Therapeutic Advantages of Nano-phytomedicines for the Prevention and Management of Metabolic Disorders

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Received: 29th April, 2023; Accepted: 6th July, 2023; Published online: 21st July, 2023

https://doi.org/10.33745/ijzi.2023.v09i02.013

Abstract: Metabolic syndrome consists of a group of diseases including hyperglycemia, dyslipidemia, hypertension, obesity, and insulin resistance. These disorders have been increasing progressively in recent years, and there is a need for rapid and effective therapeutic solutions to overcome the global and economic burden. Phytomedicines are secondary metabolites present in plants, which are excellent and potential therapeutic agents in the management of metabolic diseases with higher safety profiles and lesser adverse effects. Antioxidant, antihypertensive, hypoglycemic, antitumor, anti-inflammatory, and insulin-producing are the important properties of phytochemicals. Limited biostability and bioavailability are the major drawback for the application of phytomedicine for the prevention of metabolic diseases. Nano-phytomedicines have a promising future for strengthening the efficacy of therapeutic plants by increasing their biocompatibility, biostability, biodegradability, and targeted delivery in metabolic disorders. Nano-based formulations of phytomedicines have a significant advantage including enhancement of pharmacological activity, bioavailability, solubility, stability, and safeguarding from toxicity. Nanosized phytomedicines like curcumin, oleoresin capsicum, berberine, naringenin, quercetin, glycemic acid, scutellarin, resveratrol, silybin, myricitrin, stevioside, alpha-eleostearic acid, etc. show better therapeutics for the treatment of metabolic disorders. These phytochemicals-based Nanoparticles (NPs) were mainly formulated in form of inorganic NPs, polymeric NPs, solid-lipid NPs, nanoemulsions, colloidal nanoliposome, and quantum dots. Nonetheless, with a rising incidence, metabolic diseases are one of the major worldwide health issues and preventing/treating them by nanomaterial intervention of phytochemicals might be a possible strategy for improving the effectiveness of herbal plants for the treatment and management of various metabolic disorders.

Keywords: Phytochemicals, Nano-phytomedicines, Metabolic disorders, Diabetes, Nanoparticles


https://doi.org/10.33745/ijzi.2023.v09i02.013

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Introduction

Obesity, diabetes, hyperglycemia, hypertension, dyslipidemia, and insulin resistance are all part of the metabolic disorders. Globalization and contemporary lifestyle has led to the gradual
ranging and prevalence of these diseases in recent years (Tabatabaei-Malazy et al., 2015; McCracken et al., 2018). It raises the chance of developing other diseases, including cardiovascular diseases (CVD), non-alcoholic fatty liver disease (NAFLD) etc. High level of triglycerides, blood pressure, fasting blood glucose, and low HDL-C levels are the hallmarks of metabolic diseases, which are among the world’s major health issues in both industrialized and developing nations (Gupta et al., 2004; Krishnamoorthy et al., 2020). Lifestyle modification with pharmacological agents is marked as a conventional treatment for metabolic disorders via reducing blood pressure, blood sugar, and triglyceride levels (Dewanjee et al., 2020). A variety of herbal medicinal plants and their phytochemicals have gained significant attention in preventing diabetes and metabolic disorders due to their effective anti-diabetic potential (Chan et al., 2012). Nanoparticles have several benefits over conventional ones, including increased bioavailability, prolonged release, decreased toxicity, enhanced stability, and solubility. Additionally, it has been observed that treating metabolic abnormalities using nanoparticles coupled with phytomedicines is more effective (Taghipour et al., 2019; Dewanjee et al., 2020; Adetunji et al., 2022). This review highlights the in depth analysis of nano phytomedicines and discusses their utilization in the treatment of metabolic diseases in view of the current developments.

**Phytomedicines Role in the Prevention of Metabolic Disorders:**

Majority of individuals in industrialized as well as developing nations are affected by metabolic diseases, which raises the risk of both non-atherosclerotic and atherosclerotic cardiovascular diseases (CVD), one of the major reason of mortality worldwide (Mottillo et al., 2010). The synthetic medicine used for the prevention of metabolic diseases has several negative side effects. The foundation of all traditional medical systems around the world is natural products and their derivatives, which have been proven to be beneficial therapeutic agents since time immemorial (Cefalu et al., 2008; Dong et al., 2012). Many ethnomedical plants and natural products have been studied as an essential source of medicine and considered safer than synthetic drugs. This raised interest in the recognition of novel phytochemicals and their pharmacological targets in prevention or treatment of hyperglycemia and other metabolic disorders (Atta-Ur-Rahman and Zaman, 1989; Grover et al., 2002). Many bioactive compounds of medicinal plants have been introduced as potent anti-diabetic agents during the past few years (Bays and Stein, 2003; Chan et al., 2012) and such therapeutic plants with anti-hyperglycemic and anti-lipidemic activity may be consumed daily along with the food.

Plants evolved secondary metabolites in reaction to specific environmental influences, such as pathogen attack, nutrient deprivation, or herbivore-induced damage. These secondary metabolites not only improve their survival ability and overcome local challenges by allowing them to interact with their environment but they also help humans to protect themselves against diseases (Makheswari, 2011; Atanasov et al., 2015). These plant-derived secondary metabolites (phytochemicals) have also demonstrated notable hypoglycemic effects through different set of mechanisms, including inhibition of glucose absorption, stimulation of glucose utilization, regeneration of pancreatic cells, enhancement of insulin production, reversal of insulin resistance, and regulation mechanisms of lipid and glucose metabolism. To ensure the protection and effectiveness of the dietary supplement, it is necessary to understand the health advantages and potential risks associated with it (Dewanjee et al., 2020).

**Advantages of Nano-phytomedicines for preventing Metabolic Disorders:**

The therapeutic activities of phytochemicals include anti-inflammatory, anti-cancer, anti-hypertensive, hyperglycemia, and insulin-enhancing properties (Naseri et al., 2018). The
prospective medicinal herbs have low water solubility and limited bioavailability, which is a major drawback in the treatment of metabolic diseases. Further, drug delivery incorporated with nanotechnology has spread extensively in recent years. In order to get their enhanced bioavailability, hydrophilicity, biostability with sustained and targeted drug administration, developing phytochemical-based nanoparticles is a viable strategy (Gera et al., 2017; Pereira et al., 2018). The nanoformulation consists of either solid-lipid nanoparticles, polymeric nanoparticles, nanoemulsions, nanoliposomes, and nano-lipid carriers. Designing and creating innovative drug delivery systems for metabolic diseases may be done more effectively when nano-phytomedicine is combined with modern administration since it offers greater potency and effectiveness (Adetunji et al., 2022).

**Phytochemical-based Nanoparticles in Metabolic disorders:**

In recent years nanotechnology has attracted a great deal of attraction in medical research, both for diagnosis and treatment (des Rieux et al., 2006). Natural product based nano-formulation treatment methods enhanced management and prevention of diabetes and associated metabolic diseases (Veiseh et al., 2014; Kesharwani et al., 2018). The biggest advantage of nano-formulation as compared to the conventional formulation is their greater surface area, modified bioavailability, and targeted and prolonged drug delivery (Fig. 1). Therefore, well formulated nano-formulations of phytochemicals may provide better treatments for the control of metabolic disorders. This article focuses on a succinct report on the development and efficacy of several phytochemicals and their nano-formulation, which are beneficial in the prevention of different metabolic disorders (Table 1; Fig. 2).

1. **Alpha-eleostearic acid:**

Alpha-eleostearic acid is a trienoic acid that has been conjugated with the systematic structure trans-13-octadecatrienoic, which has a molecular composition of 66 per cent trans and 33 per cent cis. It is a geometric isomer of alpha-linolenic acid, that increases immunity and functions as an anti-inflammatory, anti-adipogenic, and antioxidant, generally found in oil extracted from seeds of the Cucurbitaceae family (Hennessy et al., 2011). Commonly referred to as "Karela," bitter gourd (*Momordica charantia* L.) is typically taken throughout Asia including India, along with linoleic, oleic, and saturated fatty acids, its seed oil contains about 50–60 per cent alpha-eleostearic acid (Yoshime et al., 2016). According to a study, bitter gourd oil nano-emulsion increases the bioavailability of conjugated linolenic acid with decreasing blood glucose and improves PPAR-γ and insulin sensitivity acid in alloxan-induced diabetes in the *in vivo* system (Paul et al., 2014). Alpha-eleostearic acid has significant scavenging activity against oxidative stress due to its high trans content thus, promote the production of GPx, SOD, and other antioxidant enzymes and decreases nitrous oxide synthase (NOS) activity, which makes it potent against diabetes mellitus (Yu et al., 2002; Saha and Ghosh, 2009). Additionally, this conjugated linolenic acid isomer may be effective as an antioxidant treatment.

2. **Baicalin:**

*Scutellaria radix*, a Chinese plant, has a significant amount of the bioactive flavone glycoside baicalin (baicalein-7-glucuronide). It has wide clinical applications with antitumor, antioxidant, anti-dyslipidemia, and anti-diabetic activity (Fang et al., 2020). Emerging evidence indicated that this flavonoid minimizes the risk of obesity and diabetes by preventing gluconeogenesis, insulin resistance, dyslipidemia and decreasing lipid peroxidation, hyperglycemia and hyperlipidemia with increased glucose disposal, GLUT-4 content in adipocytes, and skeletal muscles (Waisundara et al., 2009). However, having a glycosyl group on the ring causes baicalin to be low hydrophilic and poorly absorbed when administered orally. Therefore, some studies reported that Baicalin-loaded nanoparticles can enhance the bioavailability and bioactivity in the treatment of diabetes as compared to the baicalin group. By
Table 1: Phytochemical-based nano-formulation in managing metabolic disorders

<table>
<thead>
<tr>
<th>Phytochemicals</th>
<th>Biochemical name</th>
<th>Plant source</th>
<th>Type of Metabolic Disorder</th>
<th>Pharmaceutical limitation</th>
<th>Nano formulation</th>
<th>Mechanism of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-deeostearic acid</td>
<td>cis-9, trans-11, trans-13-octadecatrienoic</td>
<td>Momordica charantia L. (Bitter ground oil)</td>
<td>Diabetes</td>
<td>Poor stability, higher metabolic conversion, and lower bioavailability.</td>
<td>Nano emulsion</td>
<td>Decrease blood glucose level and NOS activity. Increase PPAR-Y, catalase, SOD and GPx</td>
<td>(Paul et al., 2014)</td>
</tr>
<tr>
<td>Baicalin</td>
<td>baicalein-7-glucuronide</td>
<td>Scutellaria radix</td>
<td>Obesity, Diabetes NAFLD</td>
<td>Poor absorption, bioavailability and water solubility, and higher metabolic conversion</td>
<td>Nano-lipid carrier</td>
<td>Decrease FBS, HbA1c, TC and TG level. Increase glucose disposal, GLUT-4 in adipocytes, and skeletal muscles.</td>
<td>(Shi et al., 2016)</td>
</tr>
<tr>
<td>Berberine</td>
<td>5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium</td>
<td>Berberis vulgaris (Red berries)</td>
<td>Obesity, Diabetes</td>
<td>Poor water solubility, high P-gp efflux, lesser plasma concentration, and rapid biotransformation</td>
<td>Solid-lipid nanoparticle</td>
<td>Decrease body weight, triglyceride level and inducing CPT1 expression</td>
<td>(Panda et al., 2021; Xue et al., 2015)</td>
</tr>
<tr>
<td>Curcumin</td>
<td>E,E-1,7bis[4-hydroxy-3-methoxy-phenyl]-1,6-hepadiene-3,5-ione</td>
<td>Curcuma longa (Turmeric)</td>
<td>Diabetic neuropathy</td>
<td>Low water solubility and penetrability, poor chemical stability, and absorption</td>
<td>self-nano-emulsifying drug delivery system (SNEDDS)</td>
<td>Enhances antioxidant level and reduces neuroinflammation</td>
<td>(Joshi et al, 2013)</td>
</tr>
<tr>
<td>Emodin</td>
<td>3-methyl-1,6,8-trihydroxyanthraquinone</td>
<td>Rheum officinal</td>
<td>Obesity</td>
<td>Poor solubility, intestinal absorption, and rapid metabolism</td>
<td>PEG-PLGA nanoparticle</td>
<td>Inhibits 11β-HSD1 in adipose tissue</td>
<td>(Yu et al., 2020)</td>
</tr>
<tr>
<td>Gymnemic acid</td>
<td>Triterpene glycoside</td>
<td>Gymnema sylvestre</td>
<td>Diabetes</td>
<td>Poor water solubility, lipid solubility, and bioavailability</td>
<td>Nano-suspension</td>
<td>Decrease blood glucose level and shows antihyperglycemic activity</td>
<td>(Senthilnathan et al, 2019)</td>
</tr>
<tr>
<td>Myricitrin</td>
<td>myricetin-3-O-α-rhamnoside</td>
<td>Manilkara zapota</td>
<td>Diabetes</td>
<td>Low solubility, poor gastrointestinal stability, and bioavailability</td>
<td>Solid-lipid nanoparticle</td>
<td>Enhance antioxidant activity by increasing SOD level</td>
<td>(Abhangarpour et al, 2018)</td>
</tr>
<tr>
<td>Naringenin</td>
<td>5,4'-trihydroxylavanone</td>
<td>Citrus sinensis (Orange)</td>
<td>Diabetes</td>
<td>Lower absorption and rapid metabolic transformation by the hepatic and gastric enzymes</td>
<td>Algnate coated chitosan core shell</td>
<td>Enhance therapeutic, bioavailability, water solubility properties and reduce toxicity</td>
<td>(Maity et al, 2017)</td>
</tr>
<tr>
<td>Oleoresin Capsicum</td>
<td>Capsaicin (trans-8-methyl-N-</td>
<td>Capsicum annum</td>
<td>Obesity</td>
<td>Low water solubility and</td>
<td>Nano-emulsion</td>
<td>Inhibit TG content, lipid</td>
<td>(Kim et al, 2014;</td>
</tr>
<tr>
<td>Compound</td>
<td>Molecular Structure</td>
<td>Source</td>
<td>Activity</td>
<td>Nanoparticle Type</td>
<td>Activity</td>
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<tr>
<td>Vanillyl-6-nonenamide</td>
<td>(Red pepper)</td>
<td>Highly viscous</td>
<td>Accumulation and stimulate AMPK activity</td>
<td>PLGA polymer</td>
<td>Decrease drug size and improve ROS-inactivating enzymes</td>
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<tr>
<td>Dihydrocapsaicin</td>
<td>Lobularis (Red pepper)</td>
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<tr>
<td>Quercetin</td>
<td>3,3’,5,7-pentahydroxyflavone</td>
<td>Obesity Diabetes</td>
<td>Lesser chemobiological stability, low absorption, and rapid metabolism.</td>
<td></td>
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</tr>
<tr>
<td>Resveratrol</td>
<td>3,5,4-trihydroxystilbene</td>
<td>Type-2-diabetes</td>
<td>Rapid isomerization metabolism and elimination, low plasma concentration</td>
<td>Solid-lipid particle</td>
<td>Enhance adipose and muscle insulin sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scutellarin</td>
<td>4’,5,6-trihydroxy flavone-7-O-glucuronide</td>
<td>Diabetic retinopathy, Diabetic nephropathy, Diabetic cardiomyopathy</td>
<td>Limited membrane permeability, low absorption, low water and lipid solubility, and quick metabolism</td>
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<tr>
<td>Silybin</td>
<td>(2R,3R)-2-[(2S,3S)-2,3-dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]-2,3-dihydro-3,7-trihydroxy-4H-1-benzopyran-4-one</td>
<td>Diabetes</td>
<td>Low bioavailability, weak intestinal absorption, and low water solubility</td>
<td>PLGA polymer</td>
<td>Enhance antioxidant activity and regulate glycemic index</td>
<td></td>
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</tr>
<tr>
<td>Stevioside</td>
<td>β-D-Glucopyranosyl 13-[β-D-glucopyranosyl-(1→2)]-β-D-glucopyranosyl-5β,8α,9β,10α,13α-kaur-16-en-18-oate</td>
<td>Diabetes Hyperglycemia</td>
<td>Poor intestinal absorption, rapid metabolic degradation, and low bioavailability</td>
<td>PLA nanoparticel</td>
<td>Increase bioavailability and intestinal absorption.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. **Berberine:**

An isoquinoline alkaloid found in nature, berberine is mostly isolated from *Berberis vulgaris*. They have many medicinal qualities, including antibacterial, anti-inflammatory, anticancer, and anti-diabetic ones (Imanshahidi and Hosseinzadeh, 2008). Through the stimulation of AMPK, glycolysis, and downregulation of mitochondrial activity, berberine improves the metabolism of both glucose and fat in diabetes. Despite the benefits, they exhibit clinical limits due to limited bioavailability, poor water
solubility, and GI tract absorption. By minimizing these barriers, the nano-formulated delivery method for berberine increases the bioavailability and effectiveness (Lee et al., 2006; Mirhadi et al., 2018). Lipid-based nano-formulation of berberine-like solid-lipid nanoparticle and micelle increase their stability and solubility in the GI tract and thus show better anti-diabetic properties. Oral treatment of berberine-encapsulated solid-lipid nanoparticles (BBR-SLNs) inhibits body weight gain and lowers blood alanine transaminase and triglyceride levels through activating CPT1 and suppressing the expression of SCD1, FAS, and SREBP1c (Xue et al., 2015). Berberine nanoparticles with an O-hexadecyl-dextran encasement (BC-HDD NPs) diminish oxidative stress, ROS generation, and caspase activation (Kapoor et al., 2014). Berberine-loaded PLGA-PEG nanoparticles modulate PCSK-9 and significantly decrease hypercholesterolemia and their lecithin-chitosan-loaded nanoparticles (BBR-LC-CTS NPs) expedite wound healing in diabetics (Ochin and Garelnabi, 2018; Panda et al., 2021).

4. Curcumin:

Curcumin, which is mostly extracted from the rhizome of the herbal plant *Curcuma longa*, is a strong bioactive phenolic chemical with structure E, E-1,7bis[4-hydroxy-3-methoxy-phenyl]-1,6-hepadiene-3,5-ione. It is a polyphenol that is a member of the curcuminoid subgroup and has unique pharmaceutical features, such as antioxidant, antiulcer, anticancer, and anti-inflammatory activity (Davatgaran-Taghipour et al., 2017; Taghipour et al., 2019). Numerous research investigations have shown that curcumin also contains antidiabetic activity and hypolipidemic effects and reduces metabolic dysregulation caused with obesity, including insulin resistance, hyperglycemia, and hyperlipidemia. It stimulates NF-kB and PPAR-β while suppressing the expression of TNF-α and PAI-1 (Xu et al., 2003; Aggarwal, 2010; Soetikno et al., 2011). Curcumin promotes the production of adiponectin by disrupting leptin signaling. Hence, it reduces body weight and inhibits the oxidation of LDL cholesterol (González-Castejón and Rodriguez-Casado, 2011). Curcumin’s lack of hydrophilicity is a major issue, although nanotechnology can help with drug delivery systems (Ernest et al., 2018; Suresh and Nangia, 2018). The development of curcumin nano-formulation with various methods has emerged and is designed to enhance its solubility, stability, and bioavailability along with a nanosized structure (El-Far et al., 2017; Hajalyani et al., 2018). The biological efficacy and water solubility of curcumin were improved by encapsulation in poly (gamma benzyl 1-glutamate)-poly (ethylene glycol)-poly (benzyl glutamate) nanoparticles. In cases of diabetic cardiomyopathy, it reduces the chance of heart failure (Tong et al., 2018). Furthermore, curcumin-containing self-nano-emulsifying drug delivery systems (SNEDDS) were effective at raising antioxidant levels and lowering neuroinflammation in diabetic neuropathy (Joshi et al., 2013). According to another study, curcumin encapsulated in PLGA-polyvinyl alcohol polymers, pluronic nanomicelles increased oral bioavailability and efficacy in an in vivo system (Grama et al., 2013; El-Far et al., 2017). Oral intake of PLGA- CoQ10 loaded with curcumin significantly lowered CRP, IL-6, total glyceride, and total cholesterol and simultaneously increased the level of HDL. Nano-formulation of curcumin is effective in reducing Cx43 mRNA, IL1β, and phosphorylated-Akt in the dorsal root ganglia, which in turn helps to reduce discomfort brought on by diabetic neuropathy (Devadasu et al., 2011). Therefore, rather than free curcumin, nano-formulation of curcumin has demonstrated promising therapeutic approach in the treatment of metabolic disorders.

5. Emodin:

Emodin is a trihydroxyanthraquinone, which is mainly obtained from traditional herb *Rheum officinale* (Jayasuriya et al., 1992). It contains a variety of pharmacological properties including antioxidant, anti-cancer, antinociceptive, and antidiabetic activities (Dong et al., 2020). Emodin regulates PPAR-Y and increases GLUT1 and
GLUT4 mRNA expression in differentiated 3T3-L1 adipocytes, which increases glucose absorption (Li et al., 2017). Additionally, it is a novel AMPK activator and improved glucose metabolism (Shi et al., 2015; Janković-Tomanić et al., 2017). Emodin’s nano-formulation has also been demonstrated to be potential in treating diabetic neuropathy. Their nano-formulation reduced the overexpression of the P2X3 receptor, TNF-α protein, and phosphorylation of ERK1/2 in dorsal root ganglia (Li et al., 2017). PEG-PLGA nanoparticles that have been loaded with emodin exhibit anti-obesity pharmacological effects by therapeutically targeting obesity. As an appealing therapeutic target for obesity, these nanoparticles selectively inhibit 11-HSD1 in adipose tissue (Yu et al., 2020). Thus, nano-emulsions and nano transfers have improved emodin efficiency and delivery.

6. **Gymnemic acid:**
Gymnemic acid is a triterpenoid phyto-constituents, which is isolated from the medicinal plant *Gymnema Sylvestre*. It possesses a wide range of pharmaceutical properties such as reducing glucose levels, suppressing intestinal absorption of glucose, and taste sensitivity suppression (Saneja and Sharma, 2010). Gymnemic acid shows hypoglycemic properties by increasing insulin secretion from the pancreas (Patel et al., 2012). The major drawback of gymnemic acid is its lower water solubility, which decreases its pharmacological activity (Tiwari et al., 2014). Their solubility and oral bioavailability can be enhanced using nano-formulation. The nanoparticles encapsulated with gymnemic acid demonstrated better antihyperglycemic activity and exerts hypoglycemia, by promoting insulin secretion from the pancreas and impaired pancreatic islet cells enhance enzyme-mediated sugar uptake (Patel et al., 2012; Ravichandran, 2012). To enhance oral availability, gastrointestinal absorption, and antihyperglycemic activity gymnemic acid can be
formulated in lyophilized nanocrystals, nanosuspension, gold nanoparticles, and polymer-based nanoparticles (Ravichandran, 2010; Rajarajeshwari et al., 2014). Gymnemic acid-chitosan nanoparticles synthesized by emulsion droplet coalescence method approach results in a sustained release of gymnemic acid and conformed to be effective in the prevention of diabetes (Senthilnathan et al., 2019). However, more research is required to achieve better antidiabetic efficacy to formulate an effective antidiabetic nanoformulation of gymnemic acid.

7. Myricitrin:

A naturally occurring flavanol glycoside myricitrin (myricetin-3-O-rhamnoside) is primarily derived from several medicinal plants, including Eugenia uniflora, Pouteria gender, Myrica rubra, and Manilkara zapota. It has properties that are anti-nociceptive, anxiolytic, antioxidant, and anti-inflammatory, making it a necessary supplement in medicine. Myricitrin reduces peroxide-induced oxidative damage, lowers malondialdehyde, and increases the activity of antioxidant enzymes to prevent venous endothelial cell failure brought on by reactive oxygen species (ROS) (Fernandez et al., 2009). Myricitrin-loaded nanoparticles have been shown to increase their therapeutic effectiveness and oral bioavailability since myricitrin is highly polar and cannot pass membranes (Man et al., 2019). Solid-lipid nanoparticles that were myricetin-loaded produced a prolonged release of myricetin and had excellent therapeutic effects on pancreatic apoptosis, insulin resistance, impaired glucose absorption by myotubes, and hyperglycemia both in vitro and in vivo (Ahangarpour et al., 2018). At a considerably lower dose, it was discovered that the myricetin nanoparticles were more efficient than metformin. To combat diabetes mellitus and other diabetic problems, their nanoformulation would be quite effective.

8. Naringenin:

A bioactive flavonoid molecule, naringenin (5,7,4'-trihydroxyflavanone) is mostly found in citrus fruits like oranges and grapes, and some vegetables. This phytochemical has been linked to a number of pharmacological effects, including antimitagenic, antioxidant, anti-inflammatory, anti-adipogenic, anticancer, and anti-diabetic (Cavia-Saiz et al., 2010). By improving the absorption of glucose from the gut, naringenin decreases the level of lipids and exhibits features like insulin. By suppressing gluconeogenesis and by upregulating AMPK, naringenin therapy in diabetic mice resulted in a marked enhancement of the immunological and hematological blood parameters as well as full survival. Like metformin, it also has hypoglycemic effects that reduce inflammatory conditions and cell growth (Prabu et al., 2013). With this excellent quality, naringenin's primary drawbacks are its weak water solubility, oral availability, and poor gastrointestinal absorption. As a result, the administration of this flavonoid via nanostructures may be more efficient and beneficial in treating metabolic problems like diabetes (Song et al., 2015; Ganesan et al., 2017; Gera et al., 2017). Other naringenin nanoformulations, such as self-nano emulsion, naringenin loaded solution-maltodextrin nanocarrier, and naringenin loaded liposomal nanoformulation, have increased oral bioavailability, solubility, gastrointestinal absorption, and thus its therapeutic uses (Khan et al., 2015; Chaurasia et al., 2017; Wang et al., 2017). Naringenin-encapsulated core-shell polymeric nanoparticles show improved therapeutic benefits in curing hyperglycemia, dyslipidemia, and oxidative stress. Chitosan or alginate core-shell polymeric nanoparticles ensure considerable drug entrapment and their prolonged release while exhibiting negligible toxicity (Maity et al., 2017).

9. Oleoresin capsicum:

Oleoresin capsicum (OC), an organic resin with an oil base that comes from the Capsicum genus of pepper plants, contains 80–90 per cent capsaicin and dihydrocapsaicin. It has long been employed as a food ingredient, flavoring agent, and food
preservation method (Melgar-Lalanne et al., 2017). It had therapeutic properties such as anti-cancer, anti-obesity, anti-bacterial, anti-inflammatory, and anti-oxidant properties, some organic solvent extractions, such as ethanolic and butanoic extracts, prevent their direct clinical application due to their lower water solubility and high viscosity (Sricharoen et al., 2017; da Silva Anthero et al., 2022). The benefits of using nanoemulsion encapsulation technology are used to overcome that limitation and enhance solubility, bioavailability, and stability. Nanoemulsion-oleoresin-capsicum (NOC) reduces body weight and adipogenesis by enhancing mRNA levels of gene expression related to thermogenesis or β-oxidation via inducing PPAR-α, UCP-2 (uncoupling protein-2), and palmitoyl transferase-1-α. It also stimulates AMPK activity and exhibits anti-obesity properties (Kim et al., 2014). Oleoresin capsicum encapsulated alginate double-layer nanoemulsion (OC-AN) also shows higher lipolytic efficacy in inhibiting triglyceride content and lipid accumulation by enhancing the release of glycerol and FFAs from adipocytes (Lee et al., 2017).

10. Quercetin:

A widely utilized flavonoid, quercetin (3,3′,4′,5,7-pentahydroxyflavone) is found in many plants and citrus fruits. It possess several different pharmacological actions, including anti-cancer, neuroprotective, hepatoprotective, antiplatelet, anti-bacterial, antioxidant, anti-obesity, anti-diabetic and many more (Hashemzaei et al., 2017; Patel et al., 2018). Quercetin also reduces the metabolic abnormalities of diabetes such as waist circumference, postprandial blood sugar, liver enzyme levels, and lipid profile, and their combination with different polyphenols like apigenin and luteolin can also increase insulin secretion, deactivation of NO synthase, and resistance to cytotoxicity (Rivera et al., 2008; Roshanravan et al., 2021). Despite having multiple pharmacological and nutraceutical properties, applications of quercetin in clinical studies are restricted with its low aqueous solubility, fast metabolism, rapid elimination, and poor oral availability. To overcome these limitations quercetin nanofabrication has offered excellent opportunities in the last few years as clinical applications with their higher bioavailability, target specificity, efficacy, and antidiabetic activity (Khursheed et al., 2020). By lowering the dosage considerably, quercetin-loaded PLGA nanoparticles and their nanorods increase therapeutic compliance by reciprocating hyperglycemia and redox imbalance (Chitkara et al., 2012; Alam et al., 2016). PEG-block-[poly-(ethylenediamine-glutamate)- graft- poly - (ε-benzyloxy – carbonyl - l-lysine)] and solid-lipid nanocarrier encapsulated with quercetin significantly enhance the serum content in managing diabetes and associated nephropathy (Li et al., 2009). Numerous quercetin nano-formulations, including quercetin-succinate chitosan-alginate, soluplus micelles, silver nanoparticles, and their superparamagnetic iron oxide nanoparticles, have been proposed to increase bioavailability and therapeutic potency against complications of diabetes and related diseases (Ebrahimpour et al., 2018; Mukhopadhyay et al., 2018; Singh et al., 2018).

11. Resveratrol:

The non-flavonoid polyphenol resveratrol (3,5,4-trihydroxystilbene) occurs naturally as phytoalexin. Different plant species contain it, but the stem and shell of Vitis vinifera L. (grapes) and nuts are the greatest plant sources. It contains a wide range of pharmaceutical characteristics, including neuroprotective, antiplatelet, anti-inflammatory and antioxidant activity (Burns et al., 2002; Matos et al., 2014). Resveratrol also has potential advantages on metabolic diseases like diabetes by lowering blood sugar levels, increasing lipolysis, reducing adipogenesis, activating Nrf2, inhibiting cyclooxygenase, and improving insulin production from pancreatic beta-cells (Öztürk et al., 2017; Szkudelska and Szkudelski, 2010). Resveratrol nanoformulation is more effective at preventing diabetes and its complications than traditional forms of the compound (Summerlin et al., 2015). In gestational
Fig. 2: Schematic illustration of phytochemicals with their major plant source formulated in nano-size with different nano-formulation and their therapeutic efficacy in preventing metabolic disorders.
diabetes mellitus, reducing blood glucose levels with a resveratrol-zinc oxide combination encapsulated in chitosan considerably improve the stability and efficiency of the medication (Du et al., 2020). Oral administration of nanoliposome formulation with resveratrol boosts ROS-inhibiting enzymes and controls blood pressure. By modulating the expression of SNARE, STX-4, VAMP-2, and SNAP-23 (synaptosomal-associated protein 23), their solid-lipid nanoparticles have reduced insulin resistance in muscles and adipose tissues (Shahraki et al., 2017; Mohseni et al., 2019).

12. Scutellarin:
Scutellarin, a flavonoid, is produced from the traditional Chinese plant *Erigeron brevisscapus* (Vant.) Hand-Mazz. It has multiple pharmacological and clinical applications against vascular endothelial cell dysfunction by enhancing vascular permeability, improving microcirculation and diminishing blood flow viscosity (Zheng et al., 2015; Xiong et al., 2006). Scutellarin’s recent studies show their therapeutic effects in neurodegeneration, cancer, coronary heart disease, cerebral ischemic stroke, glaucoma, and diabetes complications, like diabetic nephropathy, neuropathy, and cardiomyopathy (Wang and Ma, 2018; Di Costanzo and Angelico, 2019). Recent research has demonstrated their preventive role in diabetic cardiomyopathy via controlling oxidative stress, apoptosis, and abnormalities in cardiomyocytes (Xu et al., 2021). Scutellarin nanof ormulation is more efficient than scutellari a lone in the treatment of diabetes complications. Scutellarin-loaded hydroxypropyl-β-cyclodextrin-chitosan nanoparticles and their bovine serum albumin nanoparticles enhance solubility, bioavailability, and drug loading capacity to achieve a site-specific therapeutic effect (Wei et al., 2014; Liu and Ho, 2017). They facilitate the removal of glucose and boost Akt phosphorylation. Furthermore, scutellarin-loaded amphiphilic chitosan derivatives improve their therapeutics for treating diabetic retinopathy by reducing retinal damage, by inhibiting the functional activity of retinal factors like Von Willebrand factor (vWF), VEGF, VEGF receptor 2 (VEGFR2), with modified VEGF/ERK/FAK/Src signaling pathway (Wang et al., 2017; Long et al., 2019).

13. Silybin:
Silybin is the principal flavonolignans bioactive constituent extract from the plant *Silybum marianum* and contains therapeutic properties like antioxidant, hepatoprotective, anti-cancerous, and anti-inflammation with less toxic effect (Hoh et al., 2007). It has also been effective in obesity-induced insulin resistance and metabolic diseases. Silybin modifies the absorption of glucose by adipocytes, affects the process by which insulin acts, and prevents the generation of free radicals (Pignatelli et al., 2019). Like the other flavonolignans, silybin has limited water solubility, minimal intestinal absorption and low bioavailability, but it also considerably decreases blood glucose, lipid, and HbA1c levels (Loguercio and Festi, 2011). Nano-formulation of PLGA loaded with silybin shows more antioxidant characteristics that regulate glycemic index and regenerate pancreatic beta cells (Das et al., 2014). Additional promising methods for the delivery of silybin include solid-lipid nanoparticles and chitosan-coated solid-lipid nanoparticles (Piazzini et al., 2018).

14. Stevioside:
*Stevia rebaudiana* (Bertoni) leaves are used to make stevioside, a natural sweetener with no calories (Geuns, 2003). It is an important bioactive compound with great potential in diabetes mellitus therapy with its antioxidant and hypoglycemic properties. Numerous studies have demonstrated that it enhances insulin production and metabolism of glucose (Madan et al., 2010; Ilić et al., 2017). Despite being a powerful anti-diabetic drug, stevioside has a poor bioavailability and intestinal absorption rate, which reduces its therapeutic efficiency. Moreover, when it is encapsulated in nanoparticles, its intestinal absorption and efficacy are enhanced. It was shown that effectively incorporating stevioside
into poly-lactic acid (PLA) nanoparticles enhanced their bioavailability and intestinal absorption. These PLA nanoparticles were linked on Pluronic-F-68 copolymer which included stevioside. Compared to stevioside alone, the nano-formulation of stevioside in poly-lactic acid (PLA) demonstrated improved drug release and excellent absorption in the gut (Barwal et al., 2013; Das et al., 2020).

**Future of Nano-phytomedicines and Challenges Ahead:**

Nanotechnology has significantly impacted in the field of medicine throughout the past few years by providing a variety of administration routes, accomplishing targeted drug delivery, sustained release, enhancing bioavailability, and lowering toxicity. Similarly, phytomedicine-based nano-formulation has also fetched interest to attenuate many diseases over the past years (Khan and Gurav, 2017; Patra et al., 2018). Thus, dramatic interest is increasing in nano-formulation against diabetes and other metabolic complications. Numerous nano-phytomedicines have the increased therapeutic effectiveness and pharmacokinetic properties of medications used to treat metabolic diseases, making them potentially effective at reducing blood sugar levels (Taghipour et al., 2019). However, their existence is a significant challenge in clinical implementation and controlling their interaction with biological systems (Sharma et al., 2011). Major issues associated with phytomedicine-based nano-formulation include pharmacological, toxicological, clinical trial construction, standardization, drug interaction evaluation, safety, and efficacy assessment. Other additional complications include designing and developing these nano-phytomedicines with an incorporated drug delivery system (Thillaivanan, 2014). There is a need to overcome this limitation by developing creative and quick therapeutic techniques to fulfill several clinical and biological requirements of natural-based nanoparticles for effective and targeted drug delivery with minimal toxicity (Bilia et al., 2017; Khan and Gurav, 2017).

Considering all these, it would be expected that phytochemical-based nano-formulation with hypoglycemic activity will offer huge prospects in the future by ensuring their cost-effectiveness, and reduced toxicity in diabetes and metabolic disorders.

**Conclusion**

Metabolic disorders mainly include impaired glucose tolerance, hyperglycemia, hyperlipidemia, hyperinsulinemia, and insulin resistance. Natural compound-based nanoparticles have been demonstrated to have stronger therapeutic activity and a potential future in treating diseases, including obesity, diabetes, and associated metabolic disorders. Their nano-size and tunable properties gain a great advantage in healthcare. Furthermore, compared with chemically produced nanoparticles, biologically produced nano-materials are less harmful and more biocompatible. In conclusion, nano-phytochemicals are helpful in lowering medication size and toxicity and play a significant role in drug delivery to treat various metabolic diseases. However, there are several challenges in creating nanoparticles, including those related to particle size, cost-effectiveness, stability, and repeatability. Additionally, their regulation is still not apparent. With the incorporation of nanotechnology, it has been possible to overcome the limited bioavailability and biocompatibility of phytochemicals. This review contributes to illuminating various nano phytomedicines and their usefulness in treating metabolic disorders. The development of a prospective approach in purpose of treating chronic metabolic disorders will be made easier with a greater knowledge of the function of phytochemical-based nano-formulation and their action mechanism in the future.

**Acknowledgements**

Radhika Soni would like to express gratitude to UGC for the Junior Research Fellowship. Authors are thankful to Chhavi Bhalothia and Payal Patel who provided insight and expertise in this paper.
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