NANOPHYTOMEDICINES FOR THE PREVENTION OF METABOLIC SYNDROME

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Introduction. Metabolic syndrome (MetS), also known as "syndrome X" and "insulin-resistance syndrome", is characterized by several metabolic abnormalities, including insulin resistance, type 2 diabetes, obesity, hypertension, and dyslipidaemia (*Kaur, 2014; Dalvand et al., 2017; Ebrahimi-Mameghani et al., 2018*). About 20–30% of the world population is diagnosed with MetS, which makes the disease as a global health issue (*Beltrán-Sánchez et al., 2013; Xi et al., 2013; Vishram et al., 2014; Pucci et al., 2017*). MetS is the result of a series of genetic and environmental factors; however, the exact etiology is not yet understood (*Feldeisen and Tucker, 2007*). The underlying mechanisms encompass insulin resistance, elevated plasma free fatty acids, chronic inflammation, and oxidative stress (*Bergman et al., 2001; Pan and Kong, 2018*). The increased level of free fatty acids results in suppression of insulin clearance and is closely associated with insulin resistance in obese individuals. To overcome the resistance, pancreas secretes more insulin, leading to hyperinsulinemia (*Oh et al., 2018*). Free fatty acids cause induction and suppression of protein kinase in the liver and the muscle cells, respectively, which subsequently increases gluconeogenesis in liver and diminishes glucose uptake in muscles (*Rochlani et al., 2017*). Chronic inflammation is implicated in visceral obesity and exacerbates insulin resistance, which is characterized by the abnormal production of adipocytokines such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, leptin, and plasminogen activator inhibitor-1 (PAI-1) (*Vaziri et al., 2005; Di Lorenzo et al., 2013*). Oxidative stress induces insulin resistance and also abrogates the adiponectin production by adipocytes (*Furukawa et al., 2017*). Adiponectin is an important anti-inflammatory and anti-atherogenic adipokine and is considered as a protective factor against the development and progression of chronic diseases related to metabolic disorders and oxidative stress including diabetes, hypertension, and cardiovascular diseases (*Becic et al., 2018*).

Secretions of adipose tissue stimulate mineralocorticoid release from adrenal cells and promote the renin angiotensin aldosterone system activity. Consequently, an elevation in renal sodium retention and vascular tone, as well as an inhibition of norepinephrine reuptake occur, which leads to hypertension. There is a direct relationship between obesity and the pathogenesis of hypertension (*Ehrhart-Bornstein et al., 2003; Cabandugama et al., 2017*). Management of MetS involves lifestyle modification, which consists of particular recommendations on physical activity and dietary interventions to achieve a normal weight, modulation of glycaemic and lipid profile, as well as a decrease in blood pressure (*Grundy, 2016*).

Nano-emulsions are stable colloidal systems that are favorable and suitable vehicles for controlled delivery of lipophilic ingredients (*Aswathanarayan and Vittal, 2019*). SLNs are lipid-based NPs that can be easily fabricated by biodegradable and

biocompatible solid lipids (*Ghasemiyeh and Mohammadi-Samani, 2018*). NLCs are another type of lipid-based nano carrier systems with colloidal particles composed of both solid and liquid lipids (*Madane and Mahajan, 2016*). Nanoliposomes provide a useful technology for delivering and targeting both hydrophilic and lipophilic phytobioactive constituents (*Khorasani et al., 2018*). Biodegradable polymeric NPs offer numerous advantages, since they protect bioactive constituents from degradation, enhance solubility, and provide controlled delivery and targeting (*Pereira et al., 2018*).

Ganesan et al. (2017) reviewed the beneficial effects of nanostructured formulations of phytochemicals to counteract diabetes. In our previous study, we reviewed the beneficial effects of nano-formulation originated from phytochemicals to combat MetS and its related complications (*Taghipour et al., 2019*). There is no comprehensive review about the potential use of various nanostructured formulations fabricated from herbal extracts, as promising future drugs to treat MetS and its associated complications. The present study, for the first time, provides a comprehensive review on the beneficial effects of nano-formulated herbal extracts on MetS and related disorders considering the *in vitro* and *in vivo* experiments.

The aim of the study. This review focuses on nano-formulations of herbal extracts in MetS and related complications.

Materials and methods. Will conduct a literature analysis of pharmaceutical and biopharmaceutical studies on the effect of nano-formulation of plant extracts and comparison of different nanostructures such as lipid-based carriers (SLNs and NLCs), nano-emulsions and green synthesized metal NPs on metabolic disorders through *in vitro* and *in vivo* experiments.

Results. Administration of nano-based drug delivery systems is one of the main strategies to enhance targeting capability and also to improve the safety and efficacy of drugs (*Kesharwani et al., 2018*). Conventional drug delivery systems are often accompanied with some critical limitations such as high dosage, low efficacy, low bioavailability, lack of target specificity, and dose-dependent side effects (*Surendiran et al., 2009; Subramani et al., 2012*). *In vitro* and *in vivo* investigations showed that nano-drug delivery systems such as nanomicelles, liposomes, and hydrogel-based nanocomposites can provide drug targeting to a specific site (*Ponnappan and Chugh, 2015; Kesharwani et al., 2018*). In case of diabetes and diabetes-associated dysfunctions, effective delivery of insulin via oral route by these nanoformulations is highly preferred compared to the available parenteral preparations, due to a higher patient compliance (*Wilczewska et al., 2012; Fangueiro et al., 2015; Maity et al., 2017*). In spite of the recent advancements of insulin delivery by NPs, there is still a challenge regarding the low bioavailability and poor gastric absorption of insulin. Some strategies have been utilized to overcome this challenge.

Ficus religiosa L., commonly known as Peepal tree, possesses several pharmacological effects including antioxidant, anti-inflammatory, antidiabetic and neuroprotective activity (*Singh et al., 2011*). SLNs, formulated using an ethanolic stem

bark extract of *F. religiosa*, were assessed in streptozotocin (STZ) and fructose-induced animal model of diabetes. Results showed that extract loaded SLNs had pronounced hypoglycemic and insulin sensitizing effects compared with the extract suspension. The nano-formulations based on SLNs provided an initial burst release followed by sustained release (*Priyanka et al., 2018*). SLNs offer attractive properties including easy production, low particle size, low toxicity, and good loading capacity of active molecules (*Gordillo-Galeano and Mora-Huertas, 2018*). In spite of various advantages of SLNs, the initial burst release makes the SLNs delivery systems unfavorable for oral delivery of several natural products that can improve chronic diseases (*Ganesan et al., 2018*). One of the promising ways to overcome this drawback is surface modification of the SLNs (*Ganesan et al., 2018*). Therefore, *F. religiosa* extract loaded surface modified SLNs can be the subject of future studies.

Plicosepalus acaciae (Zucc.) Wiens & Polhill and *P. curviflorus* (Benth. ex Oliv.) Tiegh. are medicinal plants which demonstrated antidiabetic activity, probably due to their antioxidant effects (*Al-Taweel et al., 2012*). Three SLNs based on methanolic extract of *P. acacia* and *P. curviflorus* were prepared with emulsion solvent evaporation method and their antidiabetic activity was evaluated in STZ^{+} high-fat diet (HFD)-induced diabetes. It was revealed that the proportion of lipid used in NPs directly correlates with pharmacological activity, so that the formulation with higher content of lipids had a better effect to reduce blood glucose, insulin resistance, and glycated hemoglobin compared with the simple extract or pioglitazone. Also, a remarkable decrease in malondialdehyde (MDA), as well as an increase in the endogenous antioxidant mediators, including glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) were observed with the SLNs having the highest lipid ratio (*Aldawsari et al., 2014*). A further area of research is needed to elucidate the hypoglycemic mechanisms of *P. acaciae* and *P. curviflorus* extracts-loaded SLNs formulations.

Syzygium cumini (L.) is an Indian medicinal plant with previously demonstrated antidiabetic activity (*Samadder et al., 2011*). A high content of polyphenols in leaf extract of *S. cumini* is responsible for antidiabetic and anti-inflammatory effects (*Ajiboye et al., 2018*). The hypoglycemic effect of *S. cumini* is related to upregulation of GLUT4, phosphatidylinositol 3 kinase (PI3K), and peroxisome proliferator activator receptor gamma (PPAR-γ) (*Anandharajan et al., 2006*). The ameliorative effects of *S. cumini* can be augmented by encapsulation in polymeric NPs. PLGA, a biodegradable and biocompatible polymer made from lactic acid and glycolic acid monomers (*Danhier et al., 2012*), was used to prepare *S. cumini* nano-formulation by the solvent displacement method. The prepared nano-formulation, caused a significant increase in glucose uptake, glucokinase activity, and GLUT4 protein expression in L6 rat skeletal muscle cells. Additionally, reactive oxygen species (ROS) production, nuclear factor-κB (NF-κB), a key contributor to cellular inflammatory cascades (*Baker et al., 2011*), and inducible nitric oxide synthase (iNOS), the enzyme that synthesizes NO, were significantly reduced in the *in vitro* model. In the rat model of arsenic-induced diabetes, blood sugar and glycosylated

hemoglobin levels in the extract- and nano-formulation-treated groups were significantly decreased, but the decrease by nano-formulation was more remarkable than that of the simple extract. The authors claimed that formulating this extract in form of NPs could improve its penetration into blood brain barrier (*Samadder et al., 2012*). Considering the central nervous system (CNS) complications of diabetes, such antidiabetic formulation may have a dual action to control both hyperglycemia and CNS effects of the disease which can be the subject of future studies.

Argyreia nervosa (*Burm. f.*) Bojer, from the family *Convolvulaceae* has been used in traditional Indian medicine for several therapeutic indications such as antidiabetic, anti-inflammatory and diabetic wound healing (*Singhal et al., 2011; Paulke et al., 2013*). Silver NPs (AgNPs) prepared using an aqueous leaf extract of A. nervosa showed *in vitro* inhibitory effects on α-amylase and α-glucosidase, which are important enzymes in carbohydrate metabolism with IC50 values of 55.5 and 51.7 μg/ml, respectively. Adherence of the functional groups of the phytochemicals to AgNPs enhanced surface area and significantly increased the entrapment of free radicals compared with the simple extract (*Saratale et al., 2017*). Thus, the formulation may be a suitable candidate to be evaluated in an animal model of diabetes.

Eysenhardtia polystachya (Ortega) Sarg. is commonly known as "palo azul" and has shown beneficial effects on the alleviation of bladder disorders and kidney stone (*Perez et al., 1998*). According to previous studies, flavonoid enriched *E. polystachya* extract has diminished oxidative damage in an animal model of diabetes (*Perez-Gutierrez et al., 2016*). *Campoy et al.* biosynthesized Ag NPs using a hydromethanolic extract of *E. polystachya* bark. The nano-formulation elevated pancreatic β cells survival and ameliorated insulin resistance and hyperglycemia, as well as dyslipidemia in glucose-induced diabetes in zebrafish. Also, in INS1 pancreatic β cell line intoxicated with hydrogen peroxide (H_2O_2), nano-formulated extract could significantly restore the insulin secretory ability of cells, which indicates antidiabetic activity of extract to be, at least in part, attributed to its antioxidant properties (*Campoy et al., 2018*).

Pouteria sapota (Jacq.) with the common name of "sapote" is found in Mexico and South America. The highest concentration of polyphenols in the fruit of this plant are responsible for its antioxidant activity (*Ma et al., 2004*). AgNPs were green-synthesized using the aqueous leaf extract of *P. sapota* and evaluated regarding the antidiabetic activity in cellular and animal models. *In vitro* antidiabetic properties of the AgNPs was corroborated by decreasing non-enzymatic glycosylation of hemoglobin, inhibition of α-amylase, and enhancement of glucose uptake by yeast cells. In STZ-induced animal model of diabetes, biosynthesized AgNPs and extract significantly improved SOD and CAT activity, decreased blood glucose, and enhanced plasma insulin level (*Prabhu et al., 2018*). *P. sapota* extract and its biosynthesized AgNPs can be considered as an effective agent in the management of diabetes.

Costus speciosus (J. Koenig) Sm. has shown an antidiabetic effect via induction of insulin secretion and improvement in insulin sensitivity (*Ali et al., 2014*). Ethanolic leaf

extract of *C. speciosus* was loaded in PLGA NPs to enhance bioactivity and provide sustained release of active constituents. PLGA NPs increased the expression of insulin (I&II), and GLUT4 genes; while decreased the expression of GLUT2 gene. In addition, the nano-formulation diminished blood sugar, enhanced high density lipoprotein cholesterol (HDL-C) and decreased total cholesterol (TC), triacylglycerol (TAG), and low density lipoprotein (LDL-C) in STZ-induced diabetic rats. The nano-formulated extract was more effective in controlling the lipid profile and blood glucose in comparison to the simple extract (*Alamoudi et al., 2014*).

Conclusions. The findings of these studies clearly confirm that most of phytomedicines can be successfully formulated by various nano-delivery approaches and thus successfully delivered to induce the required therapeutic effect. In addition to the proven role of nano-delivery systems, various loading methods, which are also discussed here, seem to be a critical factor. Moreover, targeted delivery of nano-formulated phytomedicines can pave the way to link traditional medicine with modern pharmaceutical techniques to be used in a wide range of diseases, including metabolic disorders.

ВПЛИВ ПРОПІЛЕНГЛІКОЛЕВОГО ЕКСТРАКТУ ЛИСТЯ МАЛИНИ ЗВИЧАЙНОЇ НА ПОКАЗНИКИ АТЕРОГЕННОСТІ В КРОВІ ЩУРІВ З ІНДУКОВАНИМ МЕТАБОЛІЧНИМ СИНДРОМОМ

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Вступ. Атерогенна дисліпідемія розглядається не лише як фактор ризику розвитку та прогресування атеросклерозу, а й як компонент метаболічного синдрому (МС). Застосування різних співвідношень ліпідограми — індексів атерогенності, які є незалежними предикторами серцево-судинних захворювань — можна використовувати для скринінгу дисліпідемії. Актуальним залишається пошук нових ефективних препаратів рослинного походження для корекції різних компонентів МС.

Мета дослідження. Визначити вплив пропіленгліколевого екстракту листя малини звичайної на атерогенні порушення ліпідного спектру у щурів з МС.

Матеріали і методи. Дослідження проводили на 18 білих щурах самцях лінії Вістар масою 180–220 г (вік 9–10 тижнів), які утримувались в стандартних умовах віварію (температура повітря: 22 ± 2°C, світлий / темний цикл: 12 / 12 годин).