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Quercetin in anti-diabetic research and strategies for improved quercetin bioavailability using polymer-based carriers – A review

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With numerous pharmacological and biological functions bio-flavonoids gain appreciable attention in diabetes and other therapeutic research. Among several beneficial flavonoids quercetin exhibits impressive hypoglycaemic effects, with significant improvement, stabilization of long sustaining insulin secretion and regeneration of human islets in the pancreas without producing serious health hazards. However, in oral delivery poor solubility, stability in biological milieu, low permeation, short biological half-life, and insignificant bioavailability limit its wide application in anti diabetic research. Over last few decades polymeric carrier systems have been widely studied for improvement of quercetin bioavailability. Natural polymers are more preferred in this regard due to possessing several favourable properties like biocompatibility, biodegradability, mucoadhesiveness, non-immunogenicity and non-toxicity. This review focuses on quercetin in anti-diabetic research and the progress in the synthesis of polymer-based formulations for efficient quercetin delivery, with an emphasis on producing improved biological efficacy of the flavonoid. Diabetic complications, probable mechanism of quercetin absorption, regulation and anti diabetic effects, obstacles to produce desired bio-efficacy and possible remedies are also brought into focus. To overcome these barriers encapsulation of quercetin within various safe polymeric vehicles are discussed. Further, this review shades light on enhancing the efficacy of quercetin in novel ways for successful diabetes treatment and others.

1. Introduction

The most common endocrinopathy, diabetes is dramatically rising at an alarming rate globally over the past few decades[1] and is expected to hit about 439 million people by 2030.[2] Diabetes has become sixth most common cause of morbidity and mortality affecting the youth and middle aged people. It is a complex metabolic disorder, which results due to total or relative deficiencies in insulin secretion or defective insulin function. The insulin is a peptide hormone, secreted by pancreatic beta cells of islets of Langerhans and triggers glucose uptake of the cells in turn controls blood sugar level. In the absence of insulin, (destruction or malfunction of pancreatic beta cells) blood glucose levels would rise to dangerously leading to a condition termed hyperglycemia. Along with the high blood glucose level disturbances of carbohydrate, lipid and protein metabolism[3] are also very common features of diabetes. Severe other health problems like retinopathy, neuropathy, nephropathy, angiopathy, atherosclerosis, and impaired wound-healing[4] also encountered in long term manifestation of diabetes. Therefore awareness on this critical issue has led researchers to a vast discovery of new medications as well as natural compounds from herbal sources avoiding the side effects of orthodox anti-diabetic drugs (insulin and oral hypoglycemic agents).[5]

Since ancient times natural compounds from various plants and several dietary constituents are in practice some of which have been reported to possess pronounced anti-diabetic properties. Different countries (India, America, and China) all over the world[6] have been reported to use these plant based components for prevention or management of diabetes. These active ingredients from herbal sources not only possess therapeutic values, i.e. hypoglycemic activity, antioxidant property but also can combat hyperglycemic episode and other health problems of diabetes in a safe way. An effective control of blood sugar level is the fundamental step for prevention or reversing diabetic complications in patients of both type 1 and type 2, therefore improving the quality of life.[7] Thus management of diabetes with traditional insulin therapy or synthetic oral hypoglycemic drugs (OHDs) administration may result in serious side effects and sometimes fails to prevent typical diabetes-related health complications in many individuals. Thus the focus has now been shifted towards herbal remedies[8] as a better alternative approach in a more effective way, producing minimal or no side effects in clinical practice in a cost effective way compared to synthetic OHDs.[9] Natural compounds such as triterpenes, flavonoids, sterols, coumarins, alkaloids have drawn considerable attention of

researchers in this regard. Still extensive research work is required to explore the hidden wealth of potentially useful natural compounds for effective diabetes control and treatment.

The bio-flavonoids are most abundant in nature (present in vegetables, nuts, fruits, seeds, stem, flowers and tea)[10] and comprise an important group of phenolic secondary plant metabolites. The polyphenolic compounds of nature are classified, on the basis of their well defined chemical structure like flavonols, flavones, flavanones, isoflavones, catechins, anthocyanidins and chalcones.[11] All are well-established for their multi-directional biological activities and now it is widely accepted that dietary polyphenolics have beneficial effects in protecting chronic diseases like cardiovascular diseases, cancer and diabetes mellitus.[12] A number of investigations have already been conducted to explore the hypoglycemic effects of flavonoids[13] other beneficial effects against manifestation of the disease, either by increasing the capacity to avoid glucose absorption or by improving the glucose tolerance. It has also been suggested that flavonoids can act per se as insulin mimetics or secretagogues. Probably flavonoids influence the pleiotropic mechanisms to attenuate the complications related to diabetes.[14] Again, in peripheral tissues, glucose uptake stimulation and expression of the rate-limiting enzymes in carbohydrate metabolism are reported to be regulated by the flavonoids.[14]

Quercetin (3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-4H-chromen-4-one) is one of the most potent, frequently studied dietary flavonoid, which commonly found in onion, apple, berries, many nuts, seeds, barks, flowers, tea, brassica vegetables and leaves.[15] Generally the average daily intake of polyphenols varies in the range of 10-100 mg depending on the food habits.[16] Quercetin is reported to have versatile biological functions including anti-diabetic, anti-carcinogenic, anti-inflammatory, anti-ulcer effects, anti-allergic activity, cataract prevention, and anti-viral activities.[17, 18] Moreover, it helps to inhibits lipid peroxidation, aggregation of platelets and capillary permeability too. Being a potent anti-oxidant, it scavenges free radicals directly[19] inhibits xanthine oxidase, alters anti-oxidant defence[20] and inhibits lipid peroxidation.[21, 22] However, low aqueous solubility, poor permeability, instability in physiological medium,[23] short biological half-life, extensive first past metabolism before reaching the systemic circulation[24] resulting in low oral bioavailability have limited the wide application of quercetin in pharmaceutical field. Now-a-days, with advancement in biotechnology, scientist has attempted to circumvent these problems by entrapping quercetin into biodegradable polymeric carriers (hydrogel beads, micro or nanoparticles) for improving the solubility, bioavailability and control release of the compounds within biological system.

For designing efficient vehicles capable of overcoming the barriers, both natural and synthetic polymers in the form of hydrogels, beads, microspheres, nanoparticles,[25] and other different formulations are being used. Natural polymers like pectin, guar gum, alginate, chitosan and synthetic polymers such as poly-D, L-lactide (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(phosphoesters), poly(ϵ-caprolactone) (PCL), and others have shown better efficacy for quercetin carriage.[26-30] Polymeric carrier systems must be biodegradable, nontoxic and biocompatible, non-immunogenic, easy to synthesize and characterize, non-mutagenic (ability to be fully excreted from the system after bio-absorption) and preferably water soluble and inexpensive.[31] Molecular weights, solubility, and structure of polymers are other essential parameters which also greatly influence the drug delivery. Therefore, the current review mainly focuses on the polymeric carriers for efficient delivery of quercetin for the treatment of diabetes.

2. The problems in current diabetic therapy and flavonoids as an alternative

Till date insulin is the most effective treatment of diabetes in spite of availability of various oral anti-diabetic agents like biguanides, sulfonylureas, α-glucosidase inhibitors glinides etc which are frequently used as monotherapy or in combination to achieve improved glycemic regulation. Parenteral insulin therapy has poor patient compliance due to needle phobia, pain, skin bulges, allergic reaction, common infections, and stress generated from the difficult and long term regimen of insulin therapy.[32, 33] Moreover, compromise with said inconveniences does not solve the problems of hypoglycemic episodes. On the other hand non-parenteral routes of insulin (ocular, vaginal, rectal, oral (buccal, gastrointestinal (GI), and sublingual), nasal) also suffer from producing desired bioavailability to control the blood glucose level. Hypoglycemia continues to be a significant issue despite easier glucose monitoring options. Again non-physiological delivery to the wrong target tissues, poor pharmacodynamics, non-ideal treatment initiation and weight gain are associated with parenteral insulin.[31] The prevalence of the complications is found to be greater among the lower socio-economic people because of several behavioral factors and direct or indirect costs of the insulin therapy. Again, oral anti-diabetic agents have significant adverse impact on the health of diabetic individuals. Therefore the available current therapies are not always satisfactory to the patients regarding euglycemic episode and later stage of diabetic complications. Therefore, the overall scenario urges an implementation of cost-effective and efficient preventive measures to combat diabetes and reduce the high morbidity and mortality.[34]

Numerous traditional herbal treatments are potentially useful bio products are increasingly sought for effective control or management of diabetes. Since ancient time in India, indigenous remedies have been in practice for diabetic treatment.[35] The ethnobotanical information suggests existence of approximately 800 plants that may have significant anti-diabetic effects.[36, 37] Flavonoid, bioactive phenols with low molecular weight possessing anti-diabetic activities have been well studied as promising and significantly attractive herbal substances to enrich the current therapy of diabetes in a safe way. This particular section of the review embodies the information on promising anti-diabetic effects of certain bio-flavonoids. Numerous flavonoids are reported to have significant anti-hyperglycemic effects such as prunin, chrysin,

quercetin, silymarin, isoquercetrin, rutin, genistein derivatives, isoorientin, kaempferol[14] as shown in Table 1.

3. Quercetin

Extensive researches on natural flavonoids with anti-hyperglycemic activities have illuminated a new path with promising developmental approaches in diabetic research. Among several anti-diabetic flavonoids quercetin is one of the most frequently studied and widely distributed dietary flavonoids[15] used for treatment of diabetes and its associated complications. Quercetin (3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-4H-chromen-4-one) consists of 3 rings and 5 hydroxyl groups, where the two aromatic rings A and B, are linked by oxygen containing six membered heterocyclic ring C. Quercetin is synthesized by the glands located on the surface of leaves, flowers or fruits of the plants. It may be transported to different parts of the plants and stored in vacuoles.[47] Fig. 1 depicts the structure of quercetin and selected foods and beverages in which quercetin is found.[48] In spite of having of five –OH groups in the structure, quercetin has both lipophilic and lipo-hydrophilic derivatives. Hydrophilicity quercetin derivatives can be improved by glycosylation of at least one hydroxyl groups present in it. With increasing interest in quercetin and its derivatives in biomedical application we mainly focus on the anti-diabetes properties of quercetin in this review.

Generally, it is reported that quercetin exerts its functions by acting on liver, muscle, pancreas and small intestine (Fig. 2). It is reported to have higher antioxidant activity compared to other well-known antioxidant molecules (ascorbyl, trolox and rutin)[49] due to the number and positions of the free hydroxyl groups in its structure.[50] In muscles, quercetin accelerates the function of glucose transporter 4 (GLUT 4) and insulin receptor which in turn results in elevated glucose uptake and normal blood glucose level is maintained (Fig. 2). Again glucokinase activity in liver is increased by quercetin and results in higher glucose storage leading to controlled glycemia. A study has provided evidence that quercetin may have a protective effect against β cell damage by exerting its anti-inflammatory, antioxidant effects and anti-apoptotic effects. It facilitates regeneration of β cells by stimulating the ductal stem cells to regenerate and differentiate into pancreatic islet cells.[51] In small intestine quercetin lowers the activities of maltase and glucose transporter 2 (GLUT 2) leading to decreased glucose absorption in the intestinal milieu in turn aids normal glycemia as presented in Fig. 2. In spite of possessing such myriad biological activities[52] still the therapeutic use of this quercetin is hindered due to its low bioavailability[53] resulted from poor solubility, instability in biological milieu, poor permeability through intestine, extensive first past-pass metabolism before reaching the systemic circulation[54] and rapid elimination following oral administration.[55] Therefore, scientists are now trying to evade these said barriers in order to facilitate efficient colon targeting, sustained quercetin delivery systems retarding maximum loss in stomach and intestine while ensuring complete release in the colon. An adequate control in intestinal residence time along with the drug release patterns can significantly improve bioavailability of quercetin and finally enhance the efficacy of the medical treatment. In order to improve its solubility researchers have attempted to synthesize water soluble derivatives,[56] addition of dimethyl sulphoxide (DMSO)[57] and complexation or entrapment[58-60] with suitable carrier molecules.

4. Polymers - in quercetin delivery

Progress in biotechnology has enabled the consequent development of alternatives way using polymeric carriers to cross the hurdles for producing better result in biomedical research. Polymers from both natural and synthetic source are come in to focus in this regard. Natural polymers like alginate, pectin, guar gum, cellulose, chitosan and its derivatives, gum arabic, starch and its derivatives, carrageenan, xanthan gum, gelatine, albumin, casein, soy proteins etc. and the synthetic polymers such as PLA, PLGA, poly(phosphoesters), PCL, poly-α-cyanoacrylate alkyl esters, polyvinyl alcohol are frequently used in biotechnology and biomedical research. However, successful quercetin delivery demands biodegradable, biocompatible, non-toxic and non-immunogenic carriers, which is easy to synthesize, characterize, and preferably inexpensive and water soluble.[31] The structures of the polymers, degree of deacetylation, respective molecular weights, solubility are must be well studied as essential parameters. Formulations prepared using all of these polymers could overcome the problems and improve its delivery by increasing the residence time in the GI tract, which in turn could help in providing better oral bioavailability of quercetin. Moreover, mucoadhesion would considerably favour a specific site localization of the dosage form without producing local irritation.[61-63]

Considering the fundamental requirements in drug delivery the natural polymer, chitosan, linear and partly acetylated (1→4)-2-amino-2-deoxy-β-D-glucan[64] has gained appreciable attention for drug delivery application. It can be found by N-deacetylation of chitin a major component found in shells of crustaceans and is of low cost.[64] Being biodegradable, biocompatible, low-toxic, non-immunogenic and mucoadhesive in nature chitosan favours its wide applications in biomedical field and drug delivery research. Presence of different functional groups (amino and hydroxyl groups) on its structure makes chitosan chemically active, facilitating effective encapsulation of several bio-molecules (drugs, flavonoids, proteins, DNA). Moreover, being a renowned mucoadhesive polymer, chitosan helps to prolong mucus binding time of the drug molecules and transiently open the tight junctions between the epithelial cells, enabling good drug transport in a sustained fashion. Regarding the toxicity, an assay has revealed LD50 of chitosan in mice exceeding 16 g/kg[31] and chitosan is easily digested after oral administration by the chitosanase enzyme secreted by microorganisms in the intestine. Therefore, combination of chitosan or modified chitosan with particulate system to protect the quercetin against gut degradation, ensuring improved bioavailability of quercetin will add benefit to a better anti-hypoglycemic research. Apart from chitosan numerous other polymers can be introduced in quercetin anti-diabetic research. Some of these polymers and their essential features are discussed below.

Alginate is natural, water soluble linear polysaccharide, containing varying amounts of 1,4-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues. It is extracted from brown seaweed. It is a very popular pH sensitive polymer as it shrinks in lower pH,[65] enabling retention of encapsulated drug in the stomach and protecting it against enzymatic deactivation. Biodegradability, biocompatibility, low toxicity, low immunogenicity and good mucoadhesion also facilitate its myriad application in drug delivery.

Pectin is an important water-soluble polysaccharide of plant cell walls. It is of appreciable interest in food industry as a gelling agent and a stabilizer in fruit jellies, yogurt, jams, drinks and lactic acid beverages.[66] It is a linear polymer of D-galacturonic acid units and their methyl esters are connected with a-(1,4)-glycosidic bonds. The linear chemical structure of pectin is partly interrupted by (1,2)-linked side chains consisting of L-rhamnose residues and few other sugars.[67] Polymeric formulations incorporating pectin could be employed to successfully prolong release of quercetin for diabetic treatment.

Another natural non-ionic polysaccharide is guar gum derived from the seeds of Cymompsis tetraganolobus belongs to family: Leguminaceae.[68] It consists of a linear backbone of β-1,4-linked d-mannose units (M). The presence of randomly attached α -1,6-linked galactose units (G) helps to solubilise guar gum. Guar gum is hydrophilic and swells in cold water and has an ability to produce a highly viscous solution even at very low concentrations because of its high molecular weight and extensive intermolecular association (entanglement) through hydrogen bonding. This gelling property facilitated drug delivery application by retarding the unwanted release of the drug molecules in the upper portion of GI tract and releasing it in the colon.[69] Therefore, guar gum could serve as an efficient carrier of quercetin in anti-diabetic treatment.

Xanthan gum is a naturally occurring high molecular weight hydrophilic polymer. This extracellular hetero-polysaccharide has cellulose like back bone and is produced by the fermentation of the gram negative bacterium *Xanthomonas campestris*.[70] It consists of 1,4 linked β-D-glucose residues, having a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D-mannose which are attached to alternate D-glucose units of the main chain. The terminal D-mannose residue of the polysaccharide may provide a pyruvate function, but this may vary according to the strain of the bacteria and fermentation conditions. In the side chain a non-terminal D-mannose unit is present which carries an acetyl function.[70] The presence of both glucuronic acid and pyruvic acid groups in the side chain has provided an anionic character to this polymer. Until recently this polymer has been used only as thickening, emulsifying or suspending agent in water based systems. Now, it has been explored broadly in biomedical research, especially in sustained drug delivery. Xanthan gum is reported to provide time independent release kinetics which added special advantage of compatibility and inertness. The release of soluble drugs from xanthan gum formulations may occur mainly by diffusion. Moreover, it is recommended for use in both alkaline as well as acidic media.[71] Furthermore, it has been demonstrated that xanthan and it is demonstrated to maintain constant drug plasma levels *in vivo* models also.[72]

For last few years aliphatic polyesters like PCL, PLA and polyglycolide (PG), have also been extensively studied in biomedical research such as drug delivery, flavonoid delivery, tissue engineering and implants owing to their biodegradability and biocompatibility.[73, 74]

5. Polymeric carriers in successful elevation of quercetin oral bioavailability

Quercetin oral bioavailability is poor which hinders its wide application in biomedical research. Quercetin undergoes pre-and post absorptive metabolism through the GI tract passage (stomach → small intestine → cecum → colon). Usually, following its oral intake quercetin glycosides from diet are slightly absorbed via the intestinal epithelial cells and by the action of specific transporter systems most of them return into the GI tract. The flavonoid glycosides get rapidly hydrolysed in the small intestine or by the activity of the intestinal bacteria in the colon they generate the quercetin aglycones. Further Phase II enzymes of the intestinal cells and liver cells facilitate the metabolic conversion of this molecule to form glucuronidated or sulfated conjugates.[75] As a result a little fraction of quercetin is freely obtained in the systemic circulation. The glucuronide form and metabolites of quercetin (isorhamnetin and kaempferol) are mainly found in blood. Afterwards, quercetin conjugates exclusively circulating in the bloodstream are reported to be excreted via urine by the ingestion of quercetin glycoside-containing food. Though mechanism for the uptake and efflux of quercetin in target organs is not very clear. However, a probable mechanism of absorption, translocation and excretion of dietary quercetin is presented in Fig. 3. After oral administration, quercetin is reported to retain in the large intestine for approximately 6 hrs. But it readily becomes chemically unstable, especially in aqueous alkaline medium of the GI tract. This may occur possibly by the attack of hydroxyl ions on the C-ring of quercetin molecules.[76] Unless protected, the bioavailability of quercetin is usually less owing to its poor permeability, poor solubility, instability, and extensive fast metabolism. With remarkable progress in medical biotechnology, development of effective quercetin delivery system for better diabetes research has become a great challenge for scientists. Several polymeric formulations, colon-targeted delivery device, nanosuspension, lecithin-based novel cationic nanocarriers, solid lipid nanoparticles (SLNs), quercetin–phospholipid complex, micelles are extensively investigated in this regard.

In brief, the delivery system should fulfil the some essential criteria like:

i. Protect to the quercetin in upper GI tract (stomach and intestinal) while releasing it at colon region i.e. a pH sensitive behavior.

ii. Release ought to be 'site specific', i.e. close to absorption surface to avoid degradation of the active molecules.

iii. Prolong sustained release profile from the polymeric formulations.

iv. Release should be controlled to obtain significant bioavailability in physiological condition.

v. The vehicle for drug delivery should be biocompatible biodegradable, non toxic and non immunogenic to ensure complete safety after its delivery in animal system.

To summarize, a multi-headed carrier to slay the multiple hurdles of anti-hyperglycemic research with effective strategies to reach the ultimate goal is required.

Since last decade polymer based nanocarriers, polymeric micelles; drug polymer conjugates have been implemented in quercetin delivery owing to their robust structural organisation imparting proper stability though GI tract transit. Moreover, the hydrophilicity and the hydrophobicity within the polymeric carrier system can be adjusted accordingly to accommodate various drug molecules. Further, assurance of effective protection against unwanted drug released from the formulations till it reaches systemic circulation bypassing several physiological barriers is essential in successful drug delivery. Polymeric particles (nanoparticles) show preferential uptake via specialized Peyer's patches (microfold cells or M cells) and the isolated follicles of the gut-associated lymphoid tissue of the GI tract. The nanoformulations can readily cross enterocytes via transcellular transport after reaching the apical membrane of the intestinal cells. Finally these nanoparticles can enter the lymphatic vessels or the blood stream by the process of exocytosis. Moreover, particles having less than 500 nm diameters are reported to be easily internalized through both caveolae and clathrin-mediated endocytosis.[77] Again, cationic polymeric formulations show an added advantage of getting protection against endolysosomal degradation within the entercytes. Considering several advantages like enhanced solubilising power, small size and providing superior stability over surfactant micelles polymeric micelles are also successfully employed in oral drug delivery. To summarize, polymeric particulates furnish numerous advantages like small size (within micro or nano range), effective capability for encapsulating flavonoids, drugs etc, ability to protect drugs from enzymatic degradation in the adverse GI tract environment, enabling their easy transport and internalization through the intestinal epithelial cells or colon, and in turn improve better pharmacokinetics and bioavailability after administration.[78] In this particular section, we will discuss different polymeric (especially chitosan and other bio-polymers) formulations (nanoparticles) prepared and evaluated for quercetin delivery with special reference to anti-diabetic research. Fig. 4 shows various possible mechanisms of enhanced absorption bio-flavonoid quercetin via polymer-based carriers.

Onset of the polymeric formulation approach in quercetin delivery, with its biodegradability, better loading efficiency, non toxicity, prominent focus has been on generating improved bioavailability of the drug to exert desired effects in the body. In 2014, Caddeo et al.[79] proposed preparation and utilization of chitosan/xanthan gum microparticles to elevate the oral bioavailability of quercetin by optimizing the release in the colon. Previously, it was also shown that[80] multiparticulate tablet of liposomes and chitosan–xanthan gum complex were able to bypass the stomach and successfully delivered anti-inflammatory phycocyanin to the colon following oral administration. The spray-dried system exhibit good drug retention until it reached the colon.[80] The prepared microparticles showed significant quercetin loading with approximately 5 mm size and almost smooth spherical structure. In order to prevent acidic degradation in the stomach and to ensure controlled release in the colon quercetin loaded microparticles were compressed into tables and further coated with Eudragit®. The tablets showed pH responsive release of quercetin in the colonic environment following non-Fickian mechanism of release. Therefore chitosan/xanthan gum microparticles compressed tables could be a promising oral dosage form for successful quercetin delivery to the colon in treating diabetes and its related health problems. Further, Hazra et al.[26] investigated the potentialities of chitosan-coated alginate microspheres as favourable controlled oral dosage form for the delivery of hydrophobic flavonoid quercetin. The formulations showed excellent drug entrapment efficiency of ~80% with significant pH sensitive swelling index and drug release at simulated gastrointestinal media. Absolute retention in quercetin release was noticed in gastric fluid (pH 1.2) whereas sustained drug release profile was documented in pH 7.4 buffers. Furthermore, scanning electron microscopy (SEM) study has confirmed the smoothness of polymeric microspheres. Therefore, chitosan-coated alginate microspheres could serve as a cost effective device for successful administration oral quercetin increasing its bioavailability.

Zhang et al.[81] investigated quercetin-loaded chitosan nanoparticles were prepared by the ionic gelation of cationic chitosan with tripolyphosphate (TPP) anions to enhance oral bioavailability of the flavonoid. The study successfully revealed uniform, smooth surfaced, ellipsoidal shaped nanospheres having ~ 76.58 nm particle size. Moreover antioxidant activity of quercetin loaded particles also indicated that chitosan nanoparticles were useful in improving quercetin oral bioavailability. Again another report showed utilization of chitosan-lecithin nanoparticles for topical administration of quercetin increasing its bioactivity for treatment of several skin related problems like cutaneous oxidative stress and inflammation etc.[82] In the study nanoparticles were prepared containing D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) in order to improve quercetin solubility, entrapment efficiency, absorption and stabilization of the prepared nanocarriers. The nanoparticles showed mean particle size of ~ 95.3 nm, with 48.5% and 2.45% of quercetin encapsulation efficiency and drug loading, respectively and almost spherical shape under transmission electron microscopy (TEM). Further, *in vitro* study with excised mice skin demonstrated that nanoparticles were able to markedly enhance the cumulative quercetin accumulation in the dermal and epidermal tissues within 12 hrs of application compared to quercetin solution alone. The *in vivo* experiments also successfully showed interaction between chitosan-lecithin nanoparticles and the skin surface. The morphological alteration of the stratum corneum and disrupted close conjugation of the corneocyte layers facilitated increased permeation and

accumulation of quercetin into the mice skin. Therefore, the formulation of chitosan-lecithin nanoparticles showed a promising carrier for topical delivery of quercetin.

Apart from chitosan several other polymeric formulation approaches have been investigated for successful delivery of quercetin. In, 2011 Gulati et al.[83] prepared hydroxy propyl methyl cellulose/alginate microparticles by ionotropic gelation method for quercetin administration. The polymeric beads showed 0.726 mm to 1.179 mm size with 16.62% to 72.47% of quercetin entrapment efficiency. The *in vitro* release profile revealed that the bead formulations could provide controlled release of encapsulated quercetin. Therefore these formulations could serve as promising carrier for oral quercetin delivery. Sahu et al.[84] described preparation of quercetin loaded ethyl cellulose nanoparticles by nanoprecipitation and evaluated their efficacy in tropical quercetin delivery. The size range of the nanoparticles was around 228 nm with significant (51-53%) quercetin entrapment and loading (~34%) efficiencies, respectively. Being sub micron in size the colloidal carriers were able to enhance drug penetration through subcutaneous layers. Therefore, ethyl cellulose nanoparticle system could be a good alternative for improved quercetin delivery.

Another important study was conducted by Tan et al. in 2012[85] for delivering quercetin perorally using nanomicelles, prepared from diblock copolymer of polyethylene glycol (PEG)-derivatized phosphatidylethanolamine (PE). The size of the nanomicelles varied between 15.4 to 18.5 nm, with significant incorporation (~ 88.9%) of quercetin. Furthermore, the quercetin nanomicelles were stable in simulated gastric (pH 1.2) and intestinal (pH 7.4) fluids. No apparent toxicity was documented in animal models (intestinal epithelium). Though in this study nanomicelles were specially developed for oral anti cancer treatment, but these formulations could also be employed as potential delivery system of quercetin for anti-diabetic treatment. Recent investigations by Curcio et al.[86] demonstrated synthesis of nanoparticulate device for the controlled release of quercetin to improve its water solubility and instability in physiological medium. Quercetin imprinted nanospheres were successfully prepared exploiting the non-covalent imprinting approach. The methacrylic acid (MAA) was used as functional monomer and ethylene glycol dimethacrylate (EGDMA) as a crosslinking agent. The imprinted nanoformulations showed an average particle size of ~ 83 nm, with significant quercetin encapsulation and a well controlled release in pH 7.4. The cytotoxicity assay confirmed that these polymeric nanospheres do not interfere with the cell viability. Therefore imprinted nanospheres have enlightened a new path for effective quercetin delivery.

Zheng et al.[87] have made a comparative study with three β-cyclodextrins (β-CD) on the chemical stability and water solubility of quercetin following oral delivery. To elucidate the complexation mechanisms with quercetin they have used unsubstituted β-CD, hydroxypropyl-β-CD (HP-β-CD), and sulfobutyl ether β-CD (SBE-β-CD). They have shown that the solubility and the stability of quercetin at alkaline pH were substantially improved using three β-CDs. The Nuclear magnetic resonance (NMR) spectroscopic analysis revealed that favourable interaction between B-ring, C-ring, part of the A-ring of quercetin and the hydrophobic cavity of the β-CDs resulted in formation of an inclusion complex model. Therefore the β-CD/quercetin complexes could aid improved oral bioavailability of quercetin. In 2009 Borghetti et al.[88] designed quercetin/ β-CD complex to investigate the influence of several physical operating conditions like stirring time, temperature and excess amount of quercetin etc. on process parameter. The quercetin/ β-CD solid complex was prepared in aqueous solution followed by spray-drying. They obtained the highest aqueous solubility of quercetin under 37ºC temperature, for 24 hrs using 6 mM of quercetin. Though the solid complex yield was adequate (77%) by the spray-drying process, but it presented low concentration of quercetin (0.14%, w/w) in turn poor complexation efficiency. In order to enhance the solubility the inclusion complex was prepared by physical mixture of quercetin and β-CD at 1:1 molar ratio and quercetin concentration of 23% (w/w). Therefore, their findings suggested that the physical mixture method could be a better alternative process for quercetin/β-CD solid complex preparation. In another article, Carlotti[89] reported that preparation of the inclusion complex between quercetin and methyl-β-cyclodextrin (Me-β-CD). In their attempt, successful enhancement of quercetin solubility was resulted without significant reducing in its antioxidant activity. Furthermore a modest improvement in the photostability was also noticed. *In vitro* studies with Franz diffusion cells also revealed that the accumulation of quercetin in porcine skin was not interrupted by complexation phenomenon. Therefore, the Me-β-CD inclusion complex with quercetin has provided an indication towards the development of a potential carrier for quercetin. Testa et al.[90] demonstrated preparation of quercetin loaded (β-CD)-dodecylcarbonate nanoparticles with the hope of getting a new delivery device for improved quercetin bioavailability and anti-inflammatory activity. Actually they have reported treatment of Alzheimer's disease (AD)-related neuropathological changes using these nanoparticles. *In vitro* studies confirmed remarkable increase in anti inflammatory effects of quercetin after encapsulation within the nanoparticles. Moreover, nanoparticles were able to improve permeation across the blood-brain barrier and produce enough bioavailability to reach target cells. The present findings suggested that this quercetin delivery vehicle might be a potential new therapeutic tool for other diseases in future.

Recently, Chitkara et al.[91] reported preparation of quercetin-loaded PLGA nanoparticles involving emulsion-diffusion-evaporation method and evaluated their efficacy in anti-diabetic research. The particles showed an average particle size of 179.9±11.2 nm and − 6.06±1.51 mV zeta potential with 0.128 polydispersity index. Moreover significant quercetin entrapment (~ 86%) was obtained using these nanoparticles. The scanning microscopy was carried out for surface morphology analysis, which confirmed spherical shaped particles with smooth surface, ensuring the absence of unentrapped or adsorbed quercetin. These nanoparticles could be easily lyophilized using D-Trehalose (5% w/v) and antioxidant assays also indicated that PLGA nanoparticles were

efficient in retaining the antioxidant property of quercetin. *In vitro* release study confirmed a controlled release pattern of quercetin from the nanoparticles. *In vivo* pharmacokinetic study showed relative increase in oral bioavailability (~ 523%) of quercetin after encapsulation within nanoparticles as compared to only quercetin suspension. Additionally, the plasma quercetin concentration was sustained for 6 days *in vivo*, suggesting a reduced dosing frequency of the nanoformulations. The superoxide dismutase and the catalase level in pancreas and kidneys were observed to be significantly increased after peroral treatment of quercetin-loaded PLGA nanoparticles. Thus, the nanocarriers could offer an efficacious oral therapy for diabetes and its related complications with reduced dose as well as dosing frequency. In another approach Pool et al.[29] reported successful fabrication of quercetin loaded biocompatible copolymer PLGA nanoparticles by solvent displacement method. The nanoparticles showed relatively particles size of ~ 400 nm with 79% of encapsulation efficiency. Here, particle sizes were little larger compared to other reports,[91] because of higher molecular weight of the polymer used. The quercetin encapsulated PLGA nanoparticles showed pH dependent release profile and enhanced inhibition of the effects of free radicals and chelating properties of quercetin as compared to unbound flavonoid. Although acidic media is reported to promote PLGA degradation,[92] quercetin release was slower probably due to the interaction between existing carbonyl and carboxyl groups of the polymer and quercetin molecule. According to their observations PLGA nanoparticulate system could facilitate oral delivery of quercetin for anti-hyperglycemic research. In an article Jain and his co workers[93] reported preparation of PLGA nanoparticles co-encapsulated with quercetin and tamoxifen for effective oral administration. The synthesized particles were 185.3 nm in size with ~ 68.60% quercetin encapsulation efficiency and found to be stable in simulated gastrointestinal fluids for 8 hrs. The PLGA nanoparticles effectively preserved the functional architecture of quercetin after encapsulation and high cellular uptake by Caco-2 supported its great potential in oral quercetin delivery. Furthermore, *in vivo* pharmacokinetic study indicated ~ 3-fold increase in oral bioavailability of encapsulated quercetin as compared to free quercetin. Although the formulation was evaluated in breast cancer treatment, no measurable oxidative stress or hepatotoxicity was noticed following its administration. Therefore, the quercetin co-encapsulation strategy with PLGA nanoparticles could be a promising approach in improving oral delivery quercetin in future.

In 2010, Kumari et al.[30] explained preparation of quercetin encapsulated PLA nanoparticles using solvent evaporation method for improvement of quercetin stability and solubility. The nanoparticles showed ~ 96.7% of encapsulation efficiency and ~ 19.4% drug loading with an average 130 nm of size. Microscopic analysis revealed almost spherical shaped nanoparticles with smooth surface. Further, slow and sustained quercetin release kinetics under physiological condition was observed *in vitro* studies, where complete release and maximum quercetin retention occurred at 72 hrs and 96 hrs respectively. Again, quercetin loaded PLA nanoparticles also exhibited less fluorescence quenching efficiency on protein (bovine serum albumin or BSA) as compared to control quercetin. Therefore, it can be concluded from their investigation that PLA nanoparticles could pave way in development of better therapeutic alternatives for diabetes and its complications. In 2011, again, Kumari et al.[27] synthesized PLA nanoparticles involving solvent evaporation method resolve the problems regarding the permeability, stability and solubility of plant flavonoid quercetin. The particles of ~ 250 nm in size with approximately 40% of quercetin encapsulation showed good permeability to the plasma membrane. Furthermore, sustained *in vitro* release of quercetin might provide elevated intestinal absorption. So, these nanoparticles could be easily utilized as cost effective carriers for effective oral quercetin administration via receptor mediated endocytosis. Kumari et al.[94] explored successful fabrication of PLA nanoparticles through green process (using plant extract as stabilizers/emulsifiers) for controlled release of quercetin bioflavonoid. Small, uniformly distributed nanoparticles showed 70-140 nm size range with almost 100% quercetin encapsulation efficiency. Further slow and sustained quercetin release from the PLA nanoparticles in *in vitro* study could ensure improved cellular uptake of quercetin with suitable persistence in the systemic circulation.

The pH responsive nanoparticles composed of PCL as a hydrophobic part and PEG as a hydrophilic domain were investigated for oral quercetin delivery by Nikfarjam et al.[95] Quercetin was loaded within the nanoparticles using nanoprecipitation method. The transmission electron microscopy (TEM) study demonstrated individual spherical nanoparticles with a core-shell-corona (CSC) morphology and presence of carboxyl groups in the shell are responsible for size alteration of the nanoparticles in different pH values. At higher pH increased particle size might be furnished due to electrostatic repulsion and result in significant drug release from the nanocarriers. Again it was confirmed that the quercetin was released in two stages probably controlled by Fick's laws especially at neutral media. So, the amphiphilic brush like copolymer based nanoparticles could be a promising vehicle for successful oral delivery of quercetin. In 2015 Kumar et al.[28] aimed to develop biodegradable PCL nanoparticles involving nanoprecipitation method for oral quercetin delivery. The particles showed size range of 215 nm to 253 nm with effective quercetin encapsulation efficiency of ~ 66%. Moreover smooth surfaced spherical shaped nanoparticles provided controlled release of entreated quercetin over 48 hrs and in turn improved the physical stability. Thus the study successfully furnished a scheme of effective oral delivery system for quercetin with improved bioavailability.

Several lipid-based systems[96] have also been investigated to overcome the said barriers of oral quercetin delivery for better therapeutics. In 2011, Date et al.[97] showed the ability of novel self-assembled phospholipid based cationic nanocarriers (LeciPlex) in improvement of oral therapeutic efficacy of flavonoid quercetin. They have successfully fabricated quercetin loaded LeciPlex

exhibiting ~ 400nm size using a biocompatible solvent Transcutol HP. The formulations showed significant quercetin encapsulation efficiency (>90%) and excellent colloidal stability. Moreover TEM study demonstrated its unilamellar structure and *in vitro* studies exhibited significantly higher anti-tumorigenic activity anti-inflammatory activity ($p < 0.01$) of the LeciPlex as compared to free queretin suspension on oral administration. Therefore, LeciPlex might have great potential in improving oral delivery of quercetin and several other hydrophobic drugs. Again Liu and his group[98] formulated novel quercetin-loaded cationic nano lipid carriers and studied the *in vivo* efficacy and biodistribution following oral administration. The results demonstrated that the cationic nano lipid carriers showed 126.6 nm particle size and 89.3% of quercetin entrapment efficiency. Moreover slow and sustained quercetin release and significant quercetin accumulation in kidney, lung, and liver after oral administration suggested a promising strategy to improve bio-efficiency of quercetin. Recently, Sun et al.[99] synthesized biocompatible and biodegradable nano structured lipid carriers by a novel phase inversion method to increase quercetin aqueous solubility, stability and oral bioavailability.

The average particle size of the lipid carriers was 32 nm in diameter with ~ 95% of quercetin entrapment efficiency and ~ 11% loading capacity. Again, sufficient increase in aqueous solubility (at least 1000 folds) and a sustained release pattern confirmed potential use of the nano structured lipid carriers in oral quercetin delivery. In breast cancer treatment these nano structured lipid formulations showed enhanced anti-cancer activities along with minimized immunogenicity and other side-effects. Aditya et al.[100] compared the potential SLNs, nano structured lipid carriers (NLC) and lipid nano emulsions (LNE) in increasing bio-accessibility of quercetin. Among all these three types of lipid based carriers quercetin loaded NLC showed smallest particle size (47 nm) and >90% quercetin encapsulation efficiency. Moreover, stability in simulated stomach conditions and maximum bio-accessibility (~60%) ensure efficient device for successful oral quercetin delivery. Song et al.[101] evaluated antioxidant activity of quercetin and β-carotene by co-encapsulation within nanoparticle formulations. They demonstrated faster reaction rate of nanoparticles loaded with quercetin in comparison to β-carotene encapsulated nanoparticles.[102] In another article Kouassi et al.[103] showed effective encapsulation of linoleic acid (LA) into dual polymeric system of Kappa-carrageenan and whey protein by ultrasound in presence or absence of quercetin. Quercetin showed protective antioxidant activity against time-dependent oxidation and thermally induced LA rancidity.

Recently, Sapino et al.[104] demonstrated immobilization of quercetin within aminopropyl functionalized mesoporous silica nanoparticles (NH2-MSN) and evaluated the efficacy of this novel approach in improved topical quercetin delivery. The photostability of quercetin molecule was improved and quercetin penetration in to the skin was also increased following immobilization. Hence, NH2-MSN could be considered as a potential carrier for quercetin improving its biological functions and intrinsic stability. Jain et al.[105] successfully explained development of self-emulsifying drug delivery system (SEDDS) for enhanced oral bioavailability and antioxidant property of quercetin especially against drug induced nephrotoxicity and cardiotoxicity. These formulations could be explored in several other therapeutic regiments like diabetes, cardio vascular disorders and inflammatory diseases. Recently, Jain and his co workers,[106] showed potential anti cancer activities of quercetin entrapped self-nanoemulsifying drug delivery system (QT-SNEDDS) in MCF-7 cells. Moreover, various hepatotoxicity marker assays ensured the safety profile of the QT-SNEDDS formulation. Ghosh et al.[107] successfully demonstrated that perorally administered nanocapsulated quercetin has enhanced therapeutic potential against arsenite-induced hepatic and neuronal cell damage in animal model. Again, in 2013, Ghosh et al.[108] showed that orally delivered nanoencapsulated quercetin can improve neuronal count in the hippocampal subfields of both young and aged rats having ischemia-reperfusion-induced neuronal damage. Moreover, the nanoformulation imparted a significant antioxidant protection in different regions of the brain of the animals. Ghosh and her co workers[109] explored quercetin and meso-2,3-Dimercaptosuccinic acid (DMSA) co-encapsulated PLGA nanoformulation in successful therapeutic application combating chronic arsenic toxicity in rats model.

In 2011, Fang et al.[110] presented novel bio-nanoparticle formation with BSA and quercetin. Their study indicated that eleven quercetin molecules can be entrapped by one BSA following mainly hydrophobic interaction related to the synergy of tryptophan residues of the protein. Moreover, both in acidic and neutral media controlled quercetin release indicated that the bioactive nanoparticles could exert long-term antioxidant effects and might be a promising device in the bionanotechnology field. Gao et al.[111] stated encapsulation of quercetin with biodegradable monomethoxy poly(ethylene glycol)-poly(ε-caprolactone) (MPEG-PCL) micelles for ovarian cancer treatment. The quercetin loaded micelles showed 36 nm of mean particle size with 6.9% of drug loading and were able to render quercetin dispersion completely. Furthermore, *in vivo* studies revealed significant suppression of xenograft A2780S ovarian tumour growth by cancer cell apoptosis and angiogenesis inhibition. Thus encapsulation of quercetin within polymers will improve its therapeutic effects.

Han et al.[112] recently investigated the physical properties and ability of quercetin loaded SLNs in enhancement of skin penetration of antioxidants. The mono-dispersed SLNs showed 274.0–986.6 nm size range with uniform spherical shape and 15.2–46.2% of quercetin encapsulation efficiency. *In vitro* skin permeation study confirmed that these SLNs could be utilized as transdermal delivery device for many hydrophobic antioxidants including quercetin. In 2009, Kitagawa et al.[113] proposed intradermal quercetin delivery using a microemulsion of isopropyl myristate, 150 mM NaCl solution, Tween 80 and ethanol. They have shown deep penetration of quercetin into the skin avoiding the transfer to the receptor compartment for exerting improved antioxidative effects. Recently, Li et al.[114] demonstrated development and utilization of

core-sheath nanofibres for fast dissolving of quercetin involving coaxial electrospinning. Microscopic observation revealed that core-sheath has linear morphology and uniform structure with smooth surface. Moreover, *in vitro* dissolution study showed rapid disintegration and release of quercetin from the core-sheath composite nanofibre mats, suggesting a novel type nanocomposite drug delivery system.

Recently, imaging applications of quercetin-based carriers has been reported by scientists to provide a new concept to monitor the delivery of drugs *in vitro* and *in vivo*. Wang et al.[115], showed that quercetin co-encapsulated fluorescent Silicon quantum dots (SiQDs) in poly (ethylene glycol)-block-polylactide (PEG–PLA) nanoparticles were used for simultaneous *in vitro* imaging and for improvement of the biocompatibility of quercetin. The double emulsion method was used for nanoparticle synthesis, and fluorescent imaging described that the quercetin encapsulated PEG–PLA nanoparticle could effectively suppresses human hepatoma HepG2 cell proliferation more effectively compared to the free form. Additionally, hydrogen peroxide-induced DNA damage in HepG2 cells was significantly inhibited with nanoparticle-encapsulated quercetin treatment. Such nanoparticulate systems can allow monitoring of proper route of delivery through imaging and could improve the future of drug delivery. For useful biological imaging applications polyacrylic acid terminated SiQDs (PAAc-SiQDs) show strong luminescence characteristics and low cytotoxicity in comparison to the conventional heavy metal QDs. As the red fluorescence of the SiQDs is not strongly absorbed by cells, they are even more preferred as suitable imaging agents. Wang et al.[116,117] reported that quercetin-encapsulated PEG–PLA nanoparticles provide intrinsic orange-red photoluminescence which enabled efficient monitoring of both accumulation and degradation of the drug molecule *in vitro* and *in vivo*. In 2013, Murgia et al.[118] demonstrated successful preparation of quercetin loaded fluorescent monoolein-based cubosomes and its application for single living cell imaging analysis.

Now a days, magnetic nanoparticles, have gained considerable interest in biomedical field for magnetic resonance imaging, magnetic separation, proper targeted drug delivery, cell tracking, tissue engineering, magnetic hyperthermia bioseparation. For these applications, the nanoparticles must show biocompatibility, high magnetic saturation and interactive functions at the surface.[119,120] Metallic nanostructures are also incorporated into quercetin nanocarriers for better drug targeting. In 2011, Barreto et al.[121] proposed a new system for quercetin storage and release using magnetite nanoparticles (Fe_3O_4). The system was incorporated to a triblock copolymer of ethyleneoxide and oxyphenylethylene for improved quercetin release for sustained delivery of anticancer agent. The results indicated that the presence of magnetic nanoparticles in this system offered organ specific targeting of the drug molecule. It also showed a prolonged release time (its peak at 14.5% after 96 hrs) for the drug.[121] Verma and his group[122] also explained a biocompatible quercetin loaded magnetic core-shell nanoparticle-based system (surface coating of Fe_3O_4 magnetic nanoparticles with a polymer poly(lactic-co-glycolic acid) (PLGA) for successful targeting lung cancer cells via nebulisation.[122] Again gold nanoparticles generate lot of interest in quercetin delivery being biologically static and causing no severe side effects to the genetic systems. Quercetin conjugated gold nanoparticle synthesis by citrate reduction of chloroauric acid was shown by Pal et al., 2010.[123] Quercetin loaded gold nanoparticles have become popular for recent few past years due to their specific optical and chemical property and possible improved biological applications. [124] Silver nanoparticles being most exploited in drug delivery research due to mono-dispersity of the particles Biosynthesis of silver nanocubes containing quercetin was emonstrated by Sivakumar et al., 2013[125] showed the potential effect on antifungal activity against an antifungal agent fluconazole.[125]

6. Indication towards newer approaches

In this review, we have focused on alternative treatment of diabetes using bio-flavonoid quercetin. Drastic increase in prevalence of diabetes and its associated complications worldwide demand safe treatment with patient compliance avoiding serious health issues of traditional insulin therapy or synthetic oral hypoglycemic drugs (OHDs) administration. Several natural compounds have been explored for effective diabetes control and treatment among them bio-flavonoid quercetin is the most extensive studied dietary flavonoid, found in onion, berries, apples, many nuts, seeds, barks, flowers, tea, brassica vegetables and leaves. However, myriad applications of quercetin in anti-diabetic research have been limited in spite of having wide spectrum of pharmacological properties. Actually quercetin shows poor aqueous solubility, instability in physiological medium, low permeability producing insignificant bioavailability and of course extensive first pass metabolism rate before reaching the systemic circulation following its administration. Now the primary goal is to overcome the said barriers and use the drug for safe treatment of diabetes and other health complications successfully. Recently, effective ways to circumvent all these hindrance are to entrap/adsorb quercetin molecule into biodegradable polymeric formulations to achieve the goal. Generally polymeric drug formulation involving both natural and synthetic polymers gained considerable attention in this regard and numerous approaches have been executed. However, pH sensitive, cost effective natural polymers are more preferred rather than chemical ones to avoid the undesired side effects found in diabetic patients. Moreover, polymer formulation process should be mild and straight forward considering present circumstances. Finally, development of efficient sophisticated carrier system with maximum quercetin bioavailability, good biocompatibility without systemic toxicity having possible minimum cost is the ultimate goal.

7. Conclusions and future prospective

The state-of-the-art in the area of successful quercetin delivery using polymeric formulations is mainly discussed in the review based on recent relevant published articles. Recently, anti-hyperglycemic research involving quercetin as a safe alternative has been extensively explored. Most of the formulations are developed using biodegradable polymeric materials like natural polymers such as chitosan, alginate and synthetic polymers such as poly-D, L-

lactide (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL) in order to improve oral bioavailability of quercetin. With advancement in novel bioprocesses effective development and subsequent modifications of polymeric materials are also investigated in several reports. We can conclude that the formulation based quercetin delivery would help to improve quercetin solubility, stability to exert maximum bioavailability and destined to reach the systemic circulation overcoming the possible barriers. The ultimate goal is to exert the maximum bioavailability *in vivo*, which can reduce the blood glucose level resulting in hypoglycemic condition for a long period in effective diabetes treatment. During the course of our review, we also uncover that in spite of vast ongoing research still a wide field has remained unexplored. Therefore, more investigations are still required to address the unsolved queries.

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Caption to the Figures and Table

Fig. 1 The structure of quercetin and selected foods and beverages rich in quercetin

Fig. 2 The possible effects of quercetin on liver, muscle, pancreas and small intestine to maintain normal blood sugar level

Fig. 3 A probable mechanism of absorption, translocation and excretion of dietary quercetin in human body

Fig. 4 Several possible mechanisms of enhanced absorption bio-flavonoid quercetin via polymer-based carriers.

Table 1 Flavonoids with significant anti-hyperglycemic effects found in nature

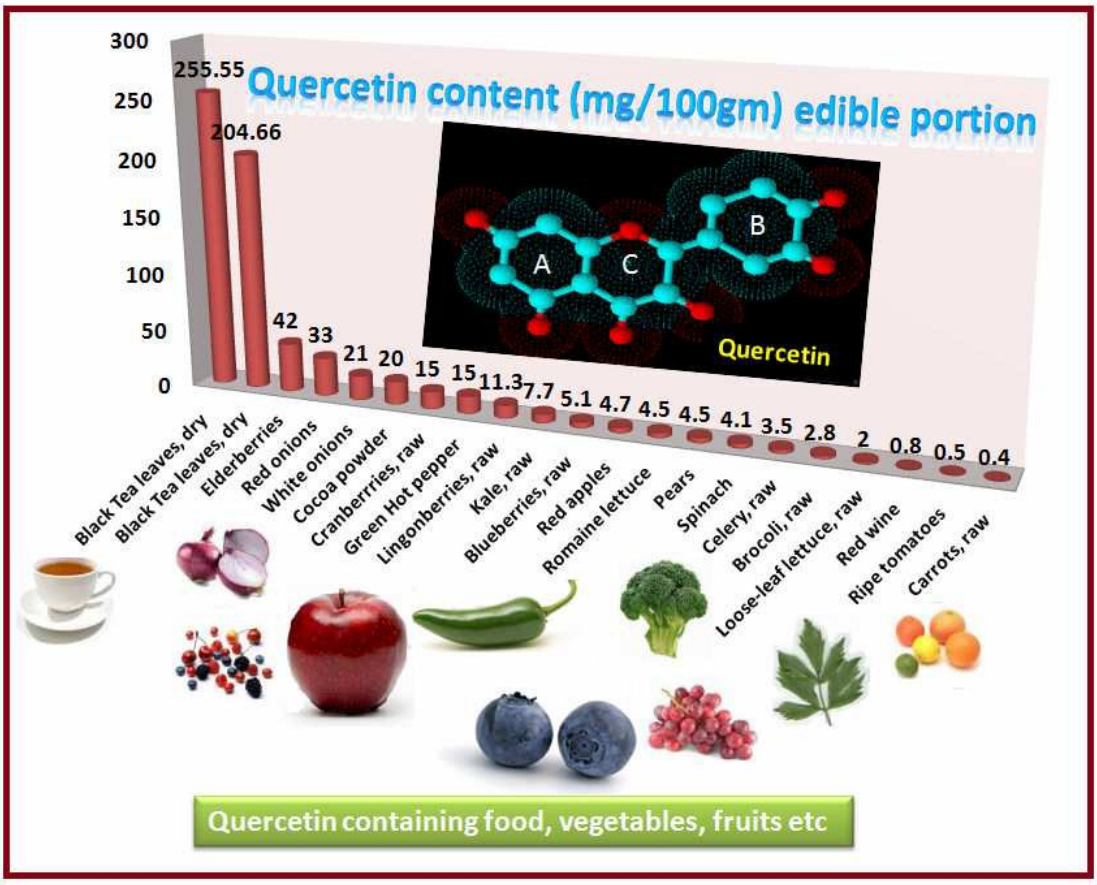


Fig. 1

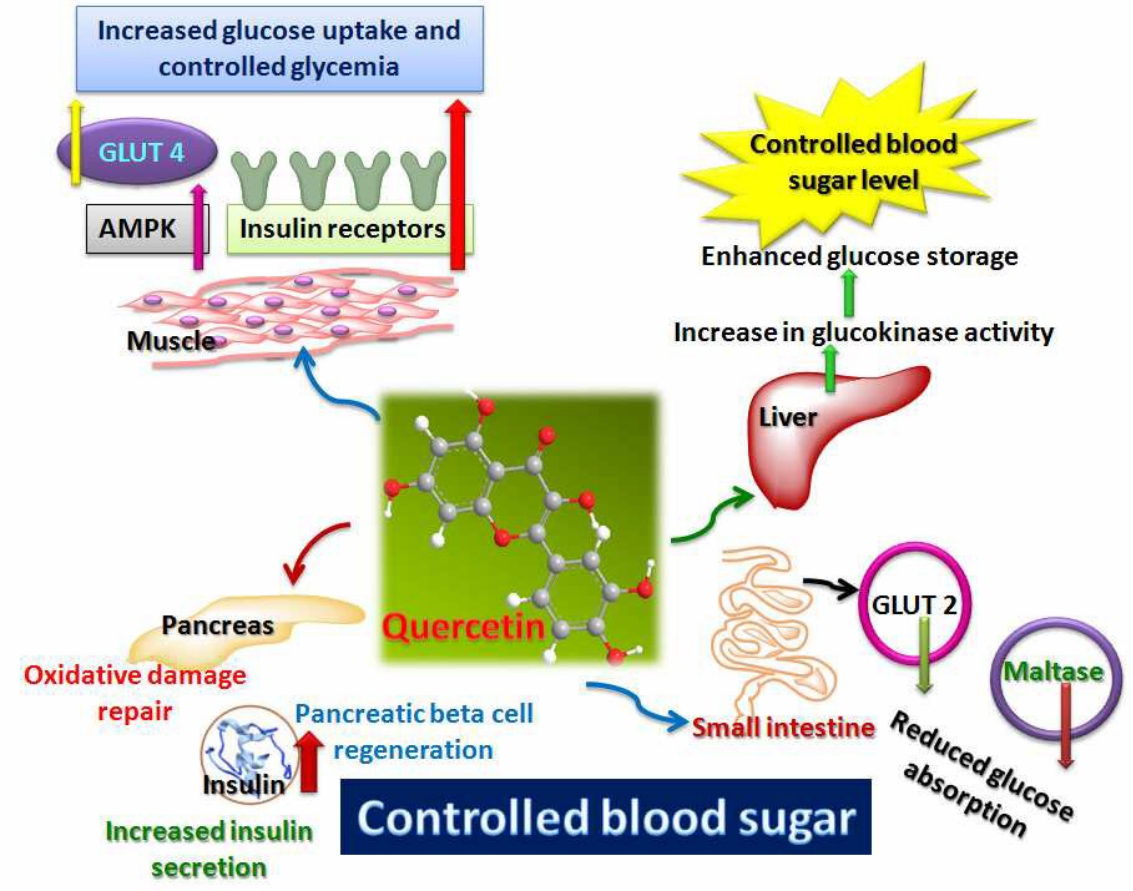


Fig. 2

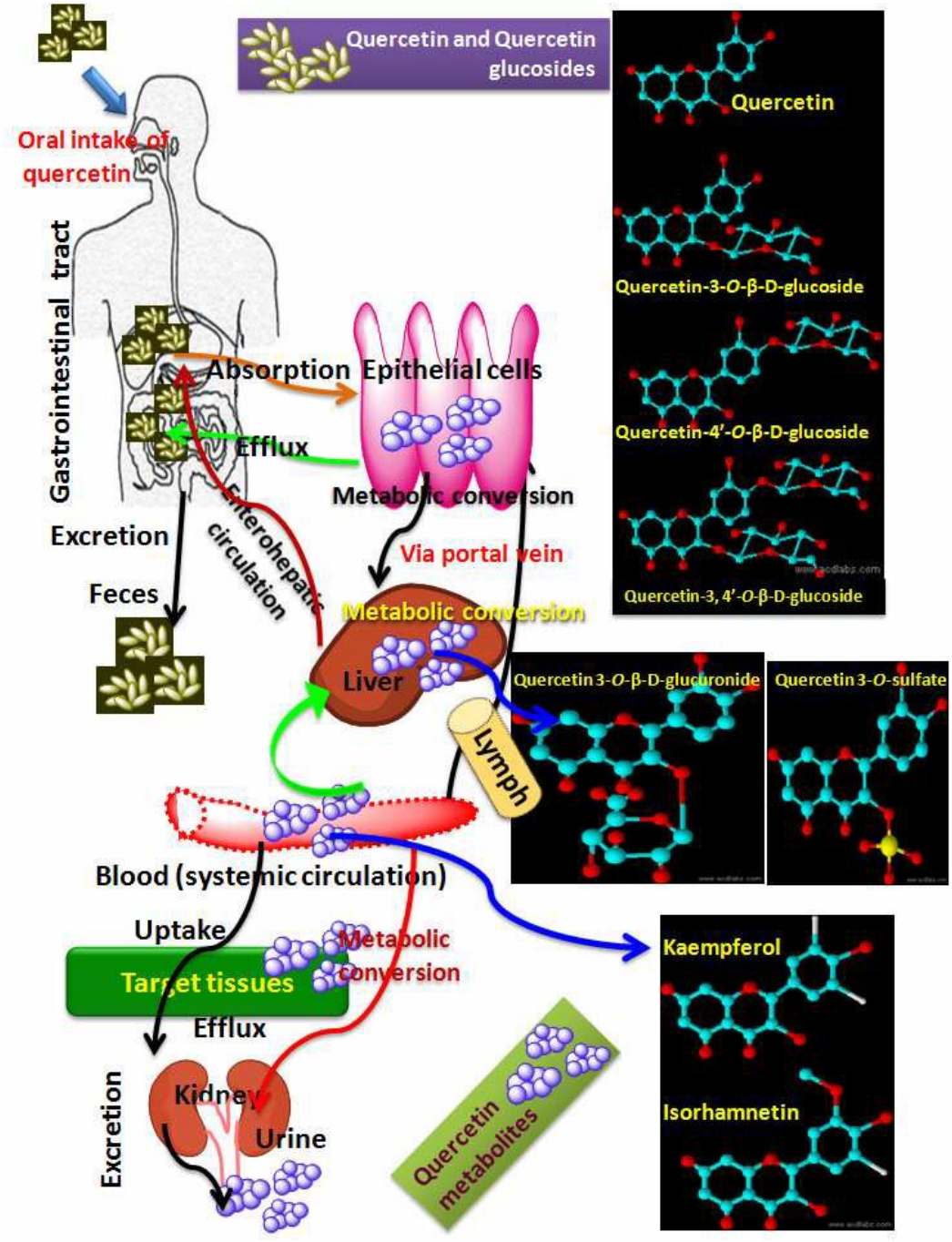


Fig. 3

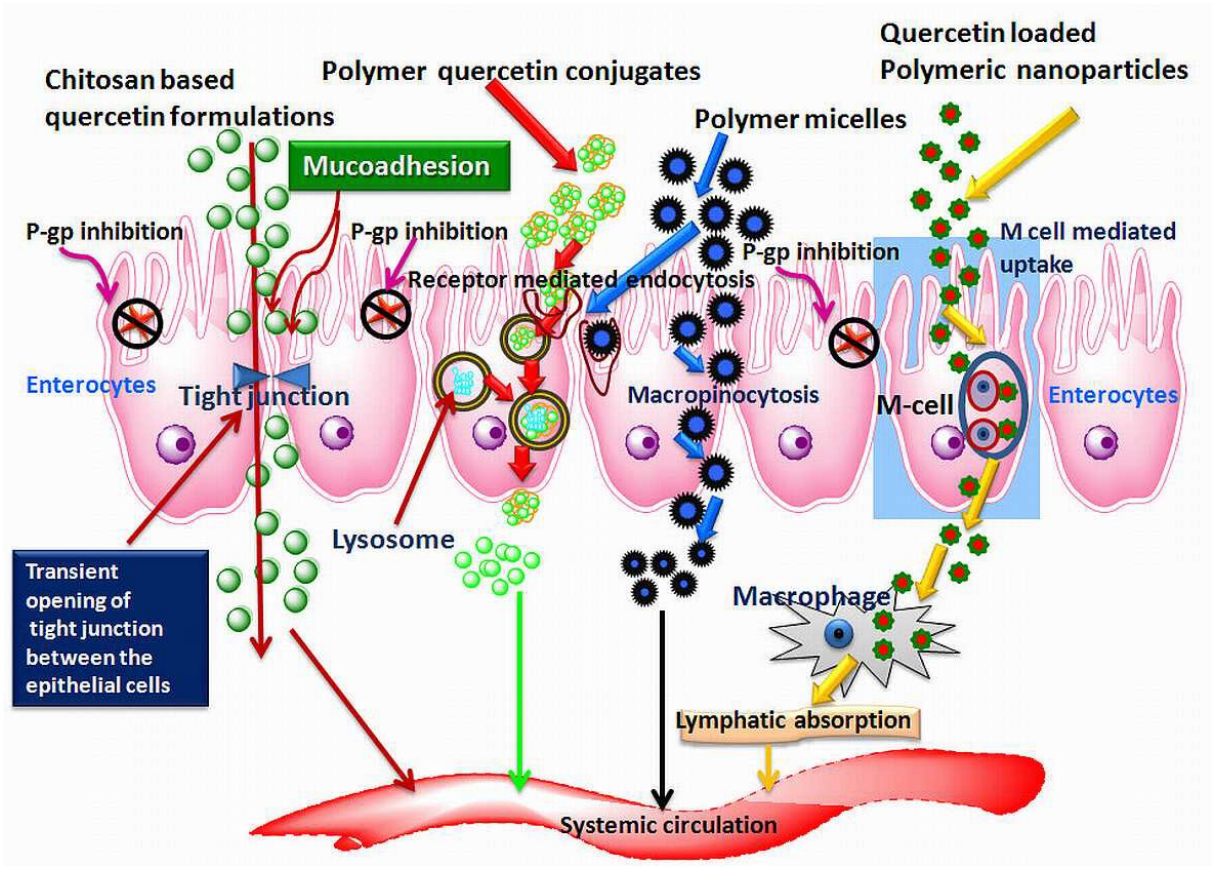
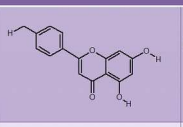
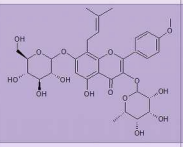
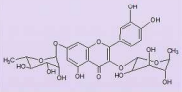
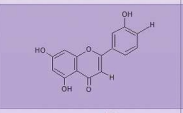
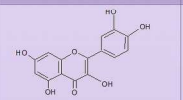
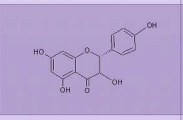
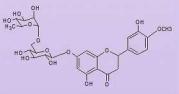
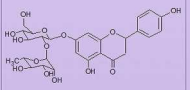
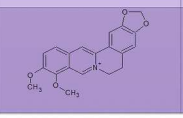


Fig. 4

Name of the Flavonoid	Source	Structure	Anti-diabetic effects
Apigenin	Averrhoa carambola (Family: Oxalidaceae)		Anti-hyperglycemicin Insulin mimetic (induce insulin secretion),induce glycogen synthesis[38]
n-butanol	Bauhinia forficata		Reduce blood glucose level[39]
Icariin	Epimedium, Berberidaceae		Reduce body weight and myocardial collagen[40]
Kaempferitin	Bauhinia forficata		Stimulatory effect on glucose uptake and acute lowering effect on blood glucose[41]
Kaemferol	Chinese medicinal herbs and Euonymus alatus		Improves insulin secretary function and synthesis of beta cells and human islets[42,43]
Quercetin	Euonymus alatus		Induce insulin secretion and glucose uptake[43]
Naringenin	Citrus fruit and juices		Inhibits uptake of glucose in intestine and reduce postprandial glucose[44]
Hesperidin & Naringin	Citrus peel & citrus fruit	 and 	Anti-diabetic,anti-oxidant and show ameliorative effects[45]
Berberine	Berberis, Hydrastis canadensis		Enhance bioavailability[46]

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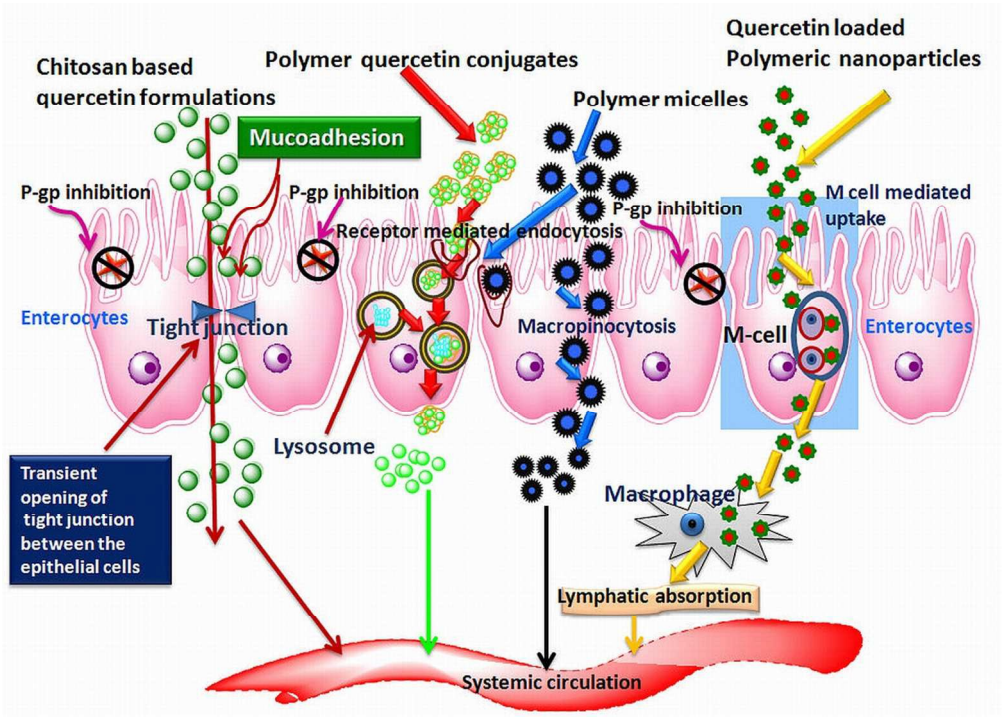

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