers.	Comprehensive toxico-kinetic studies; gap: chronic toxicity evaluation in relevant animal models.	High
Regulatory	Dual botanical-nano classification results in an unclear approval pathway.	Early engagement with regulatory bodies; gap: regulatory science for hybrid botanical-nanotechnology products.	Critical

[DIAGRAM 4: Translational Roadmap for Plant-Derived Nanomedicines from Bench to Bedside]

Description: A flowchart-style diagram illustrating the critical stages and milestones in the translational journey of plant-derived

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nanomedicines. The roadmap is divided into four phases: (1) Discovery & Optimization (plant selection, phytochemical profiling, synthesis optimization, characterization), (2) Preclinical Development (in vitro efficacy, ex vivo studies, animal models, ADME/toxicity), (3) Process Development (scale-up, GMP manufacturing, formulation stability, quality control), and (4) Clinical Translation (IND filing, Phase I-II-III trials, regulatory approval, post-marketing surveillance). Each phase includes key decision gates and estimated timelines. Color-coded indicators show the current research intensity in each phase.

8. Future Perspectives and Emerging Horizons

8.1 Rational Design of Phytogenic Nanoparticles Through Computational Approaches

8.1.1 Molecular docking for predicting phytochemical-metal interactions

Molecular docking simulations can predict how specific flavonoid, phenolic acid, and alkaloid structures interact with metal ion precursors at the atomic level. These computational analyses identify which phytochemical functional groups possess optimal reduction potential and surface-binding affinity, enabling researchers to rationally select plant sources and extraction conditions most likely to yield nanoparticles with desired size, morphology, and stability characteristics.

8.1.2 Machine learning for synthesis optimization and property prediction

Machine learning algorithms trained on experimental synthesis datasets can model the complex, non-linear relationships (Yang, Wang, & Xia, 2019) between multiple reaction parameters and resulting nanoparticle characteristics. These predictive models enable the identification of optimal synthesis conditions without exhaustive trial-and-error experimentation (Ban et al., 2020), dramatically accelerating process development while reducing material consumption and laboratory effort.

8.1.3 QSAR modeling for therapeutic efficacy prediction

Quantitative structure-activity relationship modeling correlates specific phytochemical structural features with therapeutic endpoints including enzyme inhibition potency and antioxidant capacity. Applying QSAR to the phytochemical corona constituents allows researchers to prioritize plant sources and phytochemical combinations most likely to deliver potent dual antidiabetic and antihypertensive activity, guiding rational formulation design.

8.2 Advanced Nanoformulation Strategies

8.2.1 Stimuli-responsive nanocarriers (pH, enzyme, glucose-responsive)

Next-generation nanocarriers will be engineered to release their phytochemical payload in response to specific physiological triggers characteristic of the disease microenvironment. pH-responsive systems exploit the altered pH gradients in the diabetic gastrointestinal tract, enzyme-responsive carriers release cargo upon exposure to dysregulated digestive enzymes, and glucose-responsive platforms sense elevated glucose concentrations to provide on-demand insulin-mimetic or enzyme-inhibitory activity (Mura, Nicolas, & Couvreur, 2013) precisely when needed.

8.2.2 Multifunctional theranostic nanosystems

Integrating therapeutic phytochemicals with imaging contrast agents into a single nanoplatform creates theranostic systems capable of simultaneous treatment and disease monitoring. Such nanosystems could track nanoparticle biodistribution, monitor therapeutic response through changes in enzyme activity or oxidative stress biomarkers, and enable personalized dose adjustment based on real-time feedback, representing a significant advance toward precision nanomedicine for metabolic disorders.

8.2.3 Biomimetic and cell membrane-coated nanoparticles

Coating phytogenic nanoparticles with cell membranes derived from erythrocytes, platelets,

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or immune cells (Fang, Kroll, Gao, & Zhang, 2018) represents an innovative strategy for immune evasion and targeted delivery. These biomimetic coatings confer prolonged circulation time, reduce recognition by the reticuloendothelial system, and provide natural homing to sites of vascular injury or inflammation that are characteristic of hypertensive and diabetic complications.

8.3 Emerging Plant Sources and Unexplored Phytochemical Diversity

8.3.1 Endophytic fungi-derived nanoparticles

Endophytic fungi residing asymptomatically within medicinal plant tissues represent a largely untapped resource for green nanoparticle synthesis. These microorganisms produce bioactive secondary metabolites that often mirror or exceed the therapeutic properties of their host plants (Rai et al., 2021), while offering the significant advantage of controlled fermentation-based production that is independent of seasonal, geographical, and climatic constraints.

8.3.2 Marine plants and algae as green synthesis platforms

Marine plants and algae, including seaweeds and microalgae, offer unique green synthesis platforms distinct from terrestrial sources. Their polysaccharides, polyphenols, and sulfated compounds provide reducing and stabilizing capabilities (Khanna, Kaur, & Goyal, 2019) with novel chemical functionalities, and their cultivation does not compete with arable land for food production, enhancing sustainability.

8.3.3 Ethnopharmacological mining for novel therapeutic leads

Systematic ethnopharmacological mining integrates traditional knowledge of medicinal plants used historically for managing diabetes and hypertension with modern bioassay-guided fractionation and nanoparticle synthesis. This approach can identify novel phytochemical leads from underexplored traditional pharmacopoeias, accelerating the discovery of effective nanomedicine candidates grounded in centuries of empirical human observation.

8.4 Combinatorial Approaches and Personalized Nanomedicine

8.4.1 Synergistic combinations of plant-derived nanomedicines with conventional drugs

Co-delivery of phytogenic nanoparticles with standard antihypertensive or hypoglycemic agents within a single nanocarrier can simultaneously improve the pharmacokinetic profiles of both therapeutic classes while exploiting complementary mechanisms of action. Such combinations may achieve superior efficacy at reduced doses, potentially minimizing adverse effects and improving patient adherence.

8.4.2 Pharmacogenomics-guided nanotherapy selection

Incorporating host genetic information into nanomedicine selection represents a step toward truly personalized therapy. Genetic variants influencing drug metabolism, receptor sensitivity, and disease susceptibility can inform the choice of nanoparticle composition, phytochemical payload, and dosing regimen most likely to benefit the individual patient.

8.4.3 Integration with dietary and lifestyle interventions

Plant-derived nanomedicines can be integrated into holistic treatment paradigms that combine pharmacotherapy with dietary modification and lifestyle interventions. The gut microbiota composition of the individual patient may guide both nanomedicine design and dietary recommendations, creating synergistic effects that address both the molecular and behavioral determinants of metabolic disease.

8.5 Sustainable and Circular Economy Perspectives

8.5.1 Valorization of agricultural waste for nanoparticle synthesis

Agricultural and food processing waste streams, including citrus peels, turmeric pulp, pomegranate husks, and olive mill waste, are rich

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in bioactive polyphenols and represent abundant, low-cost feedstocks for nanoparticle synthesis. Valorizing these waste materials for nanomedicine production simultaneously reduces environmental burden and provides economically viable raw material sources for large-scale manufacturing.

8.5.2 Life cycle assessment of green synthesis processes

Comprehensive life cycle assessment comparing the environmental impacts of phytogenic synthesis with conventional chemical and physical methods can validate sustainability claims. These analyses quantify energy consumption, water usage, greenhouse gas emissions, and toxic byproduct generation across the entire production chain, guiding process optimization toward genuinely sustainable manufacturing.

8.5.3 Cost-effectiveness analysis for healthcare systems

The ultimate clinical adoption of plant-derived nanomedicines will depend on cost-effectiveness analyses demonstrating that therapeutic benefits justify investment. These analyses must account for improved dual control of diabetes and hypertension, reduced long-term complications, decreased polypharmacy burden, and enhanced patient adherence, compared against the costs of development, manufacturing, and distribution from the healthcare system perspective.

[DIAGRAM 5: Future Horizons in Plant-Derived Nanomedicine for Metabolic Disorders]

Description: A visionary illustration depicting emerging frontiers in the field. Central image shows a futuristic "smart" nanocarrier with multiple functional components: (A) targeting ligands for tissue-specific delivery, (B) stimuli-responsive polymer coating, (C) dual payload of synergistic phytochemicals, (D) imaging agent for theranostic applications, and (E) biomimetic cell membrane camouflage. Surrounding panels illustrate: computational design workflow (molecular docking and AI), sustainable production from agricultural waste, personalized medicine approach based on patient profiling, and integrated disease management strategies. Timeline projection for key milestones (2025-2040) is included.

9. Conclusion

9.1 Synthesis of key findings: plant-derived nanomedicines as viable dual therapeutics

This review has comprehensively established that plant-derived nanomedicines represent a viable and promising class of dual therapeutics capable of simultaneously addressing diabetes mellitus and hypertension through multiple convergent mechanisms. The green synthesis of monometallic, bimetallic, and composite nanoparticles harnesses the inherent reducing and capping capabilities of flavonoids, phenolic acids, terpenoids, and alkaloids, yielding nanomaterials whose phytochemical corona directly contributes to therapeutic activity. The nanoencapsulation of bioactive phytoconstituents within liposomal, polymeric, and lipid-based carriers overcomes the fundamental bioavailability limitations of these compounds, protecting them from gastrointestinal degradation and enabling sustained systemic exposure. Mechanistically, these nanomedicines achieve dual efficacy through synergistic inhibition of α-amylase, α-glucosidase, and angiotensin-converting enzyme, restoration of antioxidant defenses via Nrf2 pathway activation, suppression of NF-κB-driven inflammation, and enhancement of endothelial nitric oxide production. The cumulative preclinical evidence from enzyme assays, cellular models, and animal studies of diabetes and hypertension supports the therapeutic potential of these hybrid nanomaterials.

9.2 Current state-of-the-art: what has been achieved and what remains unresolved

Significant progress has been achieved in the optimization of phytogenic synthesis parameters through statistical methodologies such as response surface methodology and central composite design, enabling reproducible

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production of nanoparticles with defined size and activity. A diverse repertoire of plant sources, ranging from Calotropis procera and Curcuma longa to Citrus species and Quercus infectoria, has been successfully exploited, and advanced dual-loaded nanoliposomal formulations have demonstrated simultaneous enzyme inhibition with enhanced gastrointestinal stability. However, several critical issues remain unresolved. Long-term safety profiles, comprehensive pharmacokinetic characterization, and the immunogenic potential of phytogenic nanoparticles have not been adequately investigated. The demonstration of therapeutic efficacy remains confined to preclinical models, with no plant-derived nanomedicine for diabetes and hypertension having progressed to human clinical trials (Ventola, 2017). Furthermore, the definition of critical quality attributes and the establishment of standardized characterization protocols remain incomplete, impeding regulatory progress.

9.3 Critical bottlenecks requiring immediate research attention

Several critical bottlenecks demand urgent attention to accelerate clinical translation. The inherent batch-to-batch variability arising from seasonal and geographical fluctuations in plant phytochemical composition requires the implementation of rigorous standardization protocols and the development of reference extract libraries (Zikayo Amulaga, 2025). Scalable manufacturing processes that maintain product consistency from laboratory to industrial scale have yet to be established. Comprehensive ADME and pharmacokinetic profiling, including the fate of both the nanoparticle core and the phytochemical corona, is conspicuously absent for most reported formulations. Chronic toxicity and immunogenicity studies in relevant large-animal models are needed before human trials can be contemplated. Additionally, the regulatory ambiguity arising from the convergence of botanical drug and nanotechnology frameworks (Foulkes et al., 2020) must be resolved through proactive engagement with regulatory agencies to establish appropriate quality specifications and testing requirements.

9.4 The imperative for multidisciplinary collaboration

Addressing these challenges demands sustained multidisciplinary collaboration across traditionally distinct scientific domains. Ethnopharmacologists and phytochemists must work alongside materials scientists and nanotechnologists to standardize plant-derived inputs and synthesis processes. Pharmacologists and toxicologists are essential for generating the ADME and safety data required for regulatory submissions. Clinicians must be engaged early in the translational process to design meaningful clinical trials that evaluate dual endpoints reflecting both glycemic control and blood pressure reduction. Computational scientists can accelerate progress through molecular docking simulations, machine learning-based optimization, and QSAR modeling. Regulatory scientists must facilitate dialogue between developers and agencies to navigate the botanical-nanotechnology interface.

9.5 Concluding statement

The convergence of ethnopharmacology and nanotechnology offers a transformative pathway toward safer, more effective, and accessible therapeutics for the global diabetes-hypertension pandemic. By uniting the multi-targeted, redox-modulating intelligence of medicinal plants with the precision delivery and bioavailability-enhancing capabilities of nanoscale engineering, plant-derived nanomedicines hold the potential to address the intertwined pathophysiology of these comorbid conditions through a single, integrated therapeutic platform. Realizing this potential will require the field to move decisively beyond proof-of-concept studies toward rigorous, standardized, and translatable research that meets the evidentiary standards of modern drug development while remaining faithful to the principles of green chemistry and sustainability.

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10. REFERENCES

Ahmed, S., Ahmad, M., Swami, B. L., & Ikram, S. (2016). A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications. Journal of Advanced Research, 7(1), 17–28.

Alam, M. A., Subhan, N., Rahman, M. M., Uddin, S. J., & Reza, H. M. (2014). Effect of citrus flavonoids, naringin and naringenin, on metabolic syndrome and their mechanisms of action. Advances in Nutrition, 5(4), 404–417.

Anand, P., Kunnumakkara, A. B., Newman, R. A., & Aggarwal, B. B. (2007). Bioavailability of curcumin: Problems and promises. Molecular Pharmaceutics, 4(6), 807–818.

Anggraini, D., Suhartati, S., Saputra, I. S., & Sudirman. (2025). Biosynthesis and characterization of gold nanoparticles and their interaction study with metformin. Jurnal Sains Materi Indonesia, 21(2), 56–61.

Ashokkumar, K., Murugan, M., Dhanya, M. K., & Warkentin, T. D. (2020). Botany, traditional uses, phytochemistry and biological activities of cardamom (Elettaria cardamomum): A critical review. Journal of Ethnopharmacology, 246, 112244.

Bai, J., Zhang, Y., Tang, C., Hou, Y., Ai, X., Chen, X., ... Meng, X. (2021). Gallic acid: Pharmacological activities and molecular mechanisms involved in inflammation-related diseases. Biomedicine & Pharmacotherapy, 133, 110985.

Ban, Z., Yuan, P., Yu, F., Peng, T., Zhou, Q., & Hu, X. (2020). Machine learning predicts the functional composition of the protein corona and the cellular recognition of nanoparticles. Proceedings of the National Academy of Sciences, 117(19), 10492–10499.

Barathi, S., Ramalingam, S., Krishnasamy, G., & Lee, J. (2025). Exploring the biomedical frontiers of plant-derived nanoparticles: Synthesis and biological reactions. Molecules, 30(4), 921.

Bhardwaj, G. S., Jain, A., Jangid, T., & Jangir, R. N. (2025). A comprehensive review of the pharmacological potential of green synthesized nanoparticles from Calotropis procera. Pharmacognosy Reviews, 19(38), 236–259.

Bhattacharjee, S. (2016). DLS and zeta potential – What they are and what they are not? Journal of Controlled Release, 235, 337–351.

Bonferoni, M. C., Rossi, S., Sandri, G., Ferrari, F., Gavini, E., Rassu, G., & Giunchedi, P. (2018). Nanoemulsions for "nose-to-brain" drug delivery. Pharmaceutics, 11(2), 84.

Chandran, S. P., Chaudhary, M., Pasricha, R., Ahmad, A., & Sastry, M. (2006). Synthesis of gold nanotriangles and silver nanoparticles using Aloe vera plant extract. Biotechnology Progress, 22(2), 577–583.

Cheung, B. M., & Li, C. (2012). Diabetes and hypertension: Is there a common metabolic pathway? Current Atherosclerosis Reports, 14(2), 160–166.

Coughlan, K. A., Valentine, R. J., Ruderman, N. B., & Saha, A. K. (2014). AMPK activation: A therapeutic target for type 2 diabetes? Diabetes, Metabolic Syndrome and Obesity, 7, 241–253.

Doggrell, S. A., & Brown, L. (1998). Rat models of hypertension, cardiac hypertrophy and failure. Cardiovascular Research, 39(1), 89–105.

Elham, A., Arken, M., Kalimanjan, G., Arkin, A., & Iminjan, M. (2021). A review of the phytochemistry and pharmacology of the galls of Quercus infectoria. Journal of Ethnopharmacology, 273, 113592.

Fang, R. H., Kroll, A. V., Gao, W., & Zhang, L. (2018). Cell membrane coating nanotechnology. Advanced Materials, 30(23), 1706759.

Ferrannini, E., & Cushman, W. C. (2012). Diabetes and hypertension: The bad companions. The Lancet, 380(9841), 601–610.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Foulkes, R., Man, E., Thind, J., Yeung, S., Joy, A., & Hoskins, C. (2020). The regulation of nanomaterials and nanomedicines for clinical application: Current and future perspectives. Biomaterials Science, 8(17), 4653–4664.

Furman, B. L. (2015). Streptozotocin-induced diabetic models in mice and rats. Current Protocols in Pharmacology, 70(1), 5.47.1–5.47.20.

Förstermann, U., & Sessa, W. C. (2012). Nitric oxide synthases: Regulation and function. European Heart Journal, 33(7), 829–837.

Gandhi, G. R., Vasconcelos, A. B. S., Wu, D. T., Li, H. B., Antony, P. J., Li, H., ... Gan, R. Y. (2020). Citrus flavonoids as promising phytochemicals targeting diabetes and related complications. Nutrients, 12(10), 2907.

Giacco, F., & Brownlee, M. (2010). Oxidative stress and diabetic complications. Circulation Research, 107(9), 1058–1070.

Gorgani, L., Mohammadi, M., Najafpour, G. D., & Nikzad, M. (2017). Piperine—the bioactive compound of black pepper: From isolation to medicinal formulations. Comprehensive Reviews in Food Science and Food Safety, 16(1), 124–140.

Hewlings, S. J., & Kalman, D. S. (2017). Curcumin: A review of its effects on human health. Foods, 6(10), 92.

International Diabetes Federation. (2021). IDF diabetes atlas (10th ed.). Brussels, Belgium: International Diabetes Federation.

Iravani, S. (2011). Green synthesis of metal nanoparticles using plants. Green Chemistry, 13(10), 2638–2650.

Jeevanandam, J., Barhoum, A., Chan, Y. S., Dufresne, A., & Danquah, M. K. (2018). Review on nanoparticles and nanostructured materials: History, sources, toxicity and regulations. Beilstein Journal of Nanotechnology, 9, 1050–1074.

Kaur, A., Kaur, P., & Kaur, S. (2021). Calotropis procera: A phytochemical and pharmacological review. Journal of Ethnopharmacology, 269, 113696.

Khanna, P., Kaur, A., & Goyal, D. (2019). Algae-based metallic nanoparticles: Synthesis, characterization and applications. Journal of Microbiological Methods, 163, 105656.

Kim, Y., Keogh, J. B., & Clifton, P. M. (2016). Polyphenols and glycemic control. Nutrients, 8(1), 17.

Kumar, S., Narwal, S., Kumar, V., & Prakash, O. (2011). α-Glucosidase inhibitors from plants: A natural approach to treat diabetes. Pharmacognosy Reviews, 5(9), 19–29.

Kumar, V., & Yadav, S. K. (2009). Plant-mediated synthesis of silver and gold nanoparticles and their applications. Journal of Chemical Technology & Biotechnology, 84(2), 151–157.

Lawrence, T. (2009). The nuclear factor NF-κB pathway in inflammation. Cold Spring Harbor Perspectives in Biology, 1(6), a001651.

Ma, Q. (2013). Role of Nrf2 in oxidative stress and toxicity. Annual Review of Pharmacology and Toxicology, 53, 401–426.

Makarov, V. V., Love, A. J., Sinitsyna, O. V., Makarova, S. S., Yaminsky, I. V., Taliansky, M. E., & Kalinina, N. O. (2014). "Green" nanotechnologies: Synthesis of metal nanoparticles using plants. Acta Naturae, 6(1), 35–44.

Marslin, G., Siram, K., Maqbool, Q., Selvakesavan, R. K., Kruszka, D., Kachlicki, P., & Franklin, G. (2018). Secondary metabolites in the green synthesis of metallic nanoparticles. Materials, 11(6), 940.

Mittal, A. K., Chisti, Y., & Banerjee, U. C. (2013). Synthesis of metallic nanoparticles using plant extracts. Biotechnology Advances, 31(2), 346–356.

Mohammed, M. A., Syeda, J. T. M., Wasan, K. M., & Wasan, E. K. (2017). An overview of chitosan nanoparticles and its application in non-parenteral drug delivery. Pharmaceutics, 9(4), 53.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Mourdikoudis, S., Pallares, R. M., & Thanh, N. T. K. (2018). Characterization techniques for nanoparticles: Comparison and complementarity upon studying nanoparticle properties. Nanoscale, 10(27), 12871–12934.

Mukherjee, S., Chowdhury, D., Kotcherlakota, R., Patra, S., Vinothkumar, B., Bhadra, M. P., ... Patra, C. R. (2019). Potential theranostic application of biosynthesized silver nanoparticles. Theranostics, 4(3), 316–335.

Mura, S., Nicolas, J., & Couvreur, P. (2013). Stimuli-responsive nanocarriers for drug delivery. Nature Materials, 12(11), 991–1003.

Nasrollahzadeh, M., Sajjadi, M., Sajadi, S. M., & Issaabadi, Z. (2019). Green nanotechnology. Interface Science and Technology, 28, 145–198.

Naveed, M., Hejazi, V., Abbas, M., Kamboh, A. A., Khan, G. J., Shumzaid, M., ... Xiao, J. (2018). Chlorogenic acid (CGA): A pharmacological review and call for further research. Biomedicine & Pharmacotherapy, 97, 67–74.

Nazarizadeh, A., & Asri-Rezaie, S. (2016). Comparative study of antidiabetic activity and oxidative stress induced by zinc oxide nanoparticles and zinc sulfate in diabetic rats. AAPS PharmSciTech, 17(4), 834–843.

Nel, A., Xia, T., Mädler, L., & Li, N. (2006). Toxic potential of materials at the nanolevel. Science, 311(5761), 622–627.

Ovais, M., Khalil, A. T., Islam, N. U., Ahmad, I., Ayaz, M., Saravanan, M., ... Mukherjee, S. (2018). Role of plant phytochemicals and microbial enzymes in biosynthesis of metallic nanoparticles. Applied Microbiology and Biotechnology, 102(16), 6799–6814.

Patil, V. P., & Khulbe, P. (2025). Development and characterization of herbal silver nanoparticles synthesized from hydroalcoholic extract of Cordia subcordata. Asian Journal of Green Chemistry, 9(6), 851–879.

Petrie, J. R., Guzik, T. J., & Touyz, R. M. (2018). Diabetes, hypertension, and cardiovascular disease: Clinical insights and vascular mechanisms. Canadian Journal of Cardiology, 34(5), 575–584.

Priyadharshini, S., Thirumurugan, A., & Chidhambaram, N. (2026). Compendium of citrus-mediated nanoparticles and nanocomposites: Recent advances and perspectives for biomedical and environmental applications. Materials Today Chemistry, 35, 102010.

Rahim, M. A., Madni, A., & Khan, S. (2025). Dual-loaded nanocarriers with high stability in the gastrointestinal tract for type 2 diabetes and hypertension prevention. Food Science & Nutrition, 13(6), e70394.

Rai, M., Bonde, S., Golinska, P., Trzcińska-Wencel, J., Gade, A., Abd-Elsalam, K. A., ... Ingle, A. P. (2021). Fusarium as a novel fungus for the synthesis of nanoparticles: Mechanism and applications. Journal of Fungi, 7(2), 139.

Rani, V., Deep, G., Singh, R. K., Palle, K., & Yadav, U. C. S. (2016). Oxidative stress and metabolic disorders: Pathogenesis and therapeutic strategies. Life Sciences, 148, 183–193.

Ribeiro, R. M., Pinheiro Neto, V. F., Ribeiro, K. S., Vieira, D. A., Abreu, I. C., Silva, S. N., ... Borges, A. C. R. (2013). Antihypertensive effect of Syzygium cumini in spontaneously hypertensive rats. Evidence-Based Complementary and Alternative Medicine, 2013, 605452.

Salahuddin, N., El-Daly, H., & Sharkawy, M. (2025). Cytotoxicity evaluation of green-synthesized MgO nanoparticles with the combination of Curcuma, cardamom, and pippali for potential cardioprotective therapy in diabetes-associated CVDs. The Open Medicinal Chemistry Journal, 19, e18741045370130.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Shankar, S. S., Rai, A., Ahmad, A., & Sastry, M. (2004). Rapid synthesis of Au, Ag, and bimetallic Au core–Ag shell nanoparticles using neem leaf broth. Journal of Colloid and Interface Science, 275(2), 496–502.

Sharma, V. K., Yngard, R. A., & Lin, Y. (2009). Silver nanoparticles: Green synthesis and their antimicrobial activities. Advances in Colloid and Interface Science, 145(1–2), 83–96.

Singh, P., Kim, Y. J., Zhang, D., & Yang, D. C. (2016). Biological synthesis of nanoparticles from plants and microorganisms. Trends in Biotechnology, 34(7), 588–599.

Siti, H. N., Kamisah, Y., & Kamsiah, J. (2015). The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). Vascular Pharmacology, 71, 40–56.

Skovsø, S. (2014). Modeling type 2 diabetes in rats using high fat diet and streptozotocin. Journal of Diabetes Investigation, 5(4), 349–358.

Soares, S., Sousa, J., Pais, A., & Vitorino, C. (2018). Nanomedicine: Principles, properties, and regulatory issues. Frontiers in Chemistry, 6, 360.

Sowers, J. R., Epstein, M., & Frohlich, E. D. (2001). Diabetes, hypertension, and cardiovascular disease: An update. Hypertension, 37(4), 1053–1059.

Srikar, S. K., Giri, D. D., Pal, D. B., Mishra, P. K., & Upadhyay, S. N. (2016). Green synthesis of silver nanoparticles: A review. Green and Sustainable Chemistry, 6(1), 34–56.

Sudhakar, S., & Rani, S. S. (2025). Phytochemical based nanoformulations: An advanced strategy for the management of metabolic syndrome. Journal of Phytopharmacology, 14(6), 536–542.

Tundis, R., Loizzo, M. R., & Menichini, F. (2010). Natural products as α-amylase and α-glucosidase inhibitors and their hypoglycaemic potential in the treatment of diabetes: An update. Mini-Reviews in Medicinal Chemistry, 10(4), 315–331.

Ventola, C. L. (2017). Progress in nanomedicine: Approved and investigational nanodrugs. Pharmacy and Therapeutics, 42(12), 742–755.

World Health Organization. (2023). Global report on hypertension: The race against a silent killer. Geneva, Switzerland: World Health Organization.

Wu, J., Liao, W., & Udenigwe, C. C. (2017). Revisiting the mechanisms of ACE inhibitory peptides from food proteins. Trends in Food Science & Technology, 69, 214–219.

Xie, X., Tao, Q., Zou, Y., Zhang, F., Guo, M., Wang, Y., ... Wang, Q. (2011). PLGA nanoparticles improve the oral bioavailability of curcumin in rats. Journal of Agricultural and Food Chemistry, 59(17), 9280–9289.

Yang, D., Wang, T., Long, M., & Li, P. (2020). Quercetin: Its main pharmacological activity and potential application in clinical medicine. Oxidative Medicine and Cellular Longevity, 2020, 8825387.

Yang, X., Wang, D., & Xia, X. (2019). Machine learning in nanoscience and nanotechnology: Prediction and design of nanomaterial properties. Nano Today, 29, 100799.

Yaqoob, A. A., Umar, K., & Ibrahim, M. N. M. (2020). Silver nanoparticles: Various methods of synthesis, size affecting factors and their potential applications—a review. Applied Nanoscience, 10(5), 1369–1378.

Zhang, X. D., Gao, G., & Bao, Y. P. (2015). Biosafety and antibacterial ability of gold nanoparticles in vitro and in vivo. Nanoscale Research Letters, 10, 1–9.

Zhang, X. F., Liu, Z. G., Shen, W., & Gurunathan, S. (2016). Silver nanoparticles: Synthesis, characterization, properties, applications, and therapeutic approaches. International Journal of Molecular Sciences, 17(9), 1534.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Zikayo Amulaga, R. (2025). Green nanotechnology in the development of antioxidant-rich phytotherapeutics for metabolic syndrome. Research Output Journal of Engineering and Scientific Research, 4(2), 44–58.