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TRANSDERMAL PATCHES FOR DIABETES AND THROMBOEMBOLIC DISORDER- A LIPOSOMAL CHALLENGE

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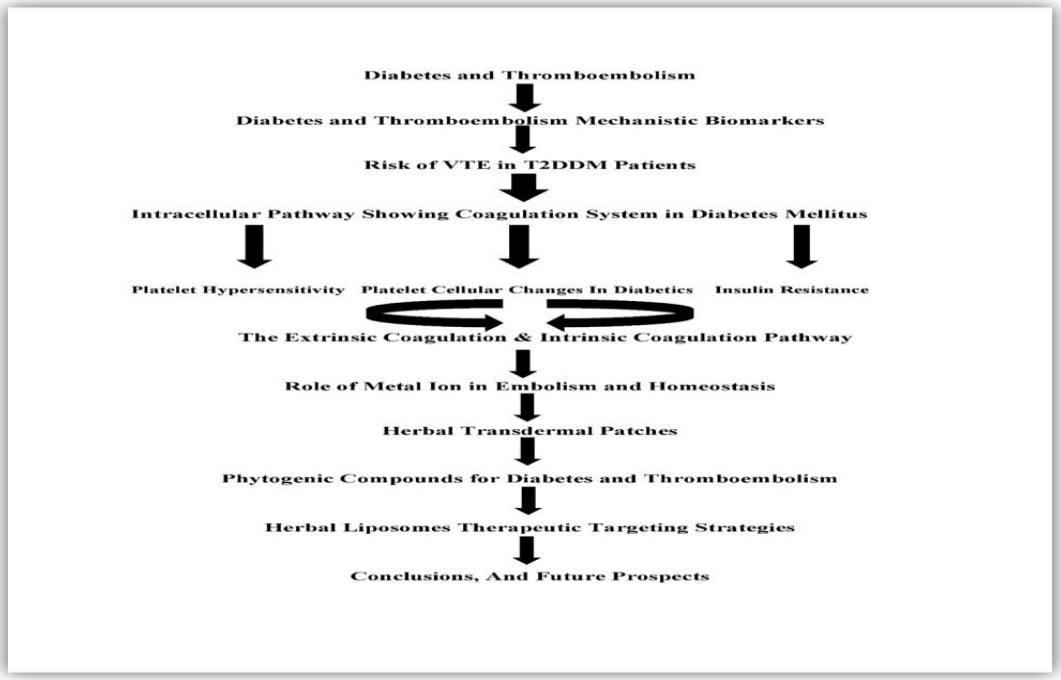
ABSTRACT

Diabetes mellitus (DM), a chronic disease with an increasing incidence and prevalence worldwide, is an established risk factor for arterial cardiovascular, cerebrovascular and peripheral vascular diseases including acute myocardial infarction, stroke and peripheral artery disease. Atherothrombosis is the leading cause of morbidity and mortality in patients with diabetes mellitus. Several mechanisms contribute to the diabetic prothrombotic state, including endothelial dysfunction, coagulative activation and platelet hyper-reactivity. Glycation of membrane proteins, hyperglycemia also decreases the membrane fluidity of platelets and results in increased intracellular calcium influx, directly promoting platelet activation and aggregation. Mg^{2+} can potentiate the activation of factor X by activated factor IX while in the presence of activated factor VIII, phospholipids and Ca^{2+}, the activation of factor IX by activated factor VII-tissue factor complex. Transdermal drug delivery system (TDDS) offers a better route of delivery, reported to have better patient compliance. Transdermal drug delivery system is a most suitable system for a long term treatment or for a multi-dose treatment and this system also increases the bioavailability of drug by avoiding the first pass metabolism and increases the therapeutic efficacy of drug by reaching into the systemic circulation. In this article, herbal liposomes are targeted for the site specific therapy of Diabetes and Thromboembolic disorders.

KEYWORD:- Liposomes, Herbs, Coagulation, Transdermal patches, Thromboembolism.

Flow diagram



INTRODUCTION

Millions of people worldwide suffer from diabetes (both type 1 and type 2). Cardiovascular illnesses are a leading cause of mortality for diabetics, partially because both forms of diabetes involve physiological alterations that impact hemostasis.[1] Atherosclerosis and heart lipotoxicity are caused by changes in lipid metabolism; other changes include the presence of pro-coagulatory microparticles, endothelial dysfunction, changes in metal ion homeostasis, hyper-activation of platelets, and altered concentrations of coagulatory proteins.[2][3]

Diabetes increases the risk of plaque buildup in the arteries, which can cause dangerous blood clots. Although blood clots routinely form as a normal function of blood cells to repair damaged blood vessel walls, clots become a problem when they prevent blood from flowing through an artery or vein inappropriately.[4] Diabetes mellitus (DM), a chronic disease with an increasing incidence and prevalence worldwide, is an established risk factor for arterial cardiovascular, cerebrovascular and peripheral vascular diseases including acute myocardial infarction, stroke and peripheral artery disease.[5] Venous and arterial thrombosis have traditionally been regarded as separate diseases, but recent studies have documented an association between these vascular complications.[6] Cardiovascular risk factors may contribute to thromboembolism and TE may be an early symptomatic event in patients at high cardiovascular risk, including diabetic patients. Diabetes mellitus along with others risks like obesity, previous VTE, malignancy, surgery, and immobility strongly contribute for Thromboembolism.[7] Chemical substances derived from animals, plants, and microbes have been used to treat diseases since the dawn of medicine while plant-derived products have dominated the human pharmacopoeia for thousands of years and have provided endless source of medicine.[8] Men have been using herbal medicines for thousands of years. The advantages of this type of therapeutics include good availability, local cultural aspects, individual preferences, the increasing demand for natural and organic products, and the already validated synergistic effects of herbal medicines.[9] Herbal medicines are in great demand in the developing world for primary health care not because they are inexpensive but also for better cultural acceptability, better compatibility with the human body and minimal side effects. Phototherapeutics need a scientific approach to delivering the components in a sustained manner to increase patient compliance and avoid repeated administration.[10] This can be achieved by designing novel drug delivery systems (NDDSs) for herbal constituents. NDDSs not only reduce the repeated administration to overcome non-compliance but also help to increase the therapeutic value by reducing toxicity and increasing the bioavailability.[11] One such novel approach is liposomal nanotechnology. Liposomes, spherical shaped nanocarriers, were discovered in the 1960s by bangham. Due to poor solubility in lipids, many of medicinal components show less bioactivity than optimal state in water Solution.[12] Due to their composition, variability and structural properties, liposomes are extremely versatile, leading to a large number of applications including pharmaceutical, cosmetics and food industrial fields. Liposomes are effective carrier systems for the delivery of herbal extracts with improved therapeutic effects by enhancing their limitations.[13][14] Among various delivery systems, liposomes have a great potential to be carriers of herbal extracts owing to their biodegradable nature and ability to enhance paracellular and transcellular drug transport.[15] Transdermal drug delivery aims to create a safe and effective method of administering drugs through the skin that attracts a lot of attention and investment due to the constant progress in the field. Literature revealed that the herbal transdermal patches increase the concentration availability, bioavailability, physicochemical properties, stability, and better drug release kinetics and also bypass GI adverse effects.[16][17]

Diabetes mellitus is an important risk factor for a first cardiovascular event and for worse outcomes after a cardiovascular event has occurred.[18] This situation might be caused, at least in part, by the prothrombotic status observed in patients with diabetes. Therefore, contemporary antithrombotic strategies, including more potent agents or drug combinations, might provide greater clinical benefit in patients with diabetes than in those without diabetes.[19] Cardiovascular disease in diabetes is a progressive process characterized by early endothelial dysfunction, oxidative stress, and vascular inflammation leading to monocyte recruitment and formation of foam cells and fatty streaks, which cause development of atherosclerotic plaques over years.[20] Plaques are at increased risk of developing superimposed thrombosis because of increased amounts of soft extracellular lipids, inflammation, and prothrombotic milieu; this situation predisposes patients with diabetes to acute cardiovascular events. Hyperglycaemia has direct effects on gene transcription of coagulation factors, and hyperglycaemia-induced oxidative stress alters the natural vasculoprotective endothelial glycocalyx.[21]

Quantitative changes in coagulation factors in patients with diabetes involve higher plasma levels of fibrinogen (the soluble precursor of solid fibrin), coagulation factor VII, and coagulation factor XII; increased endothelial expression of tissue factor and tissue factor–coagulation factor VIIa complex activity; and a reduction in the anticoagulant protein tissue factor pathway inhibitor.[22] Qualitative changes of haemostatic factors include the glycation and oxidation of fibrinogen and plasminogen, as well as the incorporation of antiplasmin, PAI1, carboxypeptidase B2, and complement C3 into the fibrin mesh, resulting in a denser clot structure and in delayed spontaneous clot lysis.[23] Increased thrombin generation activates coagulation factor XIII, which cross links and further stabilizes the fibrin network. Studies shows that

the pathophysiological steps implicated in the increased thrombotic risk of patients with diabetes includes increased thrombin and fibrin generation, delayed clot lysis, and reduced NO bioavailability.[24] Therapies should be targeted on the platelets, coagulation, fibrinolysis, and NO systems to prevent the thromboembolic cardiovascular disorders in a diabetic patient. Research also revealed that the several established cardiovascular risk factors, older age, smoking, and adiposity were consistently associated with higher VTE risk.[25][26]

The natural wealth of India includes many herbs having medicinal property. There are several literatures shows that India has been using traditional medicines since ancient times. Three major traditional systems exist in India using medicinal plants are Ayurveda, Unani and Siddha. Indian materia medica includes about 2000 drugs of natural origin which are derived from different traditional system and traditional practice.[27] Medicinal plants have considerable potential to supplement incomes and improve livelihood for rural population. Traditional plants are always the sources of the great utility for the many peoples in the world as the chemical medicines are very costly for the poor nations like the India, Africa and the other developing countries of the world.[28] Still today in whole of the world, in the many nations the medicinal plant are utilised for the several purposes. WHO report shows that still there are in many nations the plants are utilised and they are the first and the primary interest for the treatment of the diseases.[29] The main reasons of that are they have the easy availability and they are very cheap, the side effects are also very less. The safety of herbal medicinal products (HMP) is usually supposed to be high, as it is documented by their long-standing therapeutic use.[30] Medicines obtained from natural sources have become the basis for pharmaceutical drugs. Recently, the practice of herbal medicine has been diminishing, which may lead to the loss of valuable informations about healing herbs.[31] There are many medicinal plants grown in semievergreen forests of Himachal Pradesh. Therefore extensive research is required to uplift the scientific role of traditional herbal medicines to validate the ethnobotanical claim.[32] Herbs produce synergistic effects due to the interaction of two or more agents to produce a combined effect greater than the sum of their individual effects. Herbs produce hundreds to thousands of diverse chemical compound with different biological activities.[33] It was assumed that the synergistic therapeutic effects of herbal medicine derive from the complex interactions between the multiple bioactive components within the herbs and/or herbal formulations.[34] Medical science has long realized that the pathogenesis and progression of diseases are too complex for single drug treatment. For example, cardiovascular and metabolic disorders are the primary killer disorders worldwide with thromboembolism and diabetes as the most common cause of cardiovascular morbidity and mortality.[35] Their pathophysiology are very complex and warrants multifaceted treatment. Interestingly, to achieve better therapeutic outcomes and diminish side effects, multiherb therapy is an essential component of traditional herbal medicine and has been utilized for thousands of years.[36]

Phototherapeutics need a scientific approach to delivering the components in a sustained manner to increase patient compliance and avoid repeated administration. This can be achieved by designing novel drug delivery systems (NDDSs) for herbal constituents. NDDSs not only reduce the repeated administration to overcome non-compliance but also help to increase the therapeutic value by reducing toxicity and increasing the bioavailability.[37] Liposomes are nanoparticles comprising lipid bilayer membranes surrounding an aqueous interior. The amphilic molecules used for the preparation of these compounds have similarities with biological membranes and have been used for improving the efficacy and safety of different drugs.[38] Liposomes are vesicular structures composed of amphiphilic molecules, such as phospholipids. Their size can range from a few nanometers to several micrometers, being both preparation technique and components important to define their final physicochemical properties such surface charge, size, and stability. Liposomes are useful vehicles for topical drug delivery once they can provide prolonged and controlled action after application and also prevent enzymatic degradation.[39] The most common and simplest preparation technique is film hydration, where a thin lipid film is hydrated with the desired solution. Liposomes are useful vehicles for topical drug delivery once they can provide prolonged and controlled action after application and also prevent enzymatic degradation. The most common and simplest preparation technique is film hydration, where a thin lipid film is hydrated with the desired solution.[40]

The main principle of developing unconventional drug delivery technologies is to offer more convenience for patients and increase the effectiveness and protection of drug. The aim of the present review at formulation of transdermal patches incorporating herbal drug components. Transdermal patch is a medicated adhesive pad that is designed to release the active ingredient at a constant rate over a period of several hours to days after application to the skin.[41] It has been found that drugs from herbal origin can be utilized with enhanced efficacy by incorporating in transdermal drug patches. Herbal transdermal patches which aids to quit smoking, relieve stress, increase sexuality, insect repellant patches, detoxification, male energizer, postpone menopause are available. Transdermal drug delivery systems are topically administered medicaments.[42] Transdermal patches are pharmaceutical preparation of varying sizes, containing, one or more active ingredient, intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers, and it avoid first pass effect. An advantage of a transdermal drug delivery route over

other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive.[43] The herbal transdermal patches could control the release and skin permeation behavior of active drug molecule from the matrix layer. The mechanistic functions of the transdermal patch and the flow of the active drug ingredient from the patch to the circulatory system via skin transpire through different methods. For a systemically active drug to reach a target tissue, it has to take some physicochemical properties which make easy the sorption of the drug through the skin and enter the microcirculation.[44] Patches has so many advantages like patch is adhered on the skin surface to deliver the drug into the systemic circulation through the skin at predefined concentration for therapeutic effects, which avoids additional limitations due to other dosage forms. It offers constant permeation of drugs through the skin giving constant serum drug level and can be also used as an alternate to oral drug delivery system for those patients, who find difficulty in taking drugs through oral route.[45] TDDS can be used as an alternative for nauseated or unconscious patients and the patients having gastrointestinal problems can be given drugs through TDDS as there will be no direct Contact between drug and stomach and gives constant plasma level. Beside this, if toxicity develops from TDDS, patch can be removed easily, very convenient as application of drug is very easy, eliminates first pass mechanism, reduces systemic drug interactions, and offers long duration of action and self-administration can be done.[46] In addition, new dosage forms are essential for other drugs in order to enhance their performance by reducing their dose, increasing absorption, delivering to the target site etc. The patented innovations in transdermal drug delivery arena aim at these goals.

Diabetes and Thromboembolism mechanistic biomarkers relationship

Atherothrombosis is the leading cause of morbidity and mortality in patients with diabetes mellitus. Several mechanisms contribute to the diabetic prothrombotic state, including endothelial dysfunction, coagulative activation and platelet hyper-reactivity.[47] In particular, diabetic platelets are characterized by dysregulation of several signaling pathways leading to enhanced adhesion, activation and aggregation. Patients with type 2 diabetes mellitus (T2DM) have a two- to four-fold increase in the risk of CAD, and patients with DM but without previous myocardial infarction (MI) carry the same level of risk for subsequent acute coronary events as nondiabetic patients with previous MI.[48] Moreover, diabetics are two- to four-times more likely to develop stroke than people without DM. T2DM is associated with a prothrombotic state characterized by a number of changes in thrombotic and fibrinolytic coagulation factor level/activity, which together increase the risk of thrombus formation. Both glucose and insulin seem to play a role in the pathogenesis of this prothrombotic state. Also, enhanced platelet aggregation and thromboxane (TX) A_2 synthesis are detectable within days of making rats diabetic with streptozotocin.[49] The association of DM with newly diagnosed VTE was significantly greater in females (OR = 1.52, 95% CI 1.46–1.58, $p < 0.001$) resulting in a relative risk increase of 1.17 (95% CI 1.11–1.23) across all age groups with a peak of 1.65 (95% CI 1.43–1.89) between 50 and 59 years. We chose to examine the relation between DM and VTE because DM has been proposed as a risk factor for VTE, the theoretical mechanism being that hyperglycemia contributes to elevated coagulation factors, impaired fibrinolysis, and increased likelihood of thrombosis.[50] Indeed, laboratory evidence suggests that high glucose levels 1) increase oxidative stress, which in turn increases gene transcription of coagulation factors; 2) degrade the glycocalyx layer of the endothelial wall, which releases coagulation factors and stimulates the coagulation cascade; and 3) increase glycation of proteins involved in coagulation and fibrinolysis, shifting their activity towards a procoagulant state. Our study raises the possibility that female T2DM patients with HbA1c levels > 7% may have a slightly higher risk for unprovoked VTE compared to women with HbA1c levels > 6.5–7.0%. This increase may not be causal and may reflect differences in life style or other characteristics. Cardiovascular disease (CVD) is the foremost cause of morbidity and deaths in antiphospholipid syndrome (APS), driven by thrombo-inflammation and atherothrombosis mechanisms. Metabolic syndrome (MetS) is a proinflammatory and prothrombotic state characterized by increased CVD risk.[51] Metabolic syndrome (MetS) represents a constellation of interconnected cardiovascular risk factors (CVRFs), namely hypertension, abdominal obesity, insulin resistance and hyperglycemia, as well as elevated triglycerides (TGs) and low levels of high-density lipoprotein (HDL) cholesterol.[52] It is currently recognized as an independent CVRF and its presence has been associated with an approximately two-fold increase in cardiovascular events in the general population. While it has been shown that T2DM patients have a higher risk for arterial thrombosis, the association between T2DM and the risk of venous thromboembolism (VTE) has been studied less. VTE, a medical condition in which a thrombus forms in the venous system, can manifest as deep vein thrombosis (DVT) or as pulmonary embolism (PE), if the thrombus travels to the pulmonary arteries. VTE is associated with a high mortality.[53]

An increased risk of VTE in patients with DM is that hyperglycemia contributes to elevated coagulation factors and impaired fibrinolysis. A single unifying mechanism of DM complications might be hyperglycemia-induced overproduction of superoxide by the mitochondrial electron transport chain, which activates several damaging pathways. The activation of these pathways causes additional intracellular oxidative

stress, abnormalities of the gene expression of glomerular cells, hyperglycemia-induced cardiomyocyte dysfunction, and an increase of the enzyme GFAT (glutamine fructose-6 phosphate amidotransferase), resulting in a variety of effects on gene expression and advanced glycation end product formation.[54]

Among patients with preexisting CVD, (Table No. 01) individuals with HbA1c levels > 7.0% (> 53 mmol/mol) had a similar risk of VTE compared to patients with HbA1c levels between > 6.5–7.0% (> 48–53 mmol/mol). There was a slightly higher risk of VTE with increased HbA1c levels in women with CVD, but not in men.

Table No. 01: Risk of VTE in Patients with different T2DDM durations.

Sr. No.	HbA1c (%)	Number of Cases (%)	Number of Controls (%)	Adjusted ORs*
1.	≤6.5	446 (33.7)	2042 (38.6)	1.06 (0.89-1.25)
2	6.5-7.0	210 (15.9)	990 (18.7)	1 (reference)
3	7.0-7.5	172 (13.0)	651 (12.3)	1.20 (0.97-1.49)
4	7.5-8.0	86 (6.5)	326 (6.2)	1.29 (1.00-1.67)
5	8.0-9.0	104 (7.9)	336 (6.4)	1.44 (1.13-1.83)
6	≥9.0	114 (8.6)	348 (6.6)	1.39 (1.07-1.79)

HbA1c measurement before the index date, HbA1c measurements are regularly performed in the diabetic population, and median time between the index date and the last HbA1c measurement was short. This shows that the recorded HbA1c measurements provide a reliable and timely source for our analyses on the effect of glycemic control on the risk of VTE.[54] Our study population included a high proportion of patients with T2DM with HbA1c ≤ 7% (> 53 mmol/mol) who may have been healthier than the T2DM populations analyzed in other studies. Nevertheless, our population consisted of over 13′000 patients with T2DM, many of whom had HbA1c levels > 7% (> 53 mmol/mol). Therefore, we expect our results to be generalizable to those of other populations with T2DM and HbA1c levels > 7% (> 53 mmol/mol).

Intracellular pathway showing coagulation system in diabetes mellitus

Metabolic disorders disturb the physiological balance of coagulation and fibrinolysis, leading to a prothrombotic state characterized by platelet hypersensitivity, coagulation disorders and hypofibrinolysis.[56] Hyperglycemia and insulin resistance cause changes in platelet number and activation, as well as qualitative and/or quantitative modifications of coagulatory and fibrinolytic factors, resulting in the formation of fibrinolysis-resistant clots in patients with diabetes.[57] Coagulation and hemostasis involve interactions between tissue and coagulation factors as well as blood and endothelial cells, finally resulting in formation of fibrin clots stopping bleeding.

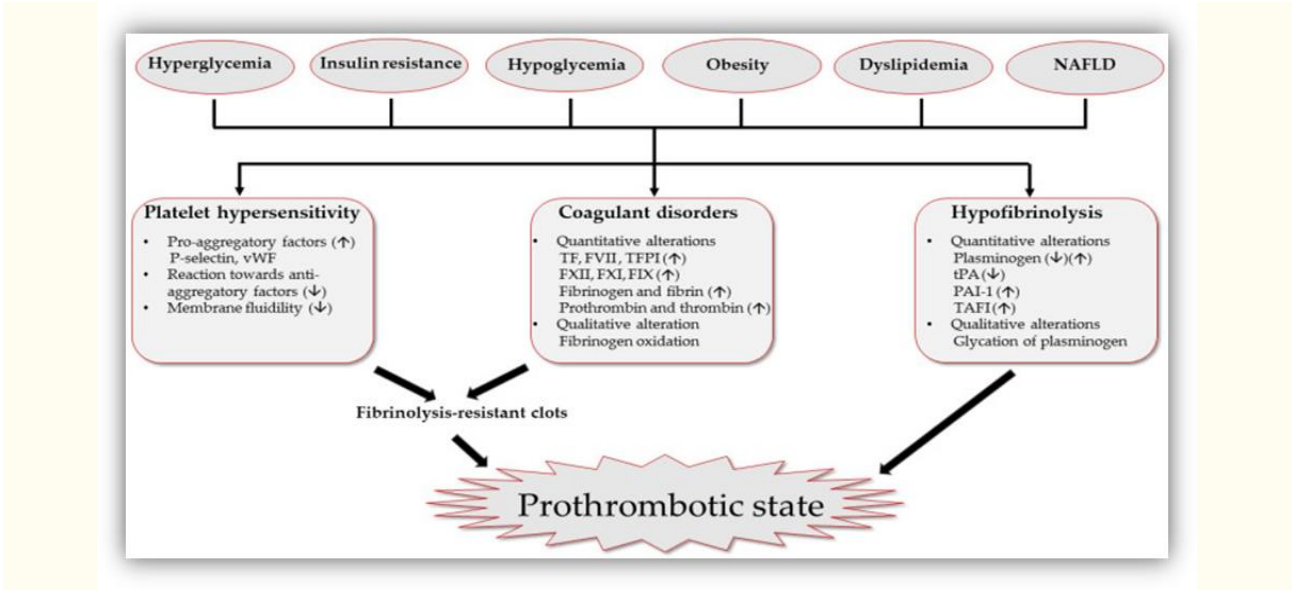


Fig. 01: Imbalance in between Coagulation and Fibrinolysis system in Diabetes mellitus leading to platelet hypersensitivity and coagulation factor disorders.

Platelet hypersensitivity

In physiological conditions, platelets circulate in the blood for five to seven days and constantly undergo a lifecycle from megakaryocyte separation to phagocytosis by macrophages, to maintain a normal platelet count of 150.000–450.000 per microliter.[58] After vascular injury, platelets are activated to aggregate, forming an occlusive thrombus and stop bleeding. Both increased platelet number and enhanced aggregation capacity, the latter referred to as platelet hypersensitivity, will contribute to a pro-thrombotic state. In patients with DM, over-activation of platelets (mainly attributed to

hyperglycemia and insulin resistance) plays a crucial role for pro-thrombotic events.

Platelet cellular changes in diabetics

Acute and chronic hyperglycemia up regulate the expression of adhesion molecules on platelet surface (e.g., CD31, CD49b and CD63), an effect that is reversible after optimizing glucose control. Chronic hyperglycemia increases expression of protease-activated receptor 4 in patients with DM, in turn promoting the release of activated platelet-derived micro particles (PMPs) via the Ca^{2+}- calpain pathway. Released PMPs then trigger the secretion of interleukin-6, a pro-thrombotic and pro-inflammatory mediator in diabetes.[59] Through glycation of membrane proteins, hyperglycemia also decreases the membrane fluidity of platelets and results in increased intracellular calcium influx, directly promoting platelet activation and aggregation. Hyperglycemia also impairs endothelial function by inducing inflammation and oxidative stress, thereby inhibiting synthesis and release of PGI_2 and NO, finally further promoting platelet aggregation.

Insulin resistance

Patients with T2DM had larger MPV and increased platelet generation compared to patients having T1DM; MPV correlated with HbA1c only in patients with T1DM.[60] Another study showed a positive correlation between MPV and homeostasis model assessment insulin resistance index. A possible underlying mechanism is a modified insulin signaling in platelets associated with insulin resistance: in healthy individuals, insulin binds with insulin receptors on platelet surfaces, leading to activation of downstream pathways, e.g., the tyrosine phosphorylation pathway and the inhibitory G-protein pathway.[61] The latter results in higher cyclic adenosine monophosphate (cAMP) generation and lower intracellular calcium inside platelets, thereby inhibiting their aggregation. Insulin resistance also reduces the sensitivity of platelets towards the anti-aggregator effects of NO and PGI_2, which in turn alters calcium influxes and promotes platelet aggregation. For instance, trim ethylamine N-oxide might directly increase the aggregation and adhesion capacity of platelet, and phenylacetylglycine facilitates platelet responsiveness and enhances thrombosis tendency.[62]

Quantitative and Qualitative alterations of coagulation factors

Thrombin is derived from prothrombin and is an essential factor that transforms fibrinogen into fibrin. In patients with DM, increased thrombin levels lead to enhanced fibrin generation and clot density, thereby contributing to the pro-thrombotic state or thromboembolism.

The extrinsic coagulation or Tissue Factor (TF) pathway is initialized with activation of tissue factor/Factor VIIa (TF/FVIIa) complexes and plays an essential role in thrombus generation. In T2DM, hyperglycemia and insulin resistance exert synergistic effects on the TF pathway, leading to increased pro-coagulatory activity and FVIIa consumption.[63] Several mechanisms are involved: hyperglycemia and hyperinsulinemia both directly promote the TF transcription in monocytes. Additionally, patients with diabetes are prone to constant inflammation, and one symptom is increased inflammatory biomarker levels (e.g., interleukins) in blood. The pathological process directly up regulates TF expression in endothelial and vascular smooth muscle cells, contributing to the hyper coagulation state in DM. Generation of advanced glycation end-products, glycated lipids or proteins formed during hyperglycemia, as well as reactive oxygen species enhance TF production through activation of the nuclear factor (NF)-κB inflammatory pathway.[64] Notably, recent studies highlight the role of micro-RNA (miR) in TF expression and diabetes-related coagulation dysfunction. For instance, miR-126, miR-19a and miR-181b are negatively associated with both TF protein and TF-mediated thrombogenicity in patients with diabetes. Further investigations showed that miR-126 and miR-19a both inhibit the TF expression in endothelial cells, and miR-181b reduced the generation of TF within monocytes.[65] These findings might explain in part the enhanced vascular TF activity in poorly controlled type 2 diabetes.

The intrinsic coagulation pathway involves sequential activations of FXII, FXI and FIX, and recent studies have reported dysfunctions of intrinsic coagulation associated with hyperglycemia and hyperinsulinemia in DM. In the Netherlands' Epidemiology of Obesity study, increases in FVIII (5.33%, 95%CI: 4.00–6.65), FIX (6.19%, 95%CI: 5.15–7.23) and FXI (2.11%, 95%CI: 1.20–3.02) were observed per mmol/L increase in fasting plasma glucose, and these associations remained significant even after adjusting for confounding factors such as age, sex and body mass index (BMI).[66] Increased synthesis of FXII, FXI and FIX in hepatocytes along with a shorter activated partial thromboplastic time (APTT) were observed in patients with impaired insulin sensitivity, probably mediated by a low-grade inflammatory reaction caused by insulin resistance.[67]

In short, patients with T1DM and T2DM are prone to thrombotic events based on a series of disorders, including platelet hypersensitivity, coagulation factor modifications and hypo fibrinolysis. Studies on the altered coagulation in DM suggest that hyperglycemia, insulin resistance and other comorbidities contribute to the hypercoagulable state.[68] Clinical studies strongly support the beneficial effects of glucose control, weight loss and lipid-lowering on coagulation dysfunctions, and glucose-lowering drugs, especially GLP-1 RAs and SGLT-2i's, tend to ameliorate diabetes related hyper coagulation. Although, sugar lowering drugs like metformin, thiazolidinedione's and sulfonylureas etc. are available in market which workout on decreasing platelet

aggregation by lowering tPA, fibrinogen, PAI-1, TF and by raising NO.

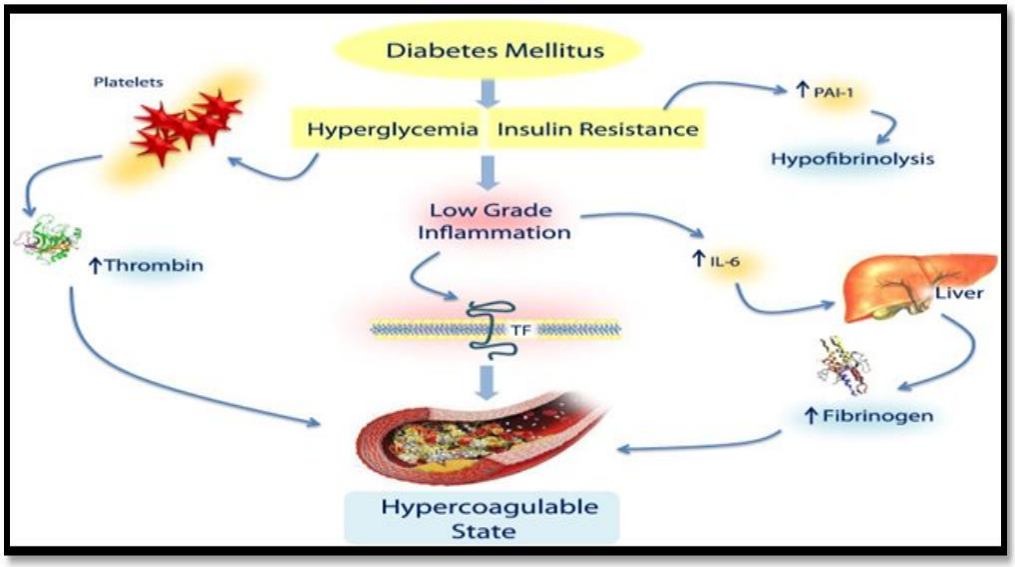


Fig. No. 02: Mechanistic scheme of coagulation, Fibrinolysis, anti-coagulation and anti-fibrinolysis.

Role of Metal ion in Embolism and Homeostasis

Metal ions play numerous roles in blood plasma, which include structural and catalytic functions. The plasma concentration of several metal ions is known to be altered in T1DM and T2DM. Ca^{2+} is an important regulator of coagulation. Ca^{2+} is released by activated platelets and is required for clotting to take place (in particular for tenase and prothrombinase complexes to function). Chelating agents that bind calcium (e.g., citrate and ethylenediaminetetraacetic acid) are common anticoagulants used when taking blood samples.[69] Several studies have found associations between high levels of calcium in the blood and risk of developing T2DM. Zn^{2+} is also released by activated platelets, as well as damaged epithelial cells and atherosclerotic plaques; it is also contained by neutrophils, lymphocytes and erythrocytes and may therefore be released at sites of injury (although this has yet to be confirmed). Zn^{2+} is involved in all steps of coagulation: pro-coagulatory, anti-coagulatory, pro-fibrinolysis and anti-fibrinolysis mechanisms, as well as platelet activation and aggregation.[70] Mg^{2+} can potentiate the activation of factor X by activated factor IX while in the presence of activated factor VIII, phospholipids and Ca^{2+}, the activation of factor IX by activated factor VII-tissue factor complex. Mg^{2+} also affects clot time by accelerating clotting at low concentrations and slowing or completely preventing fibrin clotting at high concentration (as it competes with Ca^{2+} for binding to coagulation factors.[71] Furthermore, Mg^{2+} shortens fibrin clot lysis time, possibly through an inhibition of PAI-1 in the presence of thrombin and vitronectin. Despite Cu^{+} and Cu^{2+} being essential cofactors of several coagulation proteins (e.g., coagulation factors V and VIII). Elevated dietary levels of copper in rats (which were reflected in copper concentrations in the liver) were found not to affect clot time when clotting was induced by thromboplastin and Ca^{2+} [72]

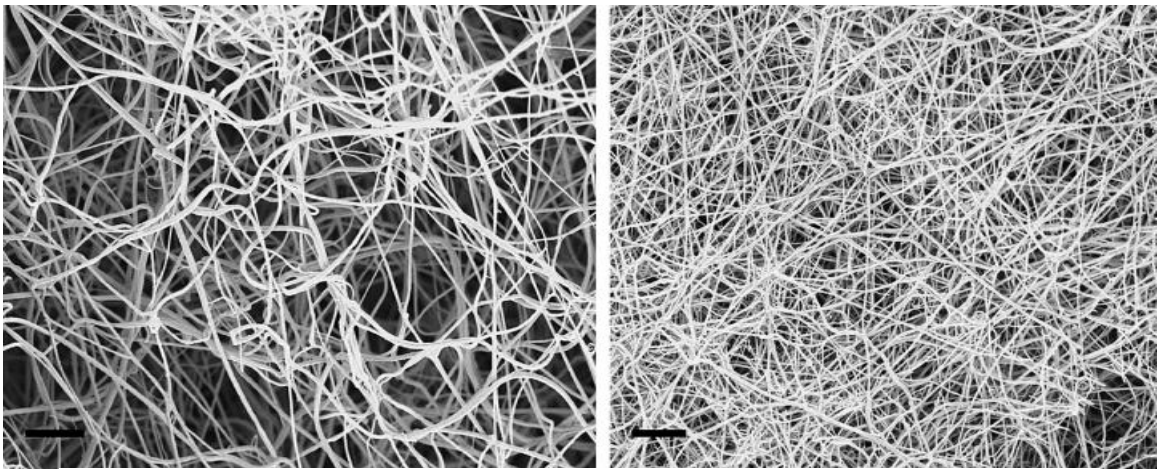


Fig. No. 03: A densely packed Fiber clot formed by fibrinogen glycation oppose fibrinolysis.

Herbal transdermal patches

Herbal transdermal patches had desirable properties and compatible, homogeneous, smooth, and compact blended ingredients. The herbal transdermal patches could control the release and skin permeation behavior. The transdermal patches containing *L. strychnifolium* extract are suitable for use in herbal medicine applications.[73] It has been found that drugs from herbal origin can be utilized with enhanced efficacy by incorporating in transdermal drug patches.[74] Transdermal drug delivery system (TDDS) thus offers a better route of delivery, reported to have better patient compliance. Transdermal drug delivery system is a most suitable system for a long term treatment or for a multi-dose treatment and this system also increases the bioavailability of drug by avoiding the first pass metabolism and increases the therapeutic efficacy of drug by reaching into the systemic circulation.[75]

The TDDS provides several advantages such as non-invasive, painless method of delivering drugs directly into the body, more effective approach to administer drugs that are broken down by stomach acids, provide controlled, consistent drugs distribution over long periods of time, fewer negative effects than oral drugs or supplements, easier to apply and remember, alternative for persons who are unable or prefer not to take drugs or vitamins orally, cost-effective.[76]

Phytogenic compounds for Diabetes and Thromboembolism

Herbal medicine is the best kinds of remedies not only to treat disorders but also have been used in the field of perfumery, nutraceuticals, fragrances, beverages, dyeing, and cosmetic industry. WHO have enlisted almost 21,000 herbal components that have established therapeutic benefits. All the herbal medicine and vegetables including various fruits contain lots of important phytochemicals which come into primary or secondary metabolites.[77] Many plants and plant-derived bioactive phytoconstituents have not yet been researched well. In order to explore and validate proper mechanistic pathways of pharmacological activities demonstrated by the reported antidiabetic phytochemicals, further investigations are warranted. Therefore, it is expected that in the next future phytochemicals-based drugs will be object of a growing interest for inflammation and oxidative stress-related diseases.[78]

Table No. 02: Current herbal phytochemicals research studies.

Sr. No.	Phytoconstituent	Animal/ Dose	NDDS (NPs)	Type of Model	Biomarkers involved	P'dynamics/ P'kinetics	Molecular Targets	Clinical Trials	Reference
1.	Berberine	Rats 75 mg/kg/oral	Berberine coated nano silver ameliorate	acetaminophen-induced diabetic rats	Inhibition of proinflammatory factor & NF-kB factors.	protective efficacy of BBR-AgNPs on APAP induced hepato-renal injuries in diabetic rats	high immunoreactivity of nuclear transcription factor (NF-kB)	double-blind, randomized, placebo-controlled, for 28 days on 50 subjects lower serum LDL-cholesterol concentrations	[79]
2.	dandelion	male Wistar rats 694 mg/kg	Dandelion leaf and petal phenolic fractions gold nanoparticle	noradrenaline-induced vascular contractions of thoracic arteries	decreased protein carbonylation, CH, lipoprotein combine index, atherogenic index of plasma, upregulated K_{ATP} channels	dandelion leaf fraction augmented acetylcholine-induced vasodilation and upregulated K_{ATP} channels	Modulator of antioxidant and lipid profile status in *in vivo* study	-	[80]
Sr. No.	**Phytoconstituent**	**Animal/ Dose**	**NDDS (NPs)**	**Type of Model**	**Biomarkers involved**	**P'dynamics/ P'kinetics**	**Molecular Targets**	**Clinical Trials**	**Reference**
3.	Piceatannol	Mouse 100 mg/kg	Silicon oxide nanoparticles	Silicon dioxide nanoparticles induce insulin resistance	activation of the NF-κB and MAPK pathways, expression of inflammatory cytokines	Silicon dioxide NPs induced IR through ER stress and generation of ROS	Inhibited SiO_2 NP-induced ROS production	90 days in a randomized, double-blind, parallel-group, placebo-controlled study	[81]
4.	Sterculia foetida	Rats 30-350 mg/kg	Metal based nanoparticles	Silver nanoparticles	bioavailability, and toxicological parameters activated	low absorption, and safety	Insulin signaling, AMPK	Double blind placebo controlled study	[82]
5.	Cinnamon	Rats/200-400 mg/kg	Gold nanoparticles	Cinnamon extract Gold nanoparticles	increase LDL receptor mRNA levels	presence of AuNPs, the fluorescence peak of eosin is quenched	hydroxyl and carboxylic groups which facilitate the complexion of Au^{3+} ions	A randomized control clinical trial	[83]
6.	Bitter Melon	Rats/200-500 mg/kg	Silver nanoparticles	Bitter melon extract silver nanoparticles	limited hemolysis of RBCs and excellent antibacterial activity against non- and drug-resistant bacterial strains	BG-AgNPs possessed higher scavenging ability and superior reducing power due to the high phenolic content	BG significantly increased SOD and decreased fasting and postprandial blood glucose levels.	A single blinded randomized controlled Trial	[84]

Herbal liposomes therapeutic targeting strategies

Genus panax: *Panax ginseng* (Meyer) belongs to the family Araliaceae, are used worldwide as medicinal and functional herbs. Numerous publications over the past decades have revealed that *P. ginseng* contain important bioactive ingredients such as ginsenosides and exert multiple pharmacological effects on nervous system and immune diseases. Ginseng contains more polysaccharides and amino acids, saponins, volatile oil, and polyacetylenes. Regarding pharmacological effects, ginseng exhibits better protective effects on cardiovascular disease, nerve disease, cancer, and diabetes mellitus, thromboembolic disorders. GPS-Lips (Genus panax saponins) could significantly increase the membrane permeability of PQS and promote its absorption in the small intestine. From the experimental results, it could be known that liposome technology could effectively improve the absorption of PQS in the small intestine.[85]

Panax notoginseng: *P. notoginseng* protects endothelial functions in diabetes and the underlying mechanisms remain to be explored. *P. notoginseng* contains several chemical components including saponins, which are commonly believed as the major bioactive ingredients. *Panax notoginseng* (Burk) F.H. Chen is a widely used medicinal plant in East Asian countries for thousands of years.[86] Radix Notoginseng, also named as Sanqi or Tianqi in Chinese, is the dried root of *P. notoginseng*, which is the main part used for medical purpose, while the leaves, fruits, and flowers liposomes possess better medicinal value than the other dosage forms.

Liriope muscari: The closely related genera *Liriope* and *Ophiopogon* (Asparagaceae), collectively known in English as liriopogons, have similar therapeutic uses in treating cough, rheumatoid arthritis, and cleaning heat. *Liriope* Lour. and *Ophiopogon* Ker Gawl. are two closely related genera, collectively known as liriopogons. They comprise a total of some 84 species and are indigenous to Asia, with many species having been traditionally used as medicines in China, with the common label 'maidong' or 'mai men dong' (for the tuberous roots)-including *Ophiopogon japonicus*, together with *Liriope spicata* and *L. muscari* as alternative sources. Different species of liriopogons exhibit similar phytopharmacological properties; they are rich in saponins, flavonoids and polysaccharides, which have been linked to relevant pharmacological activities, such as cardiovascular protective, anti-inflammatory, immunomodulatory, anti-cancer and anti-diabetic effects. It was observed that LML produced best effective profile for drug release.[87]

There are plethora herbal drugs which are available in our wild regions. These are *Ruscus aculeatus, Ophiopogon japonicas, Polygala fallax, Aesculus hippocastanum L, Stevia rebaudiana Bertoni, Zingiber officinale, Phyllanthus emblica, Azadirachta indica, Allium sativum, Punica granatum, Withania somnifera, Curcuma longa, Crataegus monogyna, Berberis vulgaris, Honey, Osmanthus fragrance, Gardenia jasminoides, Inula racemosa.* These herbs were traditionally used for Diabetes and Thromboembolic disorders simultaneously and their various dosage forms are available in the market after a vigorous regular research but still it was observed from the literature survey that liposomal dosage forms are better in their penetrations, targeted action, effectively, potency, economically and can cross barriers easily comparative to another dosage forms or formulations.[88]

Conclusions and Future prospects

Nowadays, Diabetes mellitus and thromboembolic disorder became one of the most challenging disorder amongst world. A very limited marketed formulations for the same are still available which will be targeted, site specific, more effective, slowly sustainable, safe, economic for layman people. Patches are easy to use, offer various rug delivery routes, bypass the first pass effects, reduce the risk of under and over dosing, consistent rug level, halted by removal and even there will be no restriction to the patients for their any activity. Moreover, herbal drugs are natural entity which react favorably to the body, cheaper and lesser possible side effects will be there. Here, current article targeted to give focus for the scientists to prior for herbal patches to challenge such disorders. Treatment will approve promising with growing scientific medicinal market for new discoveries in concerned field.

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