Nanoparticles-mediated delivery of herbal extract: Impact on inhibition advanced glycation end-product (AGEs): A systematic review

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Abstract. This systematic review compiles and analyzes research on the therapeutic efficacy of nanoparticle-mediated delivery systems for herbal extracts aimed at inhibiting the formation of Advanced Glycation End-products. A comprehensive search of PubMed and Google Scholar was conducted in accordance with the PRISMA systematic review statement guidelines included studies published within the past 10 years. Our examination spans several studies utilizing different nanoparticle formulations—such as gold, silver, and zinc oxide nanoparticles—and encapsulated herbal extracts, including Poria cocos, Nigella sativa, and curcumin, among others. The outcomes indicate that these nanocomplexes not only foster enhanced delivery and bioavailability of the herbal extracts but also significantly decrease inflammatory biomarkers and blood glucose levels, enhance antioxidant responses, and protect against cellular damage caused by oxidative stress. This review emphasizes the potential of nanoparticles to augment the therapeutic properties of herbal medicines for preventing and managing diabetic complications through the inhibition of AGEs formation.

1 Introduction

Advanced Glycation End-Product (AGEs) are heterogeneous molecules derived from non-enzyme products of the reaction of glucose or other saccharide derivatives with protein or lipids [1]. The formation of AGEs in the body could increase in hyperglycemic conditions, both in normal conditions and even more son in patients DM or DM-CVD [2]. Another factor that affects the formation of AGEs in the body is free radicals, which will trigger the formation of reactive oxygen species (ROS) so that activity of c-Jun N-terminal protein

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kinase (JNK) and NADPH oxidase induces mitochondrial dysfunction and oxidative stress [3].

AGEs based on their source are divided into two groups: endogenous and exogenous. Endogenous AGEs are formed spontaneously and accumulate in the body, while exogenous AGEs are mostly derived from food intake, and have a high fat and protein content [4]. Based on chemical structure and fluorescence, there are four groups, namely: a. Non crosslinked nonfluorescent products; b. Crosslinked nonfluorescent products; and c. Crosslinked fluorescent products. Fluorescence AGEs are the most abundant type of AGEs and can be measured to determine the total amount of AGEs in the body. AGEs with a high molecular weight have high pathogenic potential. Crosslinking AGEs have high affinity and are resistant to degradation, thus causing toxic effects on the body [4].

Recent research results suggest that AGEs may be a marker or biomarker for cardiovascular complications associated with DM. AGEs causes tissue stiffness by forming cross-links as well as triggering inflammation through *Receptor Advanced Glycation End Products* (RAGE) [5]. Accumulation of AGEs occurs in tissues under conditions of hyperglycemia, renal insufficiency, and smoking. AGEs have been detected in blood vessels, atherosclerotic lesions, and the heart. These findings suggest that AGEs may be a relevant target in the prevention and treatment of cardiovascular diseases, especially in patients with CVD-DM [6]. Currently, the use of medicinal plants (herbal medicine) is one of the alternatives in health maintenance and treatment. The use of medicinal plants is increasingly in demand by both patients and health professionals [7].

The use of herbal medicine for several CVDs is currently one of the alternatives [8]. Many patients with CVD already use herbal medicines or combine herbal medicines with conventional medicines given by doctors [9]. Herbal medicines contain many active compounds, such as alkaloids, polyphenols, terpenoids, flavonoids, saponins, phytosterols, and fibers, that have therapeutic benefits in CVD [10][11]. However, the bioavailability of these compounds is low because they have a large molecular size and low water solubility, making it difficult to penetrate the lipids of body cells [12][13][14]. Due to the low bioavailability of these three compounds, innovations in formulation development to improve bioavailability need to be made. The application of nanotechnology in the development of dosage formulations to improve bioavailability and bioactivity is currently widely used [15].

Nanotechnology has also been shown to reduce the negative effects of using conventional preparations. Nanoparticle-encapsulated flavonoid preparations can significantly suppress the expression of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, dan IL-18, compared to non-encapsulated flavonoid preparations [16].

The application of nanotechnology in development of preparations containing plant extracts is widely practiced by researchers today. Dosage forms in nanoparticles can increase the activity of active compounds in extracts due to their ability to release active compounds in a sustainable manner, reduce the dose required, and reduce side effects [17]. The effectiveness of herbal extract preparations in nano formulations is higher than that of conventional formulations [18]. This study can be used as literature for researchers who will develop preparations containing herbal extracts in the form of nanoparticles. In addition our Study in line with sustainable development goal (SDGs) 3 which aspires to ensure health and well-being for all, including the prevention of diabetic complications such as cardiovascular disease by inhibiting AGEs as a therapeutic target using herbal extract nanoparticle preparations.

2 Material and Methods

This review was conducted in accordance with the PRISMA systematic review statement guidelines. A comprehensive search of PubMed and Google Scholar was conducted using

the search strategy "(Nanoparticle) OR (nanotechnology) OR (polymeric nanoparticles) OR (nanomedicine) AND (advanced glycation end-product) OR (AGEs inhibition) OR (Antiglycation) AND (herbal extract) OR (phytochemical). The inclusion criteria for this systematic review included studies published in the English language within the past 10 years that evaluated of nanoparticle formulation of herbal extract inhibiting the formation of advanced glycation end-products. This study evaluates the efficacy of nanoparticle formulations of herbal extracts concerning nanoparticle characteristics (particle size or zeta potential or both it) and the active substance content of the herbal extracts employed. Furthermore, it investigates the impact of herbal extract nanoparticle formulations on the inhibition of advanced glycation end-products (AGEs). The exclusion criteria for this systematic review comprised reports of nanoparticle preparations showing no efficacy as inhibitors of AGEs formation, as well as disqualification of preparations capable of inhibiting AGEs formation but not in nanoparticle form.

2.1 Inclusion and Eligibility Criteria

In this systematic review, we employed specific inclusion and eligibility criteria to identify relevant studies investigating of nanoparticle formulation of herbal extract inhibiting the formation of advanced glycation end-products. The selected studies were original research articles published in peer-reviewed journals, focusing on evaluating the effects of various nanoparticle herbal extracts on the inhibition of advanced glycation end products. Both in vitro and in vivo studies were included, utilizing relevant disease models such as diabetes mellitus or endothelial dysfunction. The primary outcome of interest was the assessment of AGEs levels and the comparison between nanoparticles with herbal extract or control groups. Language restrictions were applied; studies published in the English language were included.

We conducted thorough search and reviewed the studies that met our criteria. The systematic review followed a specific selection process, which was reported using a PRISMA flow diagram. The identified studies were imported into Mendeley, where duplicate records were removed manually. Two reviewers independently screened the titles and abstracts of the studies against the eligibility criteria and removed those that did not meet the criteria. The remaining studies were retrieved in full for further assessment by the reviewers, and any that were deemed ineligible were removed.

3 Results and Discussion

The systematic review began by searching two databases: PubMed and Google Scholar host. A total of 256 records were identified in PubMed and Google Scholar. Before the screening process, duplicate records were removed (n = 20) and records marked as ineligible by automated tools were removed (n = 98). Additionally, 41 records were removed because they were publications other than original research, such as reviews or conference proceedings. The remaining 98 records were then screened, resulting in the exclusion of 54 records. Three reports were retrieved and assessed for eligibility along with the remaining 44 records. The eligibility assessment led to the exclusion of 41 reports that focused on nanoparticle formulations in herbal extracts, 20 reports that focused on nanoparticle formulations in herbal extracts but did not inhibit the formation of AGEs, and 7 reports that focused on formulations to inhibit AGEs but not in nanoparticle form. In total, 14 studies were included in this review.

A total of 23 studies met the eligibility criteria (6 silver nanoparticles, 3 Zn O nanoparticles, 3 gold nanoparticles, 1 Fe2O3 nanoparticles, and 1 quercetin nanoparticles), with some minor exceptions. For example, in most of the studies had incomplete nanoparticle characterization data; several studies did not present particle size data, which was accompanied by other missing nanoparticle characteristics such as FTIR. Table 1 summarizes

the main characteristics of the selected studies. The objectives of these studies are all related to investigating the effects of substances such as Moringa oleifera nanoparticles, Tamarix articulata, Gymnema sylvestre, Jatropha tanjorensis, Aloe vera, Aquilegia pubiflora, pomegranate, Rosa damascena, Couroupita guianensis, Nigella sativa, Saccharum arundinaceum, Poria cocos, Curcuma longa, and quercetin on inhibiting the formation of Advanced Glycation End-Products (AGEs) in various in vivo and in vitro models. The specific aims of each study vary, but generally involve evaluating the substances' ability to inhibit AGE formation, assessing their mechanisms of action, and assessing their potential therapeutic benefits for conditions marked by AGEs. These conditions may include diabetes, cardiovascular diseases, acute kidney injury, and various other diseases resulting from AGE formation. The studies employ a range of methodologies, including in vivo animal studies, in vitro cell culture experiments, and molecular biochemical assays.

Fig. 1. Flow diagram of search strategy and article selection

Table 1 presents information on the on the performance nanoparticles as a release system in vitro or in vivo. It includes data on the type of plant, the plant extract used, the phytochemical compound encapsulated, classification of nanoparticles based on material as well as the size and zeta potential of the nanoparticles. One of the key findings from the table is that the performance of nanoparticles as a release system can vary significantly based on the type of phytochemical compound and the composition of the nanoparticles. This variability highlights the importance of carefully selecting and designing nanoparticle systems to optimize the delivery and release of active compounds. For example, some nanoparticles demonstrate high encapsulation efficiency and are capable of storing and protecting phytochemical compounds such as phenols, flavonoids, tannins, and triterpenoids, among others. Additionally, nanoparticles can be classified based on their constituent materials, such as silver nanoparticles (Ag NPs), Zinc Oxide nanoparticles (Zn O NPs), Gold nanoparticles (Au NPs), and Iron nanoparticles (Fe_2O_3 NPs)

Table 1. Characteristics of nanoparticles as herbal extract delivery systems

Reference	Plant/Plant extract	Phytochemical compound	Nano formulation	Methodology for characterizing nanoparticles
Dolly Verma et al., 2022 [19]	Moringa oleifera/ Aqueous extract of leave	phenolic and flavonoid	silver NPs	UV–vis, HR-TEM, FTIR
Shehwaz Anwar et al.,2021[20]	Tamarix articulata/ ethanolic extract of leaves	phenolic and flavonoid	Silver NPs	UV-vis, SEM, TEM
Dolly Verma., 2022 [21]	Gymnema sylvestre/ aqueous leaf extract	phenolic and flavonoid (7-hidroksi-5-metoksi-6,8-dimetilflavanon)	Zn O NPs	Uv-vis, TEM, FTIR
Olasunkanmi Kayode Awote et al., 2023 [22]	Jatropha tanjorensis/ aqueous leaf and stem extracts	Tannin	Silver	Uv-vis, SEM, FTIR
Jalaluddin M.Ashraf et al., 2016 [23]	Aloe vera/ aqueous leaf extract	-	Silver NPs	Uv-vis, TEM, FTIR, XRD, DLS
Hasnain Jan et al., 2021 [24]	Aquilegia pubiflora/ aqueous leaf extract	flavonoid (hydroxycinnamic acid)	Zn O NPs	SEM, XRD, FTIR, HPLC, DLS
Krishnendu Manna et al., 2019 [25]	Pomegranate/ Methanol peel extract	Polyphenol (ellagic acid)	Gold NPs	AFM, FTIR, SAED, TEM, UV, XRD
Shahin Peron et al., 2021 [26]	Rosa damascena/ aqueous flower extract	flavonoids, phenol, terpenoids, ketones, carboxylic acids, aldehydes, enzymes, amides,	Silver NPs	Uv-vis, SEM, FTIR, XRD
Manimegalai Sengani et al., 2017 [27]	Couroupita guianensis/ aqueous leaf extract	phenolic and flavonoid	Gold NPs	UV, SEM

Reference	Plant/Plant extract	Phytochemical compound	Nano formulation	Methodology for characterizing nanoparticles
Maha I. Alkhalaf et al., 2020 [28]	Nigella sativa/ aqueous extract of (NS)	Thymoquinone	Silver NPs	UV, SEM
Saeed M Aldossari et al., 2023 [29]	Saccharum arundinaceum/ extract of (SA)	Tricin and apigenin, and luteolin glycoside	Fe_2O_3 NPs	FTI-R, UV−vis, SEM, XRD, and EDX
Wansen Li et al., 2020 [30]	Poria cocos/us extract aqueo	Phenolic dehydrotumulosic acid, dehydrotrametenoli c acid, dan pachymic acid.	Gold NPs	UV–Visible Spectroscopic, SEM, TEM
ShaymaaAbd ulmalek et al., 2021 [31]	Curcuma longa/ aqueous extract	Curcumin	Zn O NPs	Uv-vis, SEM, FTIR, PDI, DLS
Soha Shebel Nassar et al., 2021 [32]	Ethanol extract	Quercetin	Quercetin NPs	Uv-vis, TEM

In this review there are several phytochemical compounds made in the form of nanoparticles to inhibit the formation of advanced glycation end-products including flavonoids found in Moringa oleifera, Tamarix articulata, Gymnema sylvestre, Aloe vera, Aquilegia pubiflora, Rosa damascena, Couroupita guianensis, Saccharum arundinaceum, Curcuma longa. In addition, polyphenolic compounds in Jatropha tanjorensis, Pomegranate Poria cocos and thymoquinone essential oil in Nigella sativa plants. The flavonoid compounds in question are curcumin, quercetin, apigenin, hydroxycinnamic acid 7-hydroxy-5-methoxy-6, 8-dimethylflavanone. Flavonoids are a group of polyphenolic compounds found in all plants and have attracted attention because of their various biological activities [33]. Flavonoids have various health effects such as cardiovascular disease, cancer, obesity, and diabetes [34]. However, some flavonoids suffer from the problems of low solubility, poor absorption, and fast metabolism, making it difficult to penetrate the lipids of the body cells [12]. Therefore, innovation is needed in formulation development to improve solubility [15].

This review article discusses the preparation of nanoparticles from herbal extracts as an inhibition of advanced glycation end-product (AGEs). Classification of NPs based on materials NPs are classified into inorganic, organic, and carbon base NPs. Inorganic based NPs Inorganic NPs are defined as NPs without carbon atoms in their composition, which include metal, and metal oxide base NPs. Metal NPs: Metals such as aluminum (Al), silver (Ag), gold (Au), lead (Pb) cadmium (Cd), copper (Cu), cobalt (Co), iron (Fe), and zinc (Zn) are famously reported in this category. These materials possess specific properties due to their size and characteristics, including an increased surface area, pore size, surface charge density, spherical and cylindrical shapes, color, and crystal structure [35]. Metal oxide nanoparticles (M Ox) are an exciting class and diverse form of nanomaterials, especially with applications in chemistry, physics, and materials science. Metal Oxide NPs: Metal NPs with improved properties and higher reactivity with oxygen synthesized metal oxide NPs such as titanic oxide (TiO2), silicon oxide (SiO2), cerium oxide (CeO2), iron oxide (Fe2O3), zinc oxide (Zn O), and aluminum oxide (Al2O3) [36].

In this review, flavonoid, phenol, and thymoquinone compounds are formulated into nanoparticles using inorganic materials such as silver nanoparticles, gold nanoparticles, zinc oxide nanoparticles, and iron nanoparticles as inhibitors of AGEs through various

mechanisms. Metal nanoparticles offer numerous advantages as pharmaceutical carriers, including increased stability, extended circulation half-life, and appropriate biodistribution. They can be functionalized with various ligands to target specific tissues and cells. The functionalization of nanoparticles with flavonoid ligands has been found to enhance their selectivity and enable them to reach target sites [37].

3.1 Silver Nanoparticles

Ag NPs are particles with size between 1-100 nanometers made of silver. They have unique physical and chemical properties due to their small size, high surface area to volume ratio, and ability to absorb and scatter light in the visible and near-infrared light range. Due to relatively small size and high surface area to volume ratio, which cause chemical and physical differences in their properties compared to their bulk form, silver nanoparticles (Ag NPs) can exhibit additional antimicrobial capabilities that ionic silver does not have [38]. In the preparation of silver nanoparticles, herbal extracts were added to the $AgNO_3$ solution. The addition of $AgNO_3$ which was originally transparent changed from pale yellow to dark yellow and finally become a brown solution, indicating that all silver salts in the solution had been reduced after several hours [19] [20] [23]. The physicochemical properties of nanoparticles are important for their behavior, bio-distribution, safety, and efficacy. Therefore, characterization of Ag NPs is important to evaluate the functional aspects of the synthesized particles. Characterization was performed using various analytical technique, including UV-vis spectroscopy, X-Ray Diffractometry (XRD), Fourier Transform Infrared Spectroscopy (FTIR), X-Ray Photoelectron Spectroscopy (XPS), Dynamic Light Scattering (DLS), Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), and Atomic Force Microscopy (AFM) [39].

3.2 Zinc Oxide Nanoparticles

Zinc nanoparticles (Zn ONPs) are particle between 1-100 nm in size made of zinc. Zinc oxide (Zn O) NPs are semiconductors with a wide band gap and an anergy gap at room temperature of 3.37 eV. Their catalytic, electrical, optoelectronic, and photochemical capabilities make them highly valuable Zn O nanostructures are ideal for catalytic reaction processes [40]. The preparation of zinc oxide nanoparticles starts from putting herbal extracts into zinc oxide acetate solution at 60^0C and stirring using a magnetic stirrer for 2 hours [24]. The appearance of Zn NP (Zinc Nanoparticles) is characterized by color change from colorless to pale yellow [21]. Characterization of zinc oxide nanoparticles using various tests such as morphology, size and shape tests using SEM, X-Ray Diffractometry (XRD) to determine the crystal structure of nanoparticles and confirm the presence of zinc oxide in the form of nanoparticles, FTIR to identify chemical bonds and functional groups on the surface of zinc oxide nanoparticles, XPS to determine the elemental composition and oxidation state on the surface of nanoparticles, DLS to measure the particles size distribution in suspension, which is important to determine the homogeneity of the particle size [41].

3.3 Gold Nanoparticles

Gold Nanoparticles (Au NPs) are nanoparticles made of gold. They have unique physical and chemical properties and can absorb and emit light in the visible light and near infrared spectral ranges [42]. Gold nanoparticles were prepared by preparing a gold ion solution by diluting 30% tetrachloroaurate (HAuCl4) in double distilled water to form a stock solution (0,01%). AuNPs were prepared by adding this solution to herbal extracts of pomegranate, Couroupita guianensis and poria cocos dropwise at 60^0C while stirring vigorously. The

formation of AuNPs was confirm within a few seconds by the color change from gold to dark purple and finally to burgundy [25] [27], [30]. The characteristics of gold nanoparticles were analyzed by several methods just like silver and zinc oxide particles.

3.4 Iron Nanoparticles

Iron nanoparticles (Fe NPs) are particles with a size range of 1-100 nm made of iron [43]. Fe NPs have several potential applications, including use as catalysts, drug delivery systems, sensors, and energy storage and conversion. They have also been investigated for use in photovoltaic and solar cells, as well as for water filtration and environmental remediation. Fe NPs can also be used in magnetic resonance imaging (MRI) as a contrast agent to improve the visibility of tissues and organs. They can also be used in magnetic recording media, such as hard disk drive [35]. As with other nanoparticles, there are potential health and safety concern associated with the use of Fe NPs, for example, Fe NPs are used to deliver drugs to specific location in the body, such as cancer cells, and are use in MRI, as well as being used to remove contaminants from water [44]. Iron nanoparticles were prepared by mixing FeCl3-6H2O into the herbal extract of Saccharum arundinaceum and then stirring at 200 rpm for 2 hours at 70^0C. As a result, the color of solution changed from pale yellow to dark brown, indicating the synthesis of NPs [29].

Table 2 discusses the mechanism of action of herbal extract nanoparticle preparations on the development of diabetic complications through the mechanism of inhibiting advanced glycation end-products (AGEs). The risk cardiovascular complications in DM patients can be caused by formation of AGEs due to high glucose levels in DM patients. Advanced Glycation End Product is a compound that when accumulated can accelerate the development of CVD in DM patients [45]. In addition, the formation of advanced glycation end products (AGEs) plays and important role in the pathogenesis of diabetic complications, especially diabetic nephropathy (DN). The accumulation of AGEs in renal tissue contributes to the development of DN by causing irreversible modifications to lipids and proteins, leading to vascular and renal damage [46]. In this study, several plants containing polyphenolic flavonoids, tannins and thymoquinones were shown to have effects on the inhibition of AGEs in vitro or in vivo by various mechanisms.

Table 2. The role of nanoparticles in inhibiting Advanced Glycation End-product (AGEs)

Reference	Cell Culture/Murine model	Effect of nanoparticles on inhibiting AGEs
In vitro		
Dolly Verma et al., 2022 [19]	bovine serum albumin (BSA)	Fluorescence reduction of AGEs and fructosamine levels in MO-Ag NPs-treated tissues
Shehwaz Anwar et al.,2021 [20]	bovine serum albumin (BSA)	Protein Aggregation inhibition can prevent glycation and inhibition of carbonyl group formation, which ultimately affects the formation of AGEs.
Dolly Verma et al., 2022 [21]	bovine serum albumin (BSA)	Inhibits protein glycation process
Olasunkanmi Kayode Awote et al., 2023 [22]	bovine serum albumin (BSA)	Glycation process that can inhibit the formation of AGEs
Jalaluddin M.Ashraf et al., 2016 [23]	human albumin serum (HAS)	AGEs inhibition mechanism by reducing the reactivity of lysine and arginine residues, capturing carbonyl groups (Methylglyoxal), reducing CML

Reference	Cell Culture/Murine model	Effect of nanoparticles on inhibiting AGEs
		formation and reducing AGEs fluorescence.
Hasnain Jan et al., 2021 [24]	bovine serum albumin (BSA)	Reducing post-meal blood glucose levels, such inhibition of digestive enzyme activity also has implications for the formation of Advanced Glycation End Products (AGEs) Good inhibition against two enzymes, AGEs of pentosidine and vesperlycine
Shahin Peron et al., 2021[26]	fibroblast cells, bovine serum albumin (BSA)	Inhibiting glycation reactions, the antioxidant properties of Rosa damascene flower extract NPs can inhibit oxidative reaction associated with the formation of AGEs.
Manimegalai Sengani et al., [27]	Human serum albumin (HAS)	By capturing MGO, the GNPs-MGO complex prevents MGO from engaging in glycation reactions with amino residues on HAS proteins. The inhibits the formation of AGEs which are a major contributor in diabetic complications.
Saeed M Aldossari et al., 2023 [29]	bovine serum albumin (BSA)	Inhibits the formation of AGEs products (Advanced Glycation End Products) under hyperglycemia condition compounds. In addition, by capturing methylglyoxal and as an antioxidant that can inhibit the formation of AGEs.
In vivo		
Krishnendu Manna et al., 2019 [25]	Adult male BALB/c mice ranging from 8 to 10 weeks of age, with initial body weights of 20–22 g	Lower blood sugar levels thereby inhibiting the glycation process, besides that PPE-AuNPs reduce STZ-induced AGE-RAGE activation in nephritic tissues.
Maha I. Alkhalaf et al., 2020 [28]	male albino rats (200 ± 10 g)	Decreased blood glucose levels that can promote glucose oto-oxidative glycosylation, thereby inhibiting the formation of glycation products (AGEs)
Wansen Li et al., 2020 [30]	Healthy female Wistar rats 6–9 weeks aged, weighing 200– 220 g	PC-AuNPs have potential as anti-aging agents as they are able to reduce the formation of AGEs through various mechanisms, including the reduction of blood glucose levels, anti-inflammatory activity, antioxidant activity, and organ protection.
ShaymaaAbdulmalek et al., 2021 [31]	male Albino rats aging 8 weeks, with average body weight 130±10 g	Inhibition of intestinal α-glucosidase enzyme activity, which can reduce glucose absorption and increase glycolysis, thereby inhibiting the formation of AGEs.
Soha Shebel Nassar et al., 2021 [32]	Seventy healthy adult male syrian hamsters weighing 180± 10g	MGO-GO trapping, inhibition of aldose reductase, decreased oxidative stress, modulation of HDACs activity and decreased inflammation

3.5 Inhibition of AGEs in Vitro

The invitro assay in this study used model bovine serum albumin (BSA) and glucose to test the anti-glycation effect of biologically synthesized silver, zinc oxide, gold and iron nanoparticles. Glycation is the process by which glucose binds to proteins, forming advanced glycation end products (AGEs) that can play a role in various chronic diseases such as diabetes and its complications. In this review there are several plants that are tested for their effectiveness in inhibiting AGEs including:

Moringa Oleifera Silver Nanoparticles (MO-Ag NPs)

The results of the AGEs inhibition activity test seen from the fluorescence of AGEs in the addition of MO-Ag NPs with a concentration of 500 μg/ml reduce the fluorescence intensity of AGEs by 65% compared to the control. In addition, seen from the level of fructosamine at the end of week 4, MO-Ag NPs reduced the level of fructosamine by 15.89% - 84.56%, depending on the concentration of MO-Ag NPs used. So, it can be concluded that MO-Ag NPs proved to have an effect as an antiglycation, effective in inhibiting the formation of AGEs and fructosamine in the BSA-glucose model. The mechanism of inhibition by the addition of phytochemical on the surface of silver nanoparticles effectively reduce protein glycation and prevents its accumulation in tissues. The presence of antioxidant compounds such as phenolic, flavonoids, saponins, and alkaloids in M. Oleifera leaf extract contributes to the anti-arthritic properties of this plant [19].

Tamarix Articulata Silver Nanoparticles (T-Ag NPs)

The result of the in vitro assay using bovine serum albumin (BSA) and experiments of increased browning intensity (Brownish discoloration) were used as marker of glycation. T-Ag NPs showed significant antiglycation potential as confirmed by the decrease in browning intensity, aggregation index, and amyloid structure of glycate BSA incubated with T-Ag NPs. The conformational changes induced by glycation increased the β cross amyloid structure of the protein. The increase in β cross amyloid structure leads to protein aggregation indicating the formation of advanced glycation end products (AGEs). In this study, protein aggregation was evaluated using a specific dye for β amyloid, namely Congo Red. Tamarix crude extract also showed antiglycation activity and inhibition of AGEs formation. However, these activity on T-Ag NPs were significantly higher compared to Tamarix extracts [20]. Protein aggregation can inhibit the formation of AGEs through several mechanisms, including a decrease in free amino groups, stabilization of protein structure, and decreased interaction with reducing sugars. Proteins that have aggregated tend to have lower glycation rates compared to non-aggregated proteins [47].

Zinc Nanoparticle Gymnema Sylvestre R. Br. Extract

The results of in vitro studies using BSA induced with fructosamine show that zinc nanoparticles of Gymnema Sylvester Extract have antidiabetic activity by inhibiting α-amylase enzyme activity so as to prevent protein glycation. Inhibition of protein glycation can prevent the formation of AGEs, which can prevent complications of diabetes mellitus. In addition, Gymnema sylvetre zinc nanoparticles have an effect that can reduce oxidative stress [21]. Glycation is a non-enzymatic reaction, which is the process of forming a sugar-protein mixture consisting of reversible and irreversible reactions and the formation of free radical species. This non-enzymatic reaction produces intermediate and final products. Intermediate products are reversible products known as Amadori products or early glycation products, while end products are irreversible products such as AGE (Advanced Glycation End-products) [48].

Jatropha Tanjorensis Extract Silver Nanoparticles

Silver nanoparticles synthesized from J. tanjorensis leaf extract in vitro showed significant inhibitory activity against the α-amylase and α-glucosidase enzymes, as well as better antiglycation potential compared to the fresh extract. This suggests that the use of medicinal plant-based nanoparticles could be an effective strategy in the management of

diabetes and its complications [22]. Non-enzymatic glycation between reducing sugars and proteins results in the formation of advanced glycation end products (AGEs). AGEs play an important role in the pathogenesis of diabetic complications, so if the glycation process is inhibited, then the formation of AGEs is also inhibited [49]. The enzymes α-amylase and α-glucosidase are the enzymes responsible for carbohydrate digestion in the gastrointestinal tract [50]. They break down complex carbohydrates into simple sugars such as glucose, facilitating their absorption into the bloodstream [51]. Inhibition of AGEs formation by inhibiting α-amylase and α-glucosidase causes the breakdown of carbohydrates into sugars to be delayed and reduces blood sugar levels, thereby preventing the formation of AGEs due to hyperglycemic conditions [52].

Aloe Vera Extract Silver Nanoparticles

The results of an aloe vera extract silver nanoparticle activity test in vitro using human albumin serum induced with glucose showed that silver nanoparticles (Ag NPs) have the ability to inhibit the formation of AGEs through several mechanisms. Among them are reducing the reactivity of lysine and arginine residues in glycated HAS, reducing protein carbonyl content, which is a marker of protein oxidation, and reducing CML content, which can cause oxidative stress-induced damage [23]. Carboxymethyl-lysine (CML) is one type of Advanced Glycation End-products (AGEs), which are complex compounds formed through non-enzymatic glycation processes between sugars and proteins, lipids, or nucleic acids [53]. CML can interact with a specific receptor on the cell surface known as the Receptor for advanced glycation end-products (RAGE). Activation of RAGE by CMLs can trigger pro-inflammatory signaling pathways, which contribute to various pathological processes, including chronic inflammation and chronic diseases such as diabetes and cardiovascular disease [54]. Lysine and arginine residues play an important role in the formation of AGEs through glycation reactions. Lysine and arginine residues in proteins can compete with inhibitor compounds to react with reducing sugars, thereby reducing oxidative stress that can inhibit the formation of reactive carbonyl products [55].

Zinc Oxide Nanoparticles (Zn O-NPs) Extract of Aquilegia Pubiflora

Zn O-NPSs of aquilegia pubiflora extract in vitro showed that Zn O-NPs have significant antioxidant, anti-inflammatory, and anti-aging activities, as well as anti-aging activities such as inhibition of AGEs formation and activity enzymes such as tyrosinase, elastase, hyaluronidase, and collagenase. Zn O-NPs also have potential as an antidiabetic agent through inhibition of digestive enzymes and inhibition of AGEs formation, which can help regulate blood glucose levels and reduce diabetic complications [24]. α-Amylase plays a role in digesting carbohydrates by breaking down polysaccharides into smaller molecules such as maltose and maltotriose. While α-glucosidase plays a role in breaking down disaccharides into glucose. By inhibiting these two enzymes, the absorption of glucose from the carbohydrate chain can be slowed down, thereby reducing blood glucose levels after meals. This can help reduce the formation of AGEs (Advanced Glycation End Products) associated with diabetic complications [56].

Silver Nanoparticles Extract of Rosa Damascena Flower

In this study, both plant extracts and SNPs reduced blood glucose effects and prevented the formation of AGEs compounds. However, the anti-diabetic activity of the synthesized SNPs was generally higher than that of the extracts. This activity lasted up to three weeks, which can be said to be a long-lasting drug effect. The inhibitory effects of plant extracts and SNPs can be attributed to the presence of various antioxidant compounds. FTIR spectra were applied to identify different functional and organic groups in the control containing BSA (bovine serum albumin) and GLU (glucose). Then two concentrations including 250 μg/mL of the extract and 1000 μg/mL of the SNPs, with the highest inhibitory effect on albumin glycation among all concentrations tested [26]. Hyperglycemia in diabetes results in the production of AGEs through non-enzymatic glycation reactions on plasma proteins such as

albumin, fibrinogen, and globulin. This leads to various detrimental effects, including loss of natural functions of proteins, formation of free radicals, alterations in plasma drug binding, platelet activation, impaired fibrinolysis, and disturbance in immune system regulation [57][58].

Gold Nanoparticle Extract of Couroupita Guianensis (C. Guianensis)

In vitro results on AGEs inhibition show that gold nanoparticles (GNPs) have a significant inhibitory effect on the formation of AGEs. GNPs successfully stop the non-enzymatic glycosylation of hemoglobin by inhibiting MGO, an intermediate metabolite in the formation of AGEs. The mechanism of action of GNPs works by trapping MGO, which plays a major role in the formation of AGEs during the Maillard reaction. The combination of nanoparticles properties, sustained drug release, and the ability of polyphenols to deal with ROS (reactive oxygen species) efficiently inhibits MGO, thereby reducing the formation of AGEs [27], [59], [60].

Iron Oxide Nanoparticles Extract of Saccharum Arundinaceum

In this study, it was shown that Saccharum arundinaceum extract and Fe_2O_3 NPs have the activity of inhibiting the formation of AGEs. The antiglycation activity of the synthesized Fe_2O_3 NPs was greater than that of the extract. The dose for the best inhibition of albumin glycation was at a concentration of 1000 µg/mL [29]. One way to reduce the accumulation of AGEs is by trapping reactive dicarbonyl compounds such as MGO, GO, or 3-DG [61]. Dicarbonyl compounds such as glyoxal (GO), methylglyoxal (MGO), and 3-deoxyglucosone (3-DG) through the polio and lipid peroxidation pathways will react polymerically with protein structures to form stable AGEs compounds [4]. AGEs formed by reactions with MGO include hydroimidazolones (MG-H_1, MG-H_2, and MG-H_3), Nε-(1-carboxyethyl) lysine (CEL), and 1,3-di(Nε-lysino)-4-methyl-imidazolium dimer lysine (MOLD) [61][62]. These studies conclude that both plant extracts and Fe_2O_3 NPs have potential as effective anti-diabetic agents by inhibiting the formation of AGEs through mechanisms related to the inhibition of MGO activity [63][64].

3.6 Inhibition of AGEs in Vivo

Gold Nanoparticle Extract of Pomegranate Peel

This study was designed to investigate the ameliorative role of pomegranate peel extract-stabilized gold nanoparticle (PPE-AuNP) on streptozotocin (STZ)-induced DN in an experimental murine model. The test animals used were adult male mice of the BALB/c breed, with an age range of 8 to 10 weeks and an initial body weight of 20 to 22 grams. The model used was diabetes induction using a single intraperitoneal (IP) injection of streptozotocin (STZ) at a dose of 200 mg/kg body weight. PPE-AuNPs showed potential for reducing AGEs formation in diabetic nephropathy through several mechanisms. These include decreased blood glucose levels, enhanced antioxidant response, modulation of the NOX4/p-47phox pathway, and reduction of pro-inflammatory burden. Thus, PPE-AuNPs may act as an effective therapeutic agent in managing DN complications associated with AGEs formation [25]. STZ induction can cause hyperglycemic conditions that can increase protein glycation that produces AGEs. AGEs formed can bind to a specific receptor called RAGE (Receptor for Advanced Glycation End Products) [66][67]. Activation of RAGE by AGEs can trigger various biochemical pathways that lead to cellular damage and inflammation [68]. AGE-RAGE The binding of AGEs with RAGE activates various intracellular signaling pathways such as MAPK, ERK, p21ras, p38, and JAK-STAT [69]. Activation of these signaling pathways causes an increase in ROS levels through the activation of NADPH oxidase. In addition, the binding of AGEs with RAGE can trigger the activation of pro-inflammatory signaling pathways such as NF-κB [66]. This activation leads to increased production of pro-inflammatory cytokines (TNF-α, IL-1, IL-6), adhesion

molecules (VCAM-1 and ICAM-1), and other molecules. In DM patients, the AGEs-RAGE interaction may increase the risk of serious complications such as atherosclerosis, ischemic heart disease, heart failure, and stroke [1].

Silver Nanoparticles Using Nigella Sativa

In this study, the test animal model used was male albino rats weighing 200 ± 10 grams. The rats were induced with streptozotocin (STZ) intraperitoneally to condition the test animals in a diabetic state. Ag NPs, Nigella sativa extract, and their combination in rats with diabetic neuropathy showed a decrease in inflammatory biomarkers (TNF-α, NFκB, and S-100B). In addition, Ag NPs, Nigella sativa extract showed protective potential against cell damage caused by oxidative stress in diabetes, and the use of Nigella sativa extract showed neuroprotective effects and increased NGF expression. The inhibition of AGEs in this study was done through several mechanisms that include regulation of blood glucose, amelioration of oxidative damage, and modulation of inflammatory pathways associated with the development of diabetic neuropathy [28], [70].

Gold Nanoparticles Synthesized with Poria Cocos

Evaluation of the effects of gold nanoparticles synthesized with Poria cocos (PC-AuNPs) on obesity and complications of type 2 diabetes induced by a high-fat diet in female Wistar strain rats aged 6-9 weeks weighing 200-220 g. The results of this study showed that PC-AuNPs were effective in treating obesity and complications of type 2 diabetes induced by a high-fat diet. The results of this study indicate that PC-AuNPs have anti-obesity effects by reducing body weight and body mass index in test animals. In addition, the administration of PC-AuNPs significantly reduces blood glucose levels, indicating potential antihyperglycemic activity that can inhibit the formation of AGEs. PC-AuNPs also have an anti-inflammatory effect, reducing the levels of proinflammatory cytokines (TNF-α and IL-1b), antioxidants, and protection of the organs of the kidney and heart [30].

Zinc Oxide Nanoparticles of Curcumin Extract

The results of this study showed that gold nanoparticles synthesized with curcumin (Cur NPs) and zinc oxide (Zn ONPs) have significant antidiabetic effects on type 2 diabetes (T2DM) models induced by a high-fat diet (HFD) and streptozotocin (STZ). The test animals used in this study were 8-week-old Albino male rats with an average body weight of 130 ± 10 g. Administration of Cur NPs and Zn ONPs, along with conventional curcumin, $ZnSO_4$, and metformin, significantly improved glycemic control by lowering fasting blood glucose and insulin levels and improving insulin sensitivity, potentially through regulation of the PI3K/AKT pathway and suppression of MAPK pathway activation, with greater antidiabetic effects compared with curcumin, $ZnSO_4$, and metformin. Overall, the results of this study suggest that Cur NPs and Zn ONPs have potential as potent antidiabetic agents with better effects than conventional therapies such as curcumin, Zn SO4, and metformin. This was indicated by improved glycemic control, increased insulin sensitivity, suppression of inflammation, improved liver and kidney function, and increased antioxidant activity in HFD/STZ-induced T2DM rats. In addition, Cur NPs and Zn ONPs also show potential to reduce the risk of diabetic complications such as hypercholesterolemia, oxidative stress, and pathological changes in liver and pancreas tissues [31], [70]–[73].

Quercetin Nanoparticles

In this study, 70 healthy male adult hamsters weighing about 180 ± 10g were induced with streptozotocin (STZ). The results showed that quercetin nanoparticles can improve kidney function and glomerular filtration rate (GFR) in diabetic nephropathy (DN). This was reflected by a decrease in blood creatinine levels and an increase in IRS-1 and GLUT-4 expression in the group that received quercetin. Furthermore, quercetin, especially in nanoparticle form, has been shown to inhibit the activity of HDACs (histone deacetylases) enzymes, which can affect gene regulation and has potential as a therapeutic target in diabetes management. In addition, quercetin has also been shown to reduce the formation of AGEs

(advanced glycation end products) and inhibit the activity of TNF-α (tumor necrosis factor-alpha) and IL-6 (interleukin-6), which are inflammatory molecules that can worsen insulin resistance. The use of quercetin, especially in the form of nanoparticles, also increases antioxidant activity and reduces oxidative stress in kidney tissue [19][32][74].

3.7 Application of nanotechnology and AGEs inhibition to prevent Diabetes mellitus complications: Cardiovascular disease

The introduction highlights the significant advancements in medicine over the last century, leading to the development of numerous new medications for treating complex conditions. However, some drugs exhibit severe side effects, raising concerns about the risk-benefit balance. Innovation is essential in developing drugs that can withstand endogenous enzymes and effectively target specific tissues [75]. Nanoparticles present a promising solution by facilitating targeted drug delivery through passive or active mechanisms Passive targeting occurs when nanoparticles accumulate in the target organ due to the presence of leaky junctions, whereas active targeting involves conjugating drug carrier systems with tissue- or cell-specific ligands. An ideal nanoparticle drug delivery system should be capable of reaching, recognizing, binding, and delivering its payload to specific pathological tissues. By manipulating the size, surface characteristics, and material composition of nanoparticles, it is possible to coat their surfaces with ligands, enabling precise drug delivery to targeted tissues. This approach allows for controlled-release therapy, thereby reducing drug-related toxicity and enhancing patient compliance through less frequent dosing [76], [77].

Advanced glycation end-products (AGEs) have been identified as a cause of diabetic disease complications such as atherosclerosis and ischaemic stroke as well as other cardiovascular diseases. Therefore, therapies targeting AGEs and receptors or ligands associated with AGEs have become an important focus of research. Some types of AGEs ligands used as therapeutic targets are N-ε-carboxymethyl-lysine (CML), N-ε-carboxy-ethyl-lysine (CEL), Penticidine, Methylglyoxal-Derived Hydroimidazolone (MG-H1), Glyoxal-Derived AGEs (GOLD), Methylglyoxal-Derived AGEs (MOLD) and Receptor for Advanced Glycation End Products (RAGE) [78]. Therapies targeting AGEs ligands can reduce diabetic complications by reducing the formation and accumulation of AGEs, interrupting deleterious cross-linking, inhibiting AGEs-induced signalling pathways, protecting tissues from oxidative damage, and inhibiting the interaction of AGEs with the RAGE receptor, which is a major pathway for inflammatory signalling [79].Thus, this therapy can prevent or slow down the progression of diabetic complications, such as diabetic nephropathy, retinopathy, neuropathy, and cardiovascular disease [80].

Ligand therapy targeting RAGE presents a potential therapeutic strategy to alleviate the complications of diabetes by modulating the effects of AGEs and their interaction with RAGE [78]. RAGE activation in diabetes causes oxidative stress and inflammation by interacting with advanced glycation end products (AGEs) and other ligands, triggering intracellular signalling pathways and changes in gene expression. RAGE activation induces the production of pro-inflammatory cytokines such as interleukin-1a (IL-1a), interleukin-6 (IL-6), and tumour necrosis factor-a (TNF-a), exacerbating inflammation and tissue damage in diabetes [81]. RAGE activation stimulates the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), increasing vascular permeability and endothelial dysfunction. RAGE-mediated activation of nuclear factor-kB (NF-kB) modulates gene transcription for endothelin-1, tissue factor, and thrombomodulin, further promoting inflammation and oxidative stress in diabetes [82]. Sustained activation of RAGE by AGEs and other ligands contributes to the pathogenicity associated with diabetic complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease. RAGE activation plays a critical role in the pathogenesis of diabetic

complications by promoting oxidative stress, inflammation, endothelial dysfunction, and tissue damage through intracellular signalling pathways and the production of pro-inflammatory cytokines [81], [83].

4 Conclusion

Nanoparticles have been demonstrated to be an effective means of delivering herbal extracts, thereby enhancing their therapeutic action in inhibiting advanced glycation end products (AGEs). Nanoparticle-herbal extract complexes have demonstrated efficacy in the treatment of diabetes-related complications, including nephropathy, neuropathy, obesity, and inflammatory responses. Further research is required to ascertain the long-term safety and full physiological interactions of nanoparticle-herbal extract complexes. It is imperative that clinical trials be conducted to validate these findings and facilitate the transition toward clinical applications. The integration of nanotechnology with traditional herbal medicine represents a promising approach to the development of advanced therapeutic agents for the treatment of diabetes and its associated complications. The use of nanoparticle-mediated delivery systems for herbal extracts has the potential to significantly reduce inflammatory biomarkers, lower blood glucose levels, enhance antioxidant responses, and protect against cellular damage from oxidative stress. This review highlights the capacity of nanoparticles to enhance the therapeutic properties of herbal medicines in the prevention and management of diabetes-related complications by inhibiting the formation of AGEs.

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