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

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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

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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

rising 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 ethnomedicinal 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-ϒ 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

Phytochemicals	Biochemical name	Plant source	Type of Metabolic Disorder	Pharmaceutical limitation	Nano formulation	Mechanism of action	Reference
Alpha-eleostearic acid	cis-9, trans-11, trans-13-octadecatrienoic	*Momordica charantia L.* (Bitter ground oil)	Diabetes	Poor stability, higher metabolic conversion, and lower bioavailability.	Nano emulsion	Decrease blood glucose level and NOS activity. Increase PPAR-Y, catalase, SOD and GPx	(Paul *et al.*, 2014)
Baicalin	baicalein-7-glucuronide	*Scutellaria radix*	Obesity, Diabetes NAFLD	Poor absorption, bioavailability and water solubility, and higher metabolic conversion	Nano-lipid carrier	Decrease FBS, HbA1c, TC and TG level. Increase glucose disposal, GLUT-4 in adipocytes, and skeletal muscles.	(Shi *et al.*, 2016)
Berberine	5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a] quinolizinium	*Berberis vulgaris* (Red berries)	Obesity, Diabetes	Poor water solubility, high P-gp efflux, lesser plasma concentration, and rapid biotransformation	Solid-lipid nanoparticle	Decrease body weight, triglyceride level and inducing CPT1 expression	(Panda *et al.*, 2021; Xue *et al.*, 2015)
Curcumin	E,E-1,7bis[4-hydroxy-3-methoxy-phenyl]-1,6-hepadiene-3,5-ione	*Curcuma longa* (Turmeric)	Diabetic neuropathy	Low water solubility and penetrability, poor chemical stability, and absorption	self-nano-emulsifying drug delivery system (SNEDDS)	Enhances antioxidant level and reduces neuroinflammation	(Joshi *et al.*, 2013)
Emodin	3-methyl-1,6,8-trihydroxyanthra-quinone	*Rheum officinal*	Obesity	Poor solubility, intestinal absorption, and rapid metabolism	PEG-PLGA nanoparticle	Inhibits 11β-HSD_1 in adipose tissue	(Yu *et al.*, 2020)
Gymnemic acid	Triterpene glycoside	*Gymnema sylvestre*	Diabetes	Poor water solubility, lipid solubility, and bioavailability	Nano-suspension	Decrease blood glucose level and shows antihyperglycemic activity	(Senthilnathan *et al.*, 2019)
Myricitrin	myricetin-3-O-α-rhamnoside	*Manilkara zapota*	Diabetes	Low solubility, poor gastrointestinal stability, and bioavailability	Solid-lipid nanoparticle	Enhance antioxidant activity by increasing SOD level	(Ahangarpour *et al.*, 2018)
Naringenin	5,7,4'-trihydroxyflavanone	*Citrus sinensis* (Orange)	Diabetes	Lower absorption and rapid metabolic transformation by the hepatic and gastric enzymes	Alginate coated chitosan core shell	Enhance therapeutic, bioavailability, water solubility properties and reduce toxicity	(Maity *et al.*, 2017)
Oleoresin Capsicum	Capsaicin (trans-8-methyl-N-	*Capsicum annum*	obesity	Low water solubility and	Nano-emulsion	Inhibit TG content, lipid	(Kim *et al.*, 2014;

	vanillyl-6-nonenamide) and dihydrocapsaicin	(Red pepper)		highly viscous		accumulation and stimulate AMPK activity	Lee *et al.*, 2017)
Quercetin	3,3′,4′,5,7-pentahydroxyflavone	*Allium cepa (*Red onion)	Obesity Diabetes	Lesser chemobiological stability, low absorption, and rapid metabolism.	PLGA polymer	Decrease drug size and improve ROS-inactivating enzymes	(Chitkara *et al.*, 2012)
Resveratrol	3,5,4-trihydroxystilbene	*Vitis vinifera* L	Type-2-daibetes	Rapid isomerizationmetabolism and elimination, low plasma concentration with limited systemic distribution	Solid-lipid nanoparticle	Enhance adipose and muscle insulin sensitivity	(Mohseni *et al.*, 2019)
Scutellarin	4′,5,6-trihydroxy flavone-7-O-glucuronide	*Erigeron breviscapus* (Vant.) Hand. Mazz	Diabetic retinopathy, Diabetic nephropathy, Diabetic cardiomyopathy	Limited membrane permeability, low absorption, low water and lipid solubility, and quick metabolism	Amphiphilic chitosan derivatives	Reduces oxidative stress, Suppressing the expression of VEGF, VEGFR2 and vWF	(Wang *et al.*, 2017; Wang and Ma, 2018)
Silybin	(2R,3R)-2-[(2S,3S)-2,3-dihydro- 3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one	*Silybum marianum*	Diabetes	Low bioavailability, weak intestinal absorption, and low water solubility	PLGA polymer	Enhance antioxidant activity and regulate glycemic index	(Das *et al.*, 2014)
Stevioside	β-D-Glucopyranosyl 13-[β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyloxy]-5β,8α,9β,10α,13α-kaur-16-en-18-oate	*Stevia rebaudiana*	Diabetes Hyper-glycemia	Poor intestinal absorption, rapid metabolic degradation, and low bioavailability	PLA nanoparticles based on Pluronic-F-68 copolymer	Increase bioavailability and intestinal absorption.	(Barwal *et al.*, 2013; Ilić *et al.*, 2017)

lowering fasting blood sugar level, glycosylated hemoglobin, total cholesterol, and total triglycerides in diabetes, baicalin-nano lipid carriers exhibit anti-diabetic activities (Shi *et al.*, 2016; Dinda *et al.*, 2017).

3. *Berberine*:

An isoquinoline alkaloid found in nature, berberine is mostly isolated from *Berberis vulgaris*. They have many medicinal qualities, including antibacterial, anti-inflammatory, anti-cancer, 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; Hajialyani *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-formulaion 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-ϒ and increases GLUT1 and

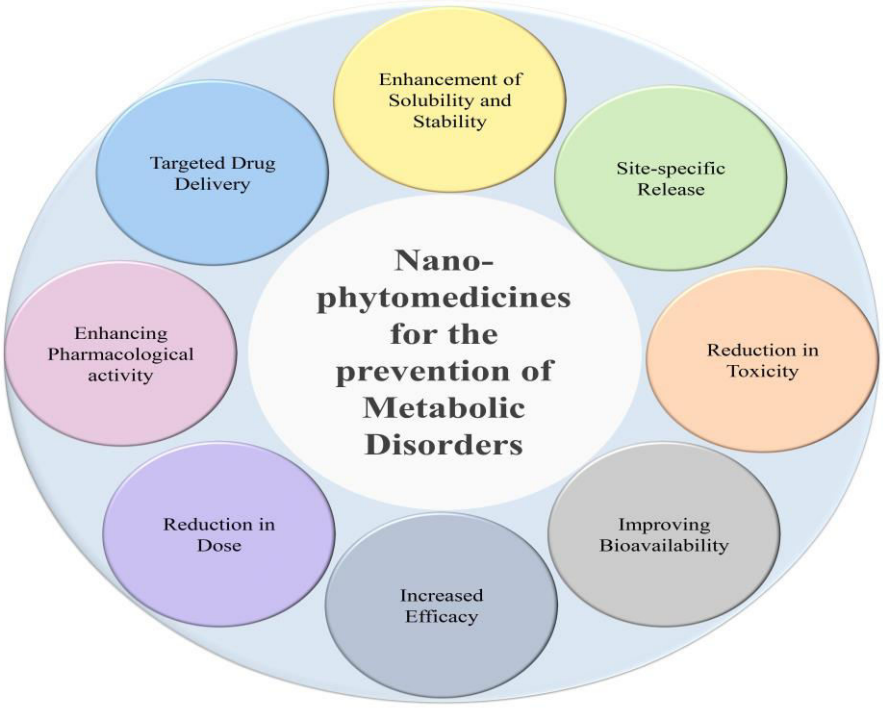

Fig. 1: A schematic demonstration of role of nano-phytomedicines for the prevention of metabolic disorders.

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 antihyper-glycemic 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*, *Pouteriagender*, *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 antimutagenic, 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 nano-particles 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

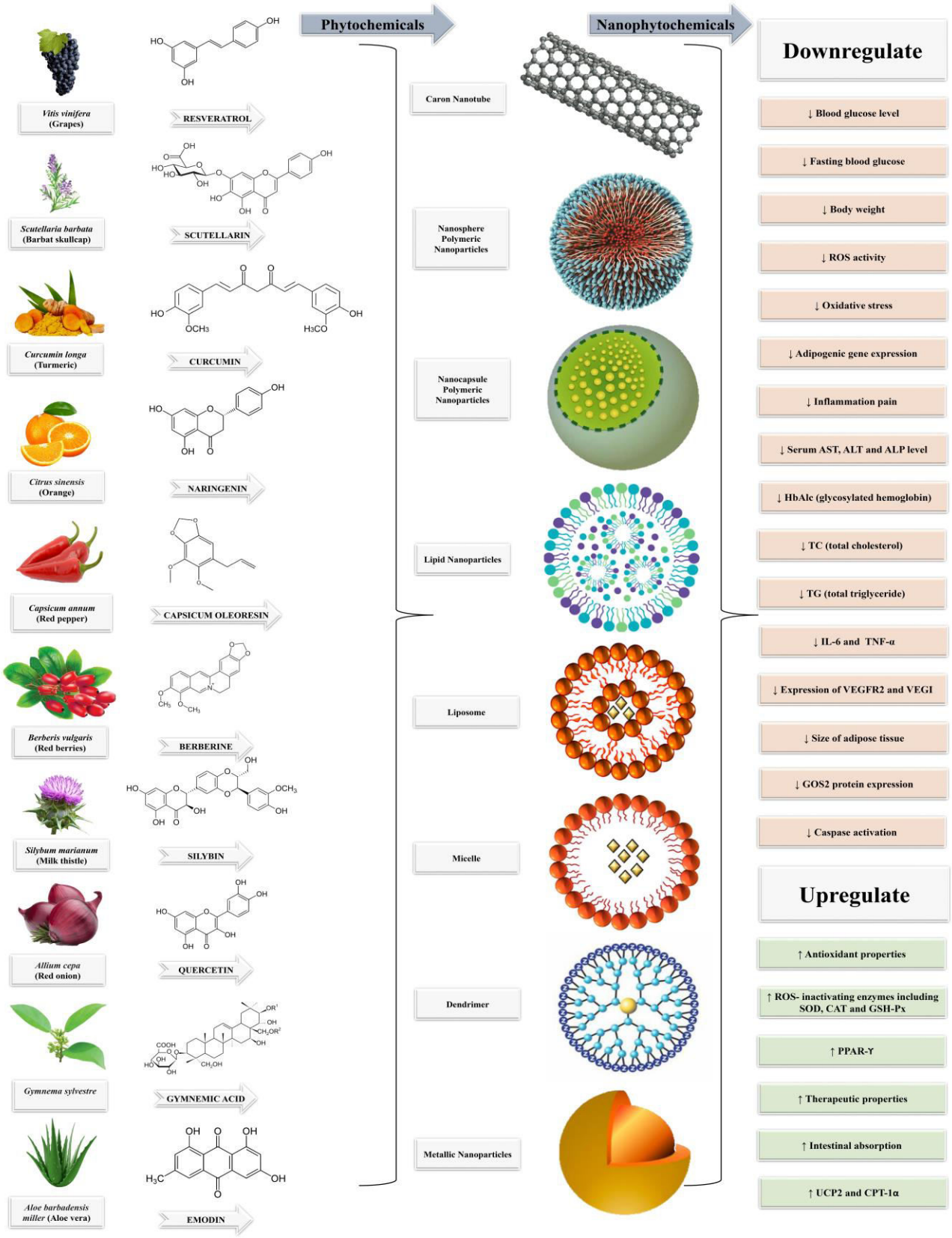

Fig. 2: Schematic illustration of phytochemicals with their major plant source formulated in nano-size with different nano-formulation and their therapeutic efficacy in preventing metabolic disorders.

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 breviscapus* (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 nano-formulation is more efficient than scutellarin alone 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 bio-compatible. 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.

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References

Adetunji CO, Michael OS, Rathee S, Singh KR, Ajayi OO, Adetunji JB, Ojha A, Singh J, and Singh RP. (2022) Potentialities of nanomaterials for the management and treatment of metabolic syndrome: A new insight. Materials Today Advances 13: 100198.

Aggarwal BB. (2010) Targeting lammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. Annual Rev Nutrition 30: 173-199.

Ahangarpour A, Oroojan AA, Khorsandi L, Kouchak M and Badavi M. (2018) Solid lipid nanoparticles of myricitrin have antioxidant and antidiabetic effects on streptozotocin-nicotinamide-induced diabetic model and myotube cell of male mouse. Oxid Med Cell Longev. 2018: 7496936.

Alam MM, Abdullah KM, Singh BR, Naqvi AH, and Naseem I. (2016) Ameliorative effect of quercetin nanorods on diabetic mice: Mechanistic and therapeutic strategies. RSC Adv. 6(60): 55092-55103.

Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, Temml V, Wang L, Schwaiger S, Heiss EH, Rollinger JM, Schuster D, Breuss JM, Bochkov V, Mihovilovic MD, Kopp B, Bauer R, Dirsch VM and Stuppner H. (2015) Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv. 33(8): 1582-1614.

Atta-Ur-Rahman, and Zaman K. (1989) Medicinal plants with hypoglycemic activity. J Ethnopharmacol. 26(1): 1-55.

Barwal I, Sood A, Sharma M, Singh B and Yadav SC. (2013) Development of stevioside Pluronic-F-68 copolymer based PLA-nanoparticles as an antidiabetic nanomedicine. Colloids Surfaces B Biointerfaces 101: 510-516.

Bays H and Stein EA. (2003) Pharmacotherapy for dyslipidaemia - Current therapies and future agents. Expert Opinion Pharmacotherapy 4(11): 1901-1938.

Bilia AR, Piazzini V, Guccione C, Risaliti L, Asprea M, Capecchi G and Bergonzi MC. (2017) Improving on nature: The role of nanomedicine in the development of clinical natural drugs. Planta Medica 83(5): 366-381.

Burns J, Yokota T, Ashihara H, Lean MEJ and Crozier A. (2002) Plant foods and herbal sources of resveratrol. J Agricult Food Chem. 50(11): 3337-3340.

Cavia-Saiz M, Busto MD, Pilar-Izquierdo MC, Ortega N, Perez-Mateos M and Muñiz P. (2010) Antioxidant properties, radical scavenging activity and biomolecule protection capacity of flavonoid naringenin and its glycoside naringin: A comparative study. J Sci Food Agricult. 90(7): 1238-1244.

Cefalu W, Ye J and Wang Z. (2008) Efficacy of dietary supplementation with botanicals on carbohydrate metabolism in humans. Endocrine Metabolic Immune Disorders-Drug Targets 8(2): 78-81.

Chan CH, Ngoh GC and Yusoff R. (2012) A brief review on anti diabetic plants: Global distribution, active ingredients, extraction techniques and acting mechanisms. Pharmacogn Rev. 6(11): 22-28.

Chaurasia S, Patel RR, Vure P and Mishra B. (2017) Oral naringenin nanocarriers: Fabrication, optimization, pharmacokinetic and chemotherapeutic efficacy assessments. Nanomed. 12(11): 1243-1260.

Chitkara D, Nikalaje SK, Mittal A, Chand M and Kumar N. (2012) Development of quercetin nanoformulation and in vivo evaluation using streptozotocin induced diabetic rat model. Drug Delivery Translational Res. 2(2): 112-123.

da Silva Anthero AG, Maria Tomazini Munhoz Moya A, Souza Torsoni A, Baú Betim Cazarin C and Dupas Hubinger M. (2022) Characterization of *Capsicum oleoresin* microparticles and in vivo evaluation of short-term capsaicin intake. Food chemistry: x. 13: 100179.

Das A, Saikia R, Pathak K, Gogoi U and Pathak MP. (2020) Anti-diabetic nano-formulation from herbal source. In: Nano Medicine Nano Safety Rec Trends Clin Evidences, (eds.) Das M.K. and Pathak Y.V., Springer, Singapore, pp. 61–84.

Das S, Roy P, Pal R, Auddy RG, Chakraborti AS and Mukherjee A. (2014) Engineered silybin nanoparticles educe efficient control in experimental diabetes. PLoS One 9(7): e101818.

Davatgaran-Taghipour Y, Masoomzadeh S, Farzaei MH, Bahramsoltani R, Karimi-Soureh Z, Rahimi R and Abdollahi M. (2017) Polyphenol nanoformulations for cancer therapy: Experimental evidence and clinical perspective. Int J Nanomed. 12: 2689-2702.

des Rieux A, Fievez V, Garinot M, Schneider YJ and Préat V. (2006) Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach. J Controlled Release 116(1): 1-27.

Devadasu VR, Wadsworth RM and Kumar MNVR. (2011) Protective effects of nanoparticulate coenzyme Q 10 and curcumin on inflammatory markers and lipid metabolism in streptozotocin-induced diabetic rats: A possible remedy to diabetic complications. Drug Delivery Translational Res. 1(6): 448-455.

Dewanjee S, Chakraborty P, Mukherjee B and De Feo V. (2020) Plant-based antidiabetic nanoformulations: The emerging paradigm for effective therapy. Int J Molec Sci. 21(6): 2217.

Di Costanzo A and Angelico R. (2019) Formulation strategies for enhancing the bioavailability of silymarin: The state of the art. Molecules 24(11): 2155.

Dinda B, Dinda S, DasSharma S, Banik R, Chakraborty A and Dinda M. (2017) Therapeutic potentials of baicalin and its aglycone, baicalein against inflammatory disorders. European J Med Chem. Vol. 131:. 68-80.

Dong H, Lu FE and Zhao L. (2012) Chinese herbal medicine in the treatment of nonalcoholic fatty liver disease. Chinese J Integrative Med. 18(2): 152-160.

Dong X, Zeng Y, Liu Y, You L, Yin X, Fu J and Ni J. (2020) Aloe-emodin: A review of its pharmacology, toxicity, and pharmacokinetics. Phytotherapy Res. 34(2):. 270-281.

Du S, Lv Y, Li N, Huang X, Liu X, Li H, Wang C and Jia YF. (2020) Biological investigations on therapeutic effect of chitosan encapsulated nano resveratrol against gestational diabetes mellitus rats induced by streptozotocin. Drug Delivery 27(1): 953-963.

Ebrahimpour S, Esmaeili A and Beheshti S. (2018) Effect of quercetin-conjugated superparamagnetic iron oxide nanoparticles on diabetes-induced learning and memory impairment in rats. Int J Nanomed. 13: 6311-6324.

El-Far YM, Zakaria MM, Gabr MM, El Gayar AM, Eissa LA and El-Sherbiny IM. (2017) Nanoformulated natural therapeutics for management of streptozotocin-induced diabetes: Potential use of curcumin nanoformulation. Nanomed. 12(14): 1689-1711.

Ernest U, Chen H-Y, Xu M-J, Taghipour Y, Asad M, Rahimi R and Murtaza G. (2018) Anti-cancerous potential of polyphenol-loaded polymeric nanotherapeutics. Molecules 23(11): 2787.

Fang P, Yu M, Shi M, Bo P, Gu X and Zhang Z. (2020) Baicalin and its aglycone: a novel approach for treatment of metabolic disorders. Pharmacol Rep. 72(1):. 13-23.

Fernandez SP, Nguyen M, Yow TT, Chu C, Johnston GAR, Hanrahan JR and Chebib M. (2009) The flavonoid glycosides, myricitrin, gossypin and naringin exert anxiolytic action in mice. Neurochem Res. 34(10): 1867-1875.

Ganesan P, Arulselvan P and Choi DK. (2017) Phytobioactive compound-based nanodelivery systems for the treatment of type 2 diabetes mellitus -Current status. Int J Nanomed. 12: 1097-1111.

Gera M, Sharma N, Ghosh M, Huynh DL, Lee SJ, Min T, Kwon T and Jeong DK. (2017) Nanoformulations of curcumin: An emerging paradigm for improved remedial application. Oncotarget 8(39): 66680-66698.

Gera S, Talluri S, Rangaraj N and Sampathi S. (2017) Formulation and evaluation of naringenin nanosuspensions for bioavailability enhancement. AAPS Pharmscitech 18(8): 3151-3162.

Geuns JMC. (2003) Stevioside. Phytochemistry 64(5): 913-921.

González-Castejón M and Rodriguez-Casado A. (2011) Dietary phytochemicals and their potential effects on obesity: A review. Pharmacol Res. 64(5): 438-455.

Grama CN, Suryanarayana P, Patil MA, Raghu G, Balakrishna N, Ravi Kumar MNV and Reddy GB. (2013) Efficacy of biodegradable curcumin nanoparticles in delaying cataract in diabetic rat model. PLoS One 8(10): e78217.

Grover JK, Yadav S and Vats V. (2002) Medicinal plants of India with anti-diabetic potential. J Ethnopharmacol. 81(1): 81-100.

Gupta R, Deedwania PC, Gupta A, Rastogi S, Panwar RB and Kothari K. (2004). Prevalence of metabolic syndrome in an Indian urban population. Int J Cardiology 97(2): 257-261.

Hajialyani M, Tewari D, Sobarzo-Sánchez E, Nabavi SM, Farzaei MH and Abdollahi M. (2018) Natural product-based nanomedicines for wound healing purposes: Therapeutic targets and drug delivery systems. Int J Nanomed. 13: 5023-5043.

Hashemzaei M, Far AD, Yari A, Heravi RE, Tabrizian K, Taghdisi SM, Sadegh SE, Tsarouhas K, Kouretas D, Tzanakakis G, Nikitovic D, Anisimov NY, Spandidos DA, Tsatsakis AM and Rezaee R. (2017) Anticancer and apoptosis-inducing effects of quercetin in vitro and in vivo. Oncology Rep. 38(2): 819-828.

Hennessy AA, Ross RP, Devery R and Stanton C. (2011) The health promoting properties of the conjugated isomers of α-linolenic acid. Lipids 46(2): 105-119.

Hoh CSL, Boocock DJ, Marczylo TH, Brown VA, Cai H, Steward WP, Berry DP and Gescher AJ. (2007) Quantitation of silibinin, a putative cancer chemopreventive agent derived from milk thistle (*Silybum marianum*), in human plasma by high-performance liquid chromatography and identification of possible metabolites. J Agricult Food Chem. 55(7): 2532-2535.

Ilić V, Vukmirović S, Stilinović N, Čapo I, Arsenović M and Milijašević B. (2017) Insight into anti-diabetic effect of low dose of stevioside. Biomed Pharmacotherapy 90: 216-221.

Imanshahidi M and Hosseinzadeh H. (2008) Pharmacological and therapeutic effects of Berberis vulgaris and its active constituent, berberine. Phytotherapy Res. 22(8): 999-1012.

Janković-Tomanić M, Todorović D, Stanivuković Z, Perić Mataruga V, Wessjohann LA and Kaluđerović GN. (2017) Mesoporous silica nanoparticles SBA-15 loaded with emodin upregulate the antioxidative defense of euproctis chrysorrhoea (L.) larvae. Turkish J Biol. 41(6): 935-942.

Jayasuriya H, Koonchanok NM, Geahlen RL, Mclaughlin JL and Chang CJ. (1992) Emodin, a protein tyrosine kinase inhibitor from polygonum cuspidatum. J Natural Products 55(5): 696-698.

Joshi RP, Negi G, Kumar A, Pawar YB, Munjal B, Bansal AK and Sharma SS. (2013) SNEDDS curcumin formulation leads to enhanced protection from pain and functional deficits associated with diabetic neuropathy: An insight into its mechanism for neuroprotection. Nanomed Nanotechnol Biol Med. 9(6): 776-785.

Kapoor R, Singh S, Tripathi M, Bhatnagar P, Kakkar P and Gupta KC. (2014) O-hexadecyl-dextran entrapped berberine nanoparticles abrogate high glucose stress induced apoptosis in primary rat hepatocytes. PLoS One 9(2): e89124.

Kesharwani P, Gorain B, Low SY, Tan SA, Ling ECS, Lim YK, Chin CM, Lee PY, Lee CM, Ooi CH, Choudhury H and Pandey M. (2018) Nanotechnology based approaches for anti-diabetic drugs delivery. Diabetes Res Clin Practice 136:. 52-77.

Khan AW, Kotta S, Ansari SH, Sharma RK and Ali J. (2015) Self-nanoemulsifying drug delivery system (SNEDDS) of the poorly water-soluble grapefruit flavonoid Naringenin: Design, characterization, in vitro and in vivo evaluation. Drug Delivery 22(4): 552-561.

Khan T and Gurav P. (2017). PhytoNanotechnology: Enhancing delivery of plant based anti-cancer drugs. Front Pharmacol.. 8: 1002.

Khursheed R, Singh SK, Wadhwa S, Gulati M and Awasthi A. (2020) Enhancing the potential preclinical and clinical benefits of quercetin through novel drug delivery systems. Drug Discovery Today 25(1): 209-222.

Kim JY, Lee MS, Jung S, Joo H, Kim CT, Kim IH, Seo S, Oh S and Kim Y. (2014) Anti-obesity efficacy of nanoemulsion oleoresin capsicum in obese rats fed a high-fat diet. Int J Nanomed. 9(1): 301-310.

Krishnamoorthy Y, Rajaa S, Murali S, Rehman T, Sahoo J and Kar SS. (2020) Prevalence of metabolic syndrome among adult population in India: A systematic review and meta-analysis. PLoS One 15(10): e0240971.

Lee MS, Jung S, Shin Y, Lee S, Kim CT, Kim IH and Kim Y. (2017) Lipolytic efficacy of alginate double-layer nanoemulsion containing oleoresin capsicum in differentiated 3T3-L1 adipocytes. Food Nutr Res. 61 (1):1339553.

Lee YS, Kim WS, Kim KH, Yoon MJ, Cho HJ, Shen Y, Ye JM, Lee CH, Oh WK, Kim CT, Hohnen-Behrens C, Gosby A, Kraegen EW, James DE and Kim JB. (2006) Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. Diabetes 55(8): 2256-2264.

Li HL, Zhao X Bin, Ma YK, Zhai GX, Li LB and Lou HX. (2009) Enhancement of gastrointestinal absorption of quercetin by solid lipid nanoparticles. J Controlled Release 133(3): 238-244.

Li L, Sheng X, Zhao S, Zou L, Han X, Gong Y, Yuan H, Shi L, Guo L, Jia T, Liu S, Wu B, Yi Z, Liu H, Gao Y, Li G, Li G, Zhang C, Xu H and Liang S. (2017) Nanoparticle-encapsulated emodin decreases diabetic neuropathic pain probably via a mechanism involving P2X3 receptor in the dorsal root ganglia. Purinergic Signalling 13(4): 559-568.

Liu S and Ho PC. (2017) Formulation optimization of scutellarin-loaded HP-β-CD/chitosan nanoparticles using response surface methodology with Box–Behnken design. Asian J Pharmaceut Sci. 12(4): 378-385.

Loguercio C and Festi D. (2011) Silybin and the liver: From basic research to clinical practice. World J Gastroenterol. 17(18): 2288-2301.

Long L, Li Y, Yu S, Li X, Hu Y, Long T, Wang L, Li W, Ye X, Ke Z and Xiao H. (2019) Scutellarin prevents angiogenesis in diabetic retinopathy by downregulating VEGF/ERK/FAK/Src pathway signaling. J Diabetes Res 2019: 4875421.

Madan S, Ahmad S, Singh GN, Kohli K, Kumar Y, Singh R and Garg M. (2010) Stevia rebaudiana (Bert.) Bertoni - A Review. Indian J Natural Products Resources 1(3): 267-286.

Maity S, Mukhopadhyay P, Kundu PP and Chakraborti AS. (2017) Alginate coated chitosan core-shell nanoparticles for efficient oral delivery of naringenin in diabetic animals—An in vitro and in vivo approach. Carbohydrate Polymers 170: 124-132.

Makheswari UM. (2011) Phytomedicine for diabetes mellitus: An overview. Res Pharmacy 1(4): 28-37.

Man N, Wang Q, Li H, Adu-Frimpong M, Sun C, Zhang K, Yang Q, Wei Q, Ji H, Toreniyazov E, Yu J and Xu X. (2019) Improved oral bioavailability of myricitrin

by liquid self-microemulsifying drug delivery systems. J Drug Delivery Sci Technol. 52: 597-606.

Matos M, Gutiérrez G, Coca J and Pazos C. (2014) Preparation of water-in-oil-in-water (W1/O/W2) double emulsions containing trans-resveratrol. Colloids Surfaces A Physicochem Engineer Aspects 442: 69-79.

McCracken E, Monaghan M and Sreenivasan S. (2018) Pathophysiology of the metabolic syndrome. Clinics Dermatol. 36(1): 14-20.

Melgar-Lalanne G, Hernández-Álvarez AJ, Jiménez-Fernández M and Azuara E. (2017) Oleoresins from *Capsicum* spp.: Extraction methods and bioactivity. Food Bioprocess Technol. 10(1): 51-76.

Mirhadi E, Rezaee M and Malaekeh-Nikouei B. (2018) Nano strategies for berberine delivery, a natural alkaloid of Berberis. Biomed Pharmacotherapy 104: 465-473.

Mohseni R, ArabSadeghabadi Z, Ziamajidi N, Abbasalipourkabir R and RezaeiFarimani A. (2019) Oral administration of resveratrol-loaded solid lipid nanoparticle improves insulin resistance through targeting expression of SNARE proteins in adipose and muscle tissue in rats with type 2 diabetes. Nanoscale Res Lett. 14(1): 227.

Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL and Eisenberg MJ. (2010) The metabolic syndrome and cardiovascular risk: A systematic review and meta-analysis. J American College Cardiology 56(14): 1113-1132.

Mukhopadhyay P, Maity S, Mandal S, Chakraborti AS, Prajapati AK and Kundu PP. (2018) Preparation, characterization and in vivo evaluation of pH sensitive, safe quercetin-succinylated chitosan-alginate core-shell-corona nanoparticle for diabetes treatment. Carbohydrate Polymers 182: 42-51.

Naseri R, Farzaei F, Haratipour P, Nabavi SF, Habtemariam S, Farzaei MH, Khodarahmi R, Tewari D and Momtaz S. (2018) Anthocyanins in the management of metabolic syndrome: A pharmacological and biopharmaceutical review. Front Pharmacol. 9: 1310.

Ochin C and Garelnabi M. (2018) Berberine encapsulated PLGA-PEG nanoparticles modulates PCSK-9 in HepG2 cells. Cardiovasc Hematol Disord Drug Targets 18(1): 61-70.

Öztürk E, Arslan AKK, Yerer MB and Bishayee A. (2017) Resveratrol and diabetes: A critical review of clinical studies. Biomed Pharmacotherapy 95: 230-234.

Panda DS, Eid HM, Elkomy MH, Khames A, Hassan RM, Abo El-Ela FI and Yassin HA. (2021) Berberine encapsulated lecithin–chitosan nanoparticles as innovative wound healing agent in type ii diabetes. Pharmaceutics. 13(8): 1197.

Patel K, Gadewar M and Tripathi R. (2012) Pharmacological and analytical aspects of gymnemic acid: A concise report. Asian Pacific J Tropical Disease 2(5): 414-416.

Patel RV., Mistry BM, Shinde SK, Syed R, Singh V and Shin HS. (2018) Therapeutic potential of quercetin as a cardiovascular agent. European J Med Chem. 155: 889-904.

Patra N, Kar D, Pal A and Behera A. (2018) Antibacterial, anticancer, anti-diabetic and catalytic activity of bio-conjugated metal nanoparticles. Adv Nat Sci Nanosci Nanotechnol. 9(3): 035001.

Paul D, Dey TK, Mukherjee S, Ghosh M and Dhar P. (2014) Comparative prophylactic effects of α-eleostearic acid rich nano and conventional emulsions in induced diabetic rats. J Food Sci Technol. 51(9): 1724-1736.

Pereira MC, Oliveira DA, Hill LE, Zambiazi RC, Borges CD, Vizzotto M, Mertens-Talcott S, Talcott S and Gomes CL. (2018) Effect of nanoencapsulation using PLGA on antioxidant and antimicrobial activities of guabiroba fruit phenolic extract. Food Chem. 240: 396-404.

Piazzini V, Cinci L, D'Ambrosio M, Luceri C, Bilia AR and Bergonzi MC. (2018) Solid lipid nanoparticles and chitosan-coated solid lipid nanoparticles as promising tool for silybin delivery: Formulation, characterization, and in vitro evaluation. Curr Drug Delivery 16(2): 142-152.

Pignatelli P, Carnevale R and Menichelli D. (2019). Silybin and metabolic disorders. Internal and Emergency Med. 14: 1-3.

Prabu SM, Renugadevi J and Shagirtha K. (2013) In vivo and in vitro antioxidative efficacy of naringenin on cadmium-induced toxicity in rats. Res Rev J Toxicol. 3(3): 9-16.

Rajarajeshwari T, Shivashri C and Rajasekar P. (2014) Synthesis and characterization of biocompatible gymnemic acid-gold nanoparticles: A study on glucose uptake stimulatory effect in 3T3-L1 adipocytes. RSC Adv. 4(108): 63285-63295.

Ravichandran R. (2010) Formulation of nanosuspensions of gymnemic acids for oral administration. Int J anoparticles 3(4): 309-325.

Ravichandran R. (2012) Studies on gymnemic acids nanoparticulate formulations against diabetes mellitus. Int J Biomed ClinEngineeri. 1(2): 1-12.

Rivera L, Morón R, Sánchez M, Zarzuelo A and Galisteo M. (2008) Quercetin ameliorates metabolic

syndrome and improves the inflammatory status in obese Zucker rats. Obesity 16(9): 2081-2087.

Roshanravan N, Askari SF, Fazelian S, Ayati MH and Namazi N. (2023) The roles of quercetin in diabetes mellitus and related metabolic disorders; special focus on the modulation of gut microbiota: A comprehensive review. Critical Rev Food Sci Nutr. 63(17):. 2990-3003.

Saha SS and Ghosh M. (2009) Comparative study of antioxidant activity of α-eleostearic acid and punicic acid against oxidative stress generated by sodium arsenite. Food Chem Toxicol. 47(10): 2551-2556.

Saneja A and Sharma C. (2010) *Gymnema sylvestre* (Gurmar): a review. Der Pharmacia 2(1): 275-284.

Senthilnathan B, Vivekanandan K, Bhavya E, Masilamani and Swarna Priya B. (2019) Impact of nanoparticulate drug delivery system of herbal drug in control of diabetes mellitus. Res Jf Pharmacy Technol. 12(4): 1688-1694.

Shahraki A, Bahadorikhalili S, Hashemzaei M, Hajinezhad M, Afsharimoghaddam A, Sarani F and Tajrobekar O. (2017) Resveratrol nano-capsule as an effi cient tool for blood pressure regulation: A study on metabolic syndrome induced mice. Biosci Biotechnol Res Communications 10(4): 623-630.

Sharma AT, Mitkare SS and Moon RS. (2011) Multicomponent Herbal Therapy: A review. Int J Pharmaceut Sci Rev Res. 6(2):. 185-187.

Shi F, Wei Z, Zhao Y and Xu X. (2016) Nanostructured lipid carriers loaded with Baicalin: An efficient carrier for enhanced antidiabetic effects. Pharmacogn Magazine 12(47): 198-202.

Shi Y, Li J, Ren Y, Wang H, Cong Z, Wu G, Du L, Li H and Zhang X. (2015) Pharmacokinetics and tissue distribution of emodin loaded nanoemulsion in rats. J Drug Delivery Sci Technol. 30: 242-249.

Singh J, Mittal P, Vasant Bonde G, Ajmal G and Mishra B. (2018) Design, optimization, characterization and in-vivo evaluation of Quercetin enveloped Soluplus®/P407 micelles in diabetes treatment. Artificial Cells Nanomed Biotechnol. 46(sup3): S546-S555.

Soetikno V, Sari FR, Veeraveedu PT, Thandavarayan RA, Harima M, Sukumaran V, Lakshmanan AP, Suzuki K, Kawachi H and Watanabe K. (2011) Curcumin ameliorates macrophage infiltration by inhibiting NF-B activation and proinflammatory cytokines in streptozotocin induced-diabetic nephropathy. Nutr Metab (Lond) 8(1): 35.

Song IS, Cha JS and Choi MK. (2015) Enhanced oral bioavailability of naringenin administered in a mixed micelle formulation with Pluronic F127 and Tween 80 in rats. J Pharmaceut Investi. 45(7): 633–640.

Sricharoen P, Lamaiphan N, Patthawaro P, Limchoowong N, Techawongstien S and Chanthai S. (2017) Phytochemicals in *Capsicum oleoresin* from different varieties of hot chilli peppers with their antidiabetic and antioxidant activities due to some phenolic compounds. Ultrasonics Sonochem. 38: 629-639.

Summerlin N, Soo E, Thakur S, Qu Z, Jambhrunkar S and Popat A. (2015) Resveratrol nanoformulations: Challenges and opportunities. Int J Pharmaceut. 479(2): 282-290.

Suresh K and Nangia A. (2018) Curcumin: Pharmaceutical solids as a platform to improve solubility and bioavailability. CrystEngComm. 20(24): 32773296.

Szkudelska K and Szkudelski T. (2010) Resveratrol, obesity and diabetes. European J Pharmacol. 635(1–3): 1-8.

Tabatabaei-Malazy O, Larijani B and Abdollahi M. (2015) Targeting metabolic disorders by natural products. J Diabetes Metab Disord 14: 57.

Taghipour YD, Hajialyani M, Naseri R, Hesari M, Mohammadi P, Stefanucci A, Mollica A, Farzaei MH and Abdollahi M. (2019) Nanoformulations of natural products for management of metabolic syndrome. Int J Nanomed. 14:. 5303-5321.

Tiwari P, Mishra BN and Sangwan NS. (2014) Phytochemical and pharmacological properties of *Gymnema sylvestre*: An important medicinal plant. BioMed Res Int. 2014: 830285.

Tong F, Chai R, Jiang H and Dong B. (2018) In vitro/vivo drug release and anti-diabetic cardiomyopathy properties of curcumin/PBLG-PEG-PBLG nanoparticles. Int J Nanomed. 13: 1945-1962.

Veiseh O, Tang BC, Whitehead KA, Anderson DG and Langer R. (2014) Managing diabetes with nanomedicine: Challenges and opportunities. Nature Rev Drug Discovery 14(1): 45-57.

Waisundara VY, Hsu A, Tan BKH and Huang D. (2009) Baicalin improves antioxidant status of streptozotocin-induced diabetic wistar rats. J Agricult Food Chem. 57(10): 4096-4102.

Wang J, Tan J, Luo J, Huang P, Zhou W, Chen L, Long L, Zhang L ming, Zhu B, Yang L and Deng DYB. (2017) Enhancement of scutellarin oral delivery efficacy by vitamin B12-modified amphiphilic chitosan derivatives to treat type II diabetes induced-retinopathy. J Nanobiotechnol. 15(1): 18.

Wang L and Ma Q. (2018) Clinical benefits and

pharmacology of scutellarin: A comprehensive review. Pharmacol Therapeut. 190: 105-127.

Wang Y, Wang S, Firempong CK, Zhang H, Wang M, Zhang Y, Zhu Y, Yu J and Xu X. (2017) Enhanced solubility and bioavailability of naringenin via liposomal nanoformulation: Preparation and In vitro and in vivo evaluations. AAPS Pharmscitech 18(3): 586-594.

Wei Y, Li L, Xi Y, Qian S, Gao Y and Zhang J. (2014) Sustained release and enhanced bioavailability of injectable scutellarin-loaded bovine serum albumin nanoparticles. Int J Pharmaceutics 476(1): 142-148.

Xiong F, Wang H, Cheng J and Zhu J. (2006) Determination of scutellarin in mouse plasma and different tissues by high-performance liquid chromatography. J Chromatography B Analytical Technol Biomed Life Sci. 835(1–2): 114-118.

Xu J, Fu Y and Chen A. (2003) Activation of peroxisome proliferator-activated receptor-γ contributes to the inhibitory effects of curcumin on rat hepatic stellate cell growth. Am J Physiol Gastrointest Liver Physiol. 285(1): G20-30.

Xu L, Chen R, Zhang X, Zhu Y, Ma X, Sun G and Sun X. (2021) Scutellarin protects against diabetic cardiomyopathy via inhibiting oxidative stress and inflammatory response in mice. Annals Palliative Med. 10(3): 2481-2493.

Xue M, Zhang L, Yang MX, Zhang W, Li XM, Ou ZM, Li ZP, Liu SH, Li XJ and Yang SY. (2015) Berberine-loaded solid lipid nanoparticles are concentrated in the liver and ameliorate hepatosteatosis in db/db mice. Int J Nanomed. 10: 5049-5057.

Yoshime LT, de Melo ILP, Sattler JAG, de Carvalho EBT and Mancini-Filho J. (2016) Bitter gourd (*Momordica charantia* L.) seed oil as a naturally rich source of bioactive compounds for nutraceutical purposes. Nutrire 41: 12.

Yu B, Pu Y, Liu J, Liao J, Chen K, Zhang J, Zhong W, Hu Y, Wang XQ, Liu B, Liu H and Tan W. (2020) Targeted delivery of emodin to adipocytes by aptamer-functionalized PEG-PLGA nanoparticles in vitro. J Drug Delivery Sci Technol. 57: 101739.

Yu Y, Correll PH and Vanden Heuvel JP. (2002) Conjugated linoleic acid decreases production of pro-inflammatory products in macrophages: Evidence for a PPARγ-dependent mechanism. Biochim Biophys Acta Molec Cell Biol Lipids 1581(3): 89-99.

Zheng C, Ou W, Shen H, Zhou Z and Wang J. (2015) Combined therapy of diabetic peripheral neuropathy with breviscapine and mecobalamin: a systematic review and a meta-analysis of Chinese studies. Biomed Res Int. 2015: 680756.