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Review Article

Impact of Nanotechnology on Diabetes: Phyto-constituents based overview

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ABSTRACT

Nanotechnology has given new hope for the formulation of various drugs against a myriad of diseases, including diabetes. Over the past few decades, herbal medicines have attracted much attention as potential therapeutic agents in the prevention and treatment of diabetic complications due to their multiple targets and less toxic side effects. This review is an endeavor to document the present armamentarium of antidiabetic herbal drug discovery and developments, highlighting mechanism-based antidiabetic properties of different phyto-constituents of various chemical categories from different plants modulating different metabolic pathways.

Key words: *Diabetes, Nanotechnology, Phyto-constituents, Review*

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INTRODUCTION

Diabetes is characterized by a progressive loss of beta cell function that results in deterioration of glucose control which increases the incidence of diabetes related complications. There is substantial data associating chronic hyperglycemic with long term micro and macro vascular complication supporting the need for stringent glycemic control. Chronic hyperglycemia is thought to contribute to pancreatic beta-cell dysfunction and loss of insulin secretory capacity by exerting a glucotoxic effect and possibly exhaustion from the increased demand. This self perpetuating cycle leads to progressive and often found insulin deficiency and such patient ultimately require insulin to maintain their A1C level at goal [1]. Decades ago, type 1 diabetes was diagnosed almost exclusively in children, and type 2-diabetes almost always in middle-aged, overweight adults. The distinction was so sharp that lab confirmation of diabetes type was usually considered unnecessary, and was often avoided because of the old test's expense and difficulty. Now, because of the childhood obesity epidemic, about a quarter of newly diagnosed children have type 2 diabetes, and for unclear reasons, a growing number of newly diagnosed adults have type 1. Type 1 diabetes is an autoimmune disease caused by an inappropriate immune-system attack on healthy tissue. As a result, patients' bodies stop making insulin, a hormone that plays a key role in processing sugar. The disease

begins when a person's own antibodies attack the insulin-producing cells in the pancreas. The auto antibodies are present in people with type 1 but not those with type 2, which is how tests distinguish between them.

Nanotechnology is an attractive area of research for medicines and the application of nanotechnology to medicine is called nanomedicine, it is defined as: “Research and technology development at the atomic, molecular and macromolecular levels in the length scale of approximately 1 – 100 nanometer range, to provide a fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices and systems that have novel properties and functions because of their small and/or intermediate size”. The size domains of components involved with nanotechnology are similar to that of biological structures. For example, a quantum dot is about the same size as a small protein (<10nm) and drug- carrying nanostructures are the same size as some viruses (<100 nm). Because of this similarity in scale and certain functional properties, nanotechnology is a natural progression of many areas of health-related research such as synthetic and hybrid nanostructures that can sense and repair [2]. Nanomedicine is booming and focus on research efforts on a disease that affects the lives of more than 350 million people around the world as, nano medicine helpful for the People with both type 1 and type 2 diabetes who faces a constant battle to manage their condition, caused when the pancreas is no longer able to make insulin, or when the body cannot make efficient use of the insulin it does produce. Daily self-management is vital and demanding, requiring regular checking of blood glucose levels. In addition, the long-term effects of high glucose levels can affect the whole body, leading to complications such as cardiovascular disease, and causing retinal, kidney and nerve damage but with the upcoming time The treatment of diabetes could be transformed by using nanotechnology to create a 'smart delivery' system that regulates glucose levels from within the body.

CHEMICAL CONSTITUENTS RESPONSIBLE FOR DIABETES THERAPY

1. *Flavonoids*

Flavonoids are reputed compounds known for their health promoting properties due to their high antioxidant capacity. Flavonoids have been described to be excellent free radical scavenging agents. This reputation of the flavonoids that have received much attention in the mainstream of pharmaceutical research especially in the management of diabetic complications. Flavonoids are the most widespread polyphenolic compounds with hypoglycemic and antidiabetic properties and constitute the active biological principals of most medicinal plants [3]. Hyperglycemia provokes irreversible tissue damage by the protein oxidation reaction, leading to the formation of advanced oxidation protein products. Flavonoids mainly act by inhibiting free radical formation and propagation of free radical reactions through hydrogen donation and aromatic hydroxylation. Flavonoids reduce oxidative stress leads to the regeneration of pancreatic ß-cells, reduces necrosis and degeneration and thus, maybe effective in treating hyperglycemia thereby

preventing diabetic complications. Flavonoids having phenolic groups are found to be effective antioxidants due to their redox properties and chemical structure. These compounds function as (i) chain-breaking electron donors by reducing ROS, (ii) as chelating metal ions which initiate the reaction, (iii) as chain-breaking electron acceptors by oxidizing R, and (iv)as detoxificant of intermediary oxygen reactive products of lipoperoxidation by increasing available GSH. The flavonoidal rich fractions increase insulin release *in-vitro* from pancreatic islets and decrease levels of LDL, triglycerides and increases HDL level. Both these actions are found to be through dual up-regulation of both the peroxisome proliferators-activated receptors (PPARa and PPARγ) up to 3–4 folds. It was found that flavonoid rich fractions have both hypoglycemic and hypolipidemic effects in the management of diabetes. Intracellular accumulation of sorbitol leads to chronic complications of diabetes such as neuropathy, retinopathy and cataracts. Flavonoids like kaempferol and quercetin, show significant inhibitory effects on NO production and thus exert beneficial effects on hyperglycemia of diabetic animals. Both kaempferol and quercetin could inhibit the expression of iNOS, cyclooxygenase- 2 and reactive C-protein and down-regulate the NF-κB pathway, which contributed to the anti-inflammatory effects of these two flavonoids. Now a day, increasing evidence shows that the inflammatory response is closely involved in the pathogenesis of type 2-diabetes. Kaempferol and Quercetin as multi targeting compounds not only activate PPARγ but also inhibit inflammatory signaling resulting in satisfactory amelioration of hyperglycemia and lesser adverse effects.

2. Saponins

Saponins are also important active constituents which can be used for management of diabetic complications. Saponins isolated from medicinal plants are found to be renoprotective as they reduce fasting blood glucose and albuminuria, reverses the glomerular hyperfilteration state [4] and ameliorates proliferative glomerular pathological changes during the early stages of diabetic nephropathy in rat models. Saponins produce a significant reduction in blood glucose and lipid profile. This hypoglycemic action is due to the nature of saponins to stimulate remnant ß-cells to produce insulin. Total araliosides obtained from *Aralia elata* (Miq.) Seem. significantly prevented diabetes- induced cardiac dysfunction and pathological damage through up-regulation of L-type calcium channel current in cardiac cells and decreased connective tissue growth factor. *Panax quinquefolius* L. has preventive effects on diabetic nephropathy and it works through a combination of mechanisms such as anti-hyperglycemic and antioxidant activities.

3. Polysaccharides

Polysaccharides increases serum insulin secretion in diabetic rats**.** The possible mechanism of action of polysaccharides for their antidiabetic activity could be correlated with promoting insulin secretion by closure of K^+-ATP channels, membrane depolarization and stimulation of Ca^{2+} influx, an initial key step in insulin secretion They also diminish serum total cholesterol and triglyceride level

significantly and these effects may be due to low activity of cholesterol enzymes or low level of lipolysis which are under the control of insulin. Among all the polysaccharides containing medicinal herbs, *Lycium barbarum* L. was found to be very effective in diabetic complications. *Lycium barbarum* Polysaccharides-4 (LBP-4) isolated form *Lycium barbarum* L. significantly prevented renal damage in diabetic rats and also attenuated diabetic retinopathy. Fructo-oligosaccharides (FOS) increased insulin-positive pancreatic cell mass distributed in small cell clusters within the exocrine parenchyma. FOS increase plasma levels of Glucagon like peptide-1(GLP-1) and consequently its systemic effects i.e. release of insulin, inhibition of glucagon and somatostatin, and maintenance of ß-cell mass. In type 1 diabetic patients, endogenous GLP- regulates postprandial glucose excursions by modulating glucagon levels and ß-cell responsiveness to glucose [5].

4. Phytosterols

Phytosterols like cardinolides play an important role in the prevention of diabetic complications by ameliorating oxidative stress and altering antioxidant enzyme levels. Persistent hyperglycemia associated with diabetes has been shown to increase the production of free radicals through glucose auto-oxidation and protein glycation. High level of glucose is known to induce ROS and upregulate TGF-ß1 and extracellular matrix expression in glomerular mesengial cells. Inhibition of these changes by antioxidants strengthens the role played by ROS in mediating glucose-induced renal injury. Anti-hyperglycemic and antioxidant effect of steroidal components of plants help in preventing renal complications associated with diabetes. Diosgenin, a major steroidal sapogenin from *Dioscorea nipponica* Makino, was found to increase Nerve Growth Factor (NGF) levels in the sciatic nerve of diabetic rats and also increased the NCV. NGF may play a major role in the pathogenesis of diabetic neuropathy. This spirostane-type steroid was also found to increase neurite outgrowth in PC12 cells and diosgenin-treated diabetic mice showed reduced disarrangement of the myelin sheath and increased area of myelinated axons measured by electron microscope studies. It exhibited improvement in the damaged axons thereby; reversing functional and ultra-structural changes and induces neural regeneration in a diabetic neuropathy model. Glucosidase inhibitors block the actions of α-glucosidase enzymes in the small intestine, which is rate-limiting in the conversion of oligosaccharides and disaccharides to monosaccharides, necessary for gastrointestinal absorption. Postprandial glucose peaks may be attenuated by delayed glucose absorption. Thus reduces total range of postprandial glucose levels [6].

5. Tannins

Tannins play an important role in preventing diabetic complications by reducing the formation of AGEs and oxidative stress. Tannins present in *A. nilotica* (L.) almost restored the normal histopathological architecture of kidney of STZ-induced diabetic rats and produced significant improvement in glomerular size and damage in diabetic nephropathy in rats [7].

6. ***Miscellaneous***

Amino acid like S-allyl cysteine decreased plasma glucose level, TBARS, hydroperoxide and GSSG in diabetic rats. In addition, the levels of plasma insulin, superoxide dismutase, catalase, GPx and reduced GSH level were also increased. Amino acid reduces oxidative damage, inhibits lipid peroxidation and enhances cellular antioxidant defense. Therefore amino acids can be useful in management of diabetes and the related complications. STZ induced diabetic nephrology and modulated the oxidative stress in kidney whereas treatment with Diallyl disulphide and trisulphide isolated from *Allium sativum* L. produced a significant decrease in TBARS generation, accompanied by a significant increase in the GSH level. Moreover, a-hydroxysuccinamic acid from *Eugenia jambolana* Lam. reported to show significant attenuation of renal dysfunction. Curcuminoids (curcumin obtained from rhizomes of *Curcuma longa* L.**)** significantly lower plasma glucose level and attenuate oxidative stress leading to amelioration of cardiomyocyte hypertrophy, myocardial fibrosis and left ventricular dysfunction. It acts by inhibiting PKC-a and ß2-MAPK pathway which may be useful as an adjuvant therapy for the prevention of diabetic cardiomyopathy. Curcumin was also reported to treat diabetic nephropathy at a dose of 150 mg/kg. Some other important plants which can be used for the management of the treatment for neuropathy or renal dysfunctions [8].

CHEMICAL CONSTITUENTS MODIFIED IN NANO SYSTEMS

Bioavailability enhancers' are drug facilitators, they are the molecules which by themselves do not show typical drug activity but when used in combination they enhance the activity of drug molecule in several ways including increasing bioavailability of the drug across the membrane, potentiating the drug molecule by conformational interaction, acting as receptors for drug molecule and making target cells more receptive to drugs. A 'bio enhancer' is an agent capable of enhancing bioavailability and bio efficacy of a particular drug with which it is combined, without any typical pharmacological activity of its own at the dose used. These are also termed as 'absorption enhancers' which are functional excipients included in formulations to improve the absorption of a pharmacologically active drug [9]. Nanoparticles act as bioavailability enhancers, some of the examples are mentioned below:

Paclitaxel

Paclitaxel (PTX, 5β, 20-epoxy-l, 2 α, 4, 7β,10β,13α-hexahydroxytax-l l-en-9-one 4,10-diacetate 2-benzoate 13-ester) is a major anticancer drug isolated from the bark of *Taxus brevifolia* Nutt. (Taxaceae) has anti-neoplastic activity particularly against various types of solid tumours. PTX is approved in many countries for its use as second line treatment of ovarian and breast cancers. Incorporation of PTX into nanoparticles enhanced its anti-tumoral activity compared to Taxol. In mice, PTX-loaded nanoparticles showed noticeable anti-tumor efficacy and enhanced survival rates, compared to Taxol. Moreover, nanoparticles can escape from the vasculature through leaky endothelial tissue that surround the tumour and then accumulate in certain solid tumours by the so-called Enhanced Permeation and Retention (EPR)

effect. Nanoparticles were also prepared by interfacial deposition method (nano precipitation) and by sequential simplex optimization method. Pacilitaxel nano-particles are stable at 4°C over 3 months thus enhance drug stability, support sustained drug release and improve bioavailability [10].

Curcumin

Curcumin or diferuloylmethane is a yellow polyphenol extracted from the rhizome of turmeric (*Curcuma longa*, L.) (Zingiberaceae). It has potent anti-cancer properties as demonstrated in plethora of human cancer cell line and animal carcinogenesis models. Despite considerable promise of being an efficacious and safe compound for cancer therapy and chemoprevention; curcumin has not been embraced by the cancer community as a "panacea for all ills". The vital reason for this reticence is the reduced bioavailability of orally administered curcumin, such that therapeutic effects are essentially limited to the tubular lower GI tract. Nanoparticles of curcumin (nano-curcumin) have been prepared by a process based on a wet-milling technique. Unlike curcumin, nano-curcumin is freely dispersible in water in the absence of any surfactants. A principal cellular target of nano-curcumin in cancer cells is activated nuclear factor kappa B (NFκB), with many of the pleiotropic effects of curcumin being ascribed to inhibition of this seminal transcription factor. NanoCurc, a recently described polymeric nano-particle formulation of curcumin, has been used to inhibit malignant brain tumor growth through modulation of cell proliferation, survival and stem cell phenotype [11].

Quercetin

Quercetin, 3, 3′, 4′, 5′-7-pentahydroxy flavonoid extracted from air dried plant part of *Spohora japonica* L. (Fabaceae) mainly from bark and leaf. The antioxidant activity of quercetin is higher than well-known antioxidant molecules like ascorbyl and trolox**.** In spite of this wide spectrum of pharmacological properties, the use of quercetin in pharmaceutical field is limited due to its low aqueous solubility and instability in physiological medium. These properties of quercetin result in poor bioavailability, poor permeability, instability and extensive fast pass metabolism before reaching the systemic circulation. To improve the aqueous solubility and stability, quercetin-loaded nano-particles with gelation of chitosan with tripolyphosphate anions poly-D, L-lactide (PLA) nano-particles by solvent evaporation method and by using bovine serum albumin have been prepared.

The nano-encapsulation of quercetin into PLA nanoparticles significantly improves the therapeutic efficacy and bioavailability of this molecule. The *in vitro* release studies showed that 40–45% quercetin was released within 0–0.5 h showing rapid burst release. This was normally attributed to the fraction of quercetin which was adsorbed close to the surface of the nanoparticles [12].

Breviscapine

Breviscapine (BVP) is a well-known bioactive flavonoid ingredient (4', 5, 6 tri-hydroxyflavone-7-glucuronide) extracted from whole plant of perennial herb *Erigeron breviscapus* Vant. (Asteraceae) which has therapeutic effect on lung and vascular diseases. Breviscapine was useful in inhibiting

pulmonary fibrosis, and could reduce the damage due to the oxygen-derived free radicals in bleomycin. Scutellarin (4′, 5, 6-tetrahydroxyflavone- 7-*O*-glucuronide), the major active component of breviscapine, prevents vascular endothelial dysfunction in diabetic rats and was capable of inhibiting the proliferation of high glucose and hypoxia-stimulated proliferation of human retinal endothelial cells (HREC), which was possibly related to its ability to suppress the vascular endothelial growth factor (VEGF) expression. Scutellarin also inhibited platelet aggregation induced by arachidonic acid (AA), adenosine diphosphate (ADP), and platelet activating factor (PAF). It is well-known that the cerebrovascular and cardiovascular diseases are chronic, and always need a drug possessing preferable bioavailability and long half-life. However, BVP has very short half-life and poor bioavailability for oral administration. Scutellarin has poor solubility in water and can dissolve in ether, chloroform, ethanol, acetic acid and acetone. It is only stable in acidic conditions and rather unstable in alkaline solutions. The lipid emulsions (LE, oil-in-water emulsions stabilized by lipid surfactants), used as carrier for breviscapine, might improve the chemical stability of drug, increase drug loading efficiency, decrease irritation on the surrounding tissue as well as control and modify its pharmacokinetics and tissue distribution. Lipid emulsions as particulate drug-carriers can be produced on large industrial scale and sterilized by autoclaving but avoid drug leakage from carriers like liposomes. Nanocoated breviscapine increases plasma concentration and pharmacological activity of breviscapine hence, enhances blood circulation [13].

Triptolide

Triptolide, a diterpenoid triepoxides isolated from extract of whole plant of *Tripterygium wilfordii* Hook. (Celastraceae), which has been reported to be effective in the treatment of variety of inflammatory and autoimmune diseases, especially rheumatoid arthritis. Ethyl-acetate extract of *T. wilfordii* and its component triptolide inhibit transcription of the iNOS gene and this produces its anti-inflammatory effect. However, its clinical use is restricted due to its scarce water solubility and some toxic effects. Poly (D,L-lactic/glycolic acid) nanoparticles encapsulating triptolide have been reported to produce anti-inflammatory effect in adjuvant induced arthritis in rats. Nano-coated triptolide also exhibited higher anti-inflammatory and higher aqueous solubility compare to their traditional dose [14].

Naringenin

Naringenin (4′, 5, 7-trihydroxyflavanone, NAR), a natural flavonoid aglycone of naringin, is widely distributed in citrus fruits, tomatoes, cherries, grapefruit and cocoa. It is a well-known antioxidant compound and this property attributed to its structure–activity relationship. The number of hydroxyl substitutions of NAR can donate hydrogen to reactive oxygen species thereby allow acquisition of stable structure, and enable scavenging of these free radicals. NAR has also been extensively investigated for its pharmacological activities, including antitumor, anti-inflammatory and hepato-protective effects. Despite of its excellent free radical scavenging ability and pharmacological activities, clinical studies exploring different schedules of

administration of this drug have been hampered by its extreme water insolubility. The absolute bioavailability of NAR was only achieved 4 % in rabbits when administered orally.

Novel naringenin-loaded nano-particles (NARN) delivery system using Eudragit E and polyvinyl alcohol as a carrier was developed by a simple nano-precipitation technique. Nano-particles delivery system considerably improved the physicochemical profile of naringenin and resulted in enhanced drug release. In addition, NARN presented better hepato-protective effects than NAR on oral administration through enhancement of its antioxidant and anti-apoptotic activities in the CCl_4-induced hepatic-toxicity rat model. The nano-precipitation technique possesses numerous advantages, being relatively straight forward, rapid, and offer reproducible particle size with a narrow distribution. NARN has successfully changed several original physicochemical properties of naringenin, including a reduction in particle size, the amorphous rendering of the crystalline structure, and an enhancement in drug release rate [15].

Silymarins

Silymarins, a group of naturally occurring penta-cyclic triterpenoid compound extracted from the fruit of milk thistle *Silybum marianum* L. (Asteraceae), exhibits remarkable therapeutic effect in of many liver disorders. Silibinin is the main biological active component, which is largely responsible for its anti-hepatotoxic activity. Silymarin loaded solid lipid nano-particles (SlySLNs) was prepared by cold homogenization technique and characterized for their mean diameter, entrapment efficiency and drug loading. Under optimal conditions, the prepared SlySLNs has a mean diameter of 190.9 nm, entrapment efficiency of 95.9%, and drug loading of 8.6%. Silibinin-loaded nano-particles are dispersed in an amorphous state and can be used for parenteral administration.

SLNs of various sizes (150, 500 and 1000 nm) prepared by Compritol 888 ATO as the material and silymarin as a model drug investigated to determine the effects of particle size on their oral absorption. It was observed that the AUC of 150 nm SLNs was 2.08 fold higher than that of 500 nm SLNs and 2.54 fold higher than that of 1000 nm SLNs administered orally to rats (P<0.05). The oral bioavailability of 150 nm SLNs was remarkably higher than the other two sizes. Oral bioavailability of SlySLNs in Beagle dogs confirmed that SLN was a good carrier for improving the oral bioavailability of poorly soluble drugs [16].

Genistein

Genistein (5, 7, 4’ triatomic isoflavone) is a primary active component of soybean, scoparius and other leguminous plants. It’s a phytoestogen, antioxidant and also decreases risk of osteoporosis, cardiovascular disease, breast and uterine cancer. Due to its poor aqueous solubility and low serum level after administration, there is need to develop smart drug delivery system for this important isoflavone. Various drug delivery systems including self-nano-emulsified system, super-magnetic system and chitosan microspheres have been used to increase the dissolution and bioavailability of genistein. Genistein encapsulated in Fe_3O_4-carboxymethylatted

chitosan nanoparticles shows greater water solubility than free genistein. Genistein nanoparticles by nano-precipitation method with utilizing Eudragit E have been prepared.
Eudragit E cationic copolymers widely utilize to improve the solubility of poorly water soluble drugs. It has a basic site containing tertiary amine group which are ionized in gastric fluid. Therefore, it easily dissolves in gastric environment. It was found that genistein-loaded nano-particles possessed higher (241.8%) relative bioavailability compared to genistein alone. There were two mechanism to explain this enhance drug dissolution rate (1) both genistein and Eudragit E are hydrophobic substances, which generated strong affinity between them (2) enhancement of drug dissolution could be attributed to the reduction of particle size, the enhanced hydrophilic properties of the drug when encapsulated in Eudragit E polymer and enhanced wettability at the acidic pH provided by the dissolved Eudragit E. Finally the hydrophilic and hydrophobic portion of poloxamer penetrates into genistein nano-particles during the nano-precipitation process to form a stable nano-particle delivery system [17].

Berberine

Berberine, a naturally occurring isoquinoline alkaloid, is present in the roots, rhizome and stem bark of a number of medicinal plants such as *Berberis vulgaris* L. (Berberidaceae), *Hydrastis canadensis* L. (Ranunculaceae), *Phellodendron amurense* Rupr. (Rutaceae), *Coptis chinensis* Finet & Gagnepain (Ranunculaceae) and *Tinospora cordifolia* Thunb. (Menispermaceae). Berberine has tremendous potential to cure many physiological disorders; hence it has been used in the Ayurvedic, Unani, and Chinese as well as Homoeopathic system of medicine. Berberine inhibits activator protein 1, a key transcription factor in inflammation and carcinogenesis, in human cell lines possesses antitumor properties and effectively inhibit cyclooxygenase-2 transcriptional activity in human colon cancer cells. Berberine is known to inhibit DNA topo-isomerase II. Moreover, the anti-tumor properties of berberine are now recognized by researchers and clinical oncologists. The effects of berberine on human malignant brain tumor, esophageal cancer and human leukemic and human colon cancer cell lines have been achieved. Berberine loaded NPs are successfully prepared using single emulsion, multiple emulsion and ionic gelation methods for sustained drug release [17].

Camptothecin

Camptothecin (CPT) is a cytotoxic quinoline alkaloid isolated from bark and stem of Happy tree (*Camptotheca acuminata* Decne) (Nyssaceae). It has anticancer properties and inhibits DNA enzyme topoisomerase. CPT shows poor aqueous solubility and sever toxicity. To overcome these disadvantages certain analogues of CPT like Topotecan, Lurtotecan, Irrinotecan (CPT-11) and 9-aminocaptothecin (9-AC) were synthesized. These synthetic derivatives have better aqueous solubility, tumor efficiency and lesser toxic effect as compared to camptothecin. However, these analogues require larger in quantity to obtain high efficacy and they also exhibits slow pharmacological actions. CPT loaded nanoparticles by using poly (DL-lactic acid) (PLA) and poly (ethylene glycol)-block-

poly (propylene glycol)-block-poly (ethylene glycol) (PEG-PPG-PEG) and by self-assembly method have been prepared. Compared to traditional and their derivatives these nanoloaded CPT having high water solubility, high dose retention in body and they also worked at lower concentration [18].

Piperine

Piperine modifies the rate of glucuronidation by lowering the endogenous UDP-glucuronic acid content and also by inhibiting the transferase activity. Piperine inhibits human P-glycoprotein and cytochrome P450 3A4 (CYP3A4). Both the proteins contribute to a major extent to first-pass elimination of many drugs. Some of the metabolizing enzymes inhibited or inducedby piperine include CYP1A1, CYP1B1, CYP1B2, CYP2E1, CYP3A4 etc. Most of the drugs metabolized by these enzymes will therefore be influenced by bioenhancers. Some other suggested mechanisms include making target receptors more responsive to drugs, acting as receptors for drug molecules, increasing GIT vasculature by vasodilation to increase absorption of drugs, modulation of the cell membrane dynamics to increase transport of drugs across cell membranes [19].

Sinomenine

Sinomenine (7,8-didehydro-4-hydroxy-3,7-dimethoxy-17-methylmor phinan-6-one) is an alkaloid extracted from *Sinomenium acutum* Thunb. Paeoniflorin is a bioactive monoterpene glucoside, which has been widely used to treat inflammation and arthritic conditions. Paeoniflorin has a poor absorption rate and thus a very low bioavailability (3-4%) when administered orally. Co-administration with sinomenine dramatically altered the pharmacokinetic behaviors of paeoniflorin in rats [20].

Glycyrrhizin

Glycyrrhizin [(3,18)-30-hydroxy-11,30-dioxoolean-12- en-3-yl 2-O-glucopyranuronosyl-Dglucopyranosiduronic acid] is a triterpenoid saponin found in *Glycyrrhiza glabra* L. (Leguminosae). Glycyrrhizin showed a more potent absorption enhancing activity than caproic acid at the same concentration tested. The absorption-enhancing activity obtained from the simultaneous treatment of sodium deoxycholate and dipotassium-glycyrrhizin was much greater than sodium deoxycholate alone in CaCO-2 cell monolayers. The absorption enhancing activity of glycyrrhizin was increased by presence of the other absorption enhancers [21].

Nitrile glycosides

Nitrile glycosides and its derivatives are components derived from the pods of *Moringa oleifera* L. They do not possess drug activity of their own but are reported to promote and augment the biological activity, bioavailability or the uptake of drugs in combination therapy. The nitrile glycoside (e.g. niaziridin) has enhanced the absorption of commonly used antibiotics such as rifampicin, tetracycline and ampicillin, vitamins and nutrients.

PLANT EXTRACTS

Ginkgo bioloba L.

The leaf extract of *Ginkgo biloba* L. (Ginkgoaceae) has been widely marketed for its brain cell activation properties .However, the existing powder of *G. biloba* extract as such has not shown any remarkable effect for brain cell activation because the granule size

and insufficient absorption of active ingredient into the body and plant cell wall is not destroyed. Further it is evident that *G. biloba* contains ginkgolic acid which is a kind of hydrophobic, salicylic acid derivative causing allergy or polyphenolic compound (proanthocyanidin) with water solubility and browning reaction. They must be removed when *G. biloba* extract is used in drugs, food or in cosmetic materials.

G. biloba nanoparticles were developed by the combination of dry (gas-phase grinding techniques) and wet processes (liquid-phase grinding techniques). It was demonstrated that extract of *G. biloba* containing nanoparticles increase acetylcholine releasing activity from cerebral cortical synapses and the improvement of stimulation response of hippocampal pyramidal cell. Thus, the nanosized *G. biloba* extract is expected to activate the brain cell and work on the treatment of Alzheimer's dementia (like loss of memory, thinking, language, judgment, and behavior) [22].

Salvia miltiorrhiza L.

The dried roots of *S. miltiorrhiza* L. (Lamiaceae), commonly known as Danshen, are widely used as medicines for promoting circulation and improving blood stasis. Danshen is extensively used for treatment of coronary heart, cerebrovascular diseases, and hyperlipidemia. Salvianolic acid B regarded as active components of this plant. Slow pharmacological action is the major drawback of this herbal drug. Nano-coated *S. miltiorrhiaza* that exhibited stronger antioxidant bioactivities and also the polar active constituent in nanotechnology samples were released faster than the traditionally powdered samples. Phospholipids complex loaded nanoparticles also enhanced oral bioavailability of salvianolic acid [23].

Cuscuta chinensis

Cuscuta chinensis Lam. (Convolvulaceae), a parasitic plant which attacks on many valuable crops and trees. Its seeds are commonly used as herbal medicine and food as a tonic for the liver and the kidney. In clinical setting, *C. chinensis* has been used to improve sexual function, prevent senescence, and regulate the immune system. Its other pharmacological activities include anticancer, anti-ageing and immuno-stimulatory effects. The major chemical constituents are flavonoids and lignans. These compounds may be responsible for its pharmacological activities. Nano-particles of this plant have been developed by using nano-precipitation method. In this method nanonized ethanolic extract of *C. chinensis* seed produce the nano-coated *C. chinenesis* nanoparticles (CN). CN is a water soluble nonionic surface-active co-polymers, possessed solubilizing, emulsifier and suspension stabilizer properties with its two hydrophilic polyoxyethylene chains that are connected by a hydrophobic polyoxypropylene chains. Compare to ethanolic seed extract, CN exhibits higher hepato-protective and antioxidant effects at lower dose concentration.

Centella asiatica

A small herbaceous creeping plant, *C. asiatica* (L.) Urban. (Apiaceae) is used as a medicinal herb in Ayurvedic medicine. It possesses anxiolytic activity. It increases pentobarbitone-induced sleeping time and decreases immobility in the forced swim test. It also elicits anti-anxiety effects in the

elevated plus maze. Its aqueous extract was reported to have cognitive-enhancing as well as antioxidant effects in rats. Moreover, it is also used for the treatment of leprosy, wounds, cancer, fever, and syphilis, acnes and allergy. The most prominent group of biologically active compounds isolated from *C. asiatica* are the terpenes, e.g. asiaticoside, madecassic acid, madecassoside and asiatic acid. Asiaticoside is the most abundant triterpene glycoside, which is effective in wound. Several derivatives of asiaticoside and asiatic acid were found to show protective effect against beta amyloid-induced neurotoxicity associated with the dementia of Alzheimer's disease. Dermatological, extract of *C. asiatica* has been used in scar management and in cosmetic formulation. The antitumor and cytotoxic properties of the crude extract and partially purified fractions of *C. asiatica* were also reported. Partially purified extract was more effective on tumor cells than the crude extracts. *C. asiatica* extract (CAE) possesses high potential biological activities; its clinical usage is limited to some extent due to its poor physical stability. CAE shows high hygroscopicity. The powder extract is promptly liquefied within a few minutes when exposed to normal environment. Therefore, the development of nano-particles which the extract is entrapped inside could lead to significant advantage as the extract is protected from external moisture. Chitosan-alginate nano-particle of CAE has been prepared by using ionic gelation principle. Nano-capsulation of CAE provided physical stability compared to its non nano-particle form.

***Artemisia annua* L.**

A single stemmed annual herb, *Artemisia annua* L. (Asteraceae) is indigenous to Asia and grows to a height of about 2 m. Artemisinin or qinghaosu is the active principle of *A. annua*. Artemisinin is an endoperoxide containing sesquiterpene lactone. Despite the potent antimalarial action of ART, it suffers from poor pharmacokinetic properties and short half-lives Artemisinin is chemically unstable and poorly soluble in water or oil. Nano-coated artemisinin by self assembly procedure using polyelectrolyte on natural drug crystals have been developed and these nano-capsules dispersed well in aqueous solutions and hydrophilicity of ART crystals were also improved after encapsulation.

Cuminum cyminum

Cuminum cyminum Linn. is a small and thin annual herb, grown extensively in South-East Europe and North Africa bordering the Mediterranean sea. It is an effective gastric stimulant, beneficial in abdominal lump and flatulence. It has therapeutically been used as an anti-diarrheal, galactagogue, diuretic and also beneficial in hoarseness of voice. Bioavailability/bioefficacy enhancing activity of *Cuminum cyminum* L. was revealed toward a number of drugs. Various volatile oils and luteolin and other flavonoids were seemed to attribute the bioavailability/bio-efficacy enhancing activity.

CONCLUSION

In the foreseeable future, the most important clinical application of nanotechnology will probably be in pharmaceutical development and this will be more realistic and beneficial when entities were taken from natural sources. Since some natural compounds having less

bioavailability; in that case nano-techniques are better option to modified and deliver them in efficient way.

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