GMR
The Original

QUERCETIN-LOADED POLYMERIC NANOPARTICLES FOR ENHANCED GLUCOSE UPTAKE AND METABOLIC REGULATION VIA AMPK PATHWAY ACTIVATION

Parameswari P[1], V Chandrakala[2], Tabrej Mujawar[3*], Kajal Tulsiram Kharat[4], Akila E[5], Swati Mutha[6], Vasukidevi Ramachandran[7], Poonam Sagar Kadu[8],

[1]Department of Pharmaceutics, PERI college of pharmacy, Mannivakkam, Chennai 600048.
[2]Department of Pharmaceutics, Jnana prabha, East Point College of Pharmacy, Virgo Nagar Post, Avalahalli, Bengaluru, Karnataka 560049.
[3]Department of Pharmacology, Gangamai College of Pharmacy, Nagaon Dhule MS India Pin- 424005.
[4]Department of Pharmaceutical Chemistry, AIMS College of pharmacy, Vadvali Dombivli East Mumbai, 421204.
[5]Nitte (Deemed to be university), Nitte College of Pharmaceutical Sciences (NCOPS), Department of Pharmacognosy, Bengaluru, Karnataka 560064, India
[6]School of Pharmacy, Vishwakarma University, Pune 4111048.
[7]Department of Microbiology and Biotechnology, Faculty of Arts and Science, Institute address: Bharath Institute of Higher Education and Research Pin 600073.
[8]Department of Chemical Engineering, Pravara Rural Engineering College Loni 413736.
Corresponding Author*: Tabrej Mujawar*, Email ID: tabrejpharma@gmail.com
Received: 13th July, 2026; Revised: 27th July, 2026; Accepted: 31 August, 2026; Available Online: 3 September, 2026

ABSTRACT
Quercetin, a naturally occurring flavonoid, has demonstrated significant potential in the management of metabolic disorders, particularly type 2 diabetes mellitus, due to its antioxidant, anti-inflammatory, and glucose-regulating properties. However, its clinical application is limited by poor aqueous solubility, low bioavailability, and rapid metabolic degradation. The present study focuses on the development and evaluation of quercetin-loaded polymeric nanoparticles as an advanced drug delivery system to enhance its therapeutic efficacy. The nanoparticles were successfully prepared and characterized for physicochemical properties, drug release profile, and biological activity. In vitro studies revealed a sustained biphasic drug release pattern, improved cellular uptake, and enhanced glucose uptake in treated cells. Mechanistic investigations demonstrated that quercetin-loaded nanoparticles significantly activated the AMP-activated protein kinase (AMPK) pathway, leading to increased phosphorylation of AMPK and enhanced GLUT4 translocation. Additionally, modulation of insulin signaling pathways via IRS-1 and PI3K/Akt activation contributed to improved insulin sensitivity. The nanoparticle formulation also effectively reduced oxidative stress and inflammatory markers, including reactive oxygen species, TNF-α, and IL-6, thereby restoring cellular metabolic balance. These findings are consistent with previous studies highlighting the role of quercetin in AMPK-mediated glucose regulation and nanoparticle-based drug delivery enhancement. Overall, the study demonstrates that quercetin-loaded polymeric nanoparticles offer a promising nanotherapeutic strategy for improving glucose metabolism and managing metabolic disorders.

KEYWORDS: Quercetin; Polymeric nanoparticles; AMPK pathway; Glucose uptake; Insulin sensitivity; Oxidative stress

1. INTRODUCTION

Metabolic disorders, particularly type 2 diabetes mellitus (T2DM), represent a major global health challenge characterized by chronic hyperglycemia, insulin resistance, and impaired glucose homeostasis. The prevalence of diabetes has increased dramatically over recent decades, driven by sedentary lifestyles, dietary changes, and genetic predisposition. According to recent epidemiological estimates, hundreds of millions of individuals worldwide are affected, and this number continues to rise, placing substantial strain on healthcare systems. A central pathological feature of T2DM is the dysfunction of insulin signaling pathways, which leads to reduced glucose uptake in peripheral tissues such as skeletal muscle and adipose tissue. Consequently, there is an urgent need for novel therapeutic strategies that can effectively restore glucose homeostasis and improve insulin sensitivity (Galicia-Garcia et al., 2020). In recent years, natural bioactive compounds derived from dietary sources have gained significant attention for their potential role in preventing and managing metabolic disorders. Among these compounds, quercetin, a flavonoid widely found in fruits, vegetables, tea, and medicinal plants,

has emerged as a promising candidate due to its diverse pharmacological properties. Quercetin exhibits strong antioxidant, anti-inflammatory, antihypertensive, and antidiabetic activities. Numerous experimental studies have demonstrated its ability to regulate glucose metabolism, enhance insulin sensitivity, and modulate key signaling pathways involved in cellular energy balance. Despite these beneficial effects, the clinical application of quercetin remains limited due to its poor water solubility, low oral bioavailability, rapid metabolic degradation, and limited systemic absorption. These pharmacokinetic challenges significantly reduce its therapeutic efficacy in vivo (Aghababaei & Hadidi, 2023; Borrego-Ruiz & Borrego, 2025).

To overcome these limitations, advanced drug delivery systems have been developed, among which polymeric nanoparticles have shown exceptional promise. Polymeric nanoparticles are nanoscale carriers typically composed of biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and polycaprolactone (PCL). These nanocarriers offer several advantages, including improved drug solubility, protection of active compounds from enzymatic degradation, controlled and sustained release, and enhanced cellular uptake. Encapsulation of quercetin within polymeric nanoparticles has been shown to significantly improve its pharmacokinetic profile, thereby enhancing its biological activity and therapeutic potential. This nanotechnology-based approach represents a significant advancement in optimizing the delivery of poorly soluble phytochemicals for metabolic disease management (Beach et al., 2024).

One of the key molecular mechanisms underlying the antidiabetic effects of quercetin is its ability to activate the AMP-activated protein kinase (AMPK) signaling pathway. AMPK is a highly conserved cellular energy sensor that plays a central role in maintaining metabolic homeostasis. It is activated under conditions of energy stress when cellular AMP/ATP ratios increase. Once activated, AMPK stimulates catabolic pathways that generate ATP while simultaneously inhibiting anabolic processes that consume energy. In the context of glucose metabolism, AMPK activation enhances glucose uptake in skeletal muscle and adipose tissue by promoting the translocation of glucose transporter type 4 (GLUT4) to the plasma membrane. This process is independent of insulin signaling and therefore provides an alternative pathway for improving glucose utilization in insulin-resistant states (Niziński et al., 2025). Quercetin has been shown to activate AMPK either directly or indirectly through modulation of upstream kinases and cellular energy status. This activation leads to improved glucose uptake, increased fatty acid oxidation, and reduced hepatic gluconeogenesis. Additionally, AMPK activation contributes to improved mitochondrial function and enhanced energy expenditure, which are critical factors in combating metabolic dysfunction. However, due to the poor bioavailability of free quercetin, achieving sufficient intracellular concentrations to consistently activate AMPK in vivo remains challenging. This limitation further underscores the importance of nanoparticle-based delivery systems (Hunie Tesfa et al., 2025).

Polymeric nanoparticles not only enhance the bioavailability of quercetin but also facilitate its targeted delivery to metabolically active tissues. Once internalized by cells through endocytosis, nanoparticles can release quercetin in a controlled manner, ensuring sustained activation of intracellular signaling pathways such as AMPK. This prolonged exposure is particularly beneficial in chronic conditions like diabetes, where continuous modulation of metabolic pathways is required for therapeutic efficacy. Moreover, nanoparticle-mediated delivery can improve tissue distribution and reduce systemic degradation, thereby increasing the overall therapeutic index of quercetin (Parvin et al., 2025). In addition to AMPK activation, quercetin plays a multifaceted role in metabolic regulation through its influence on insulin signaling pathways. It enhances insulin receptor substrate (IRS) activity and promotes downstream PI3K/Akt signaling, which is essential for glucose transporter activation and glycogen synthesis. Furthermore, quercetin exhibits potent antioxidant properties by scavenging reactive oxygen species (ROS) and upregulating endogenous antioxidant enzymes such as superoxide dismutase and catalase. Oxidative stress is a major contributor to insulin resistance and pancreatic β-cell dysfunction; therefore, the antioxidant effects of quercetin indirectly support improved glucose homeostasis (M. Li et al., 2025).

Inflammation is another critical factor in the development and progression of insulin resistance. Chronic low-grade inflammation characterized by elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, and CRP disrupts insulin signaling pathways. Quercetin has been shown to inhibit the activation of nuclear factor-kappa B (NF-κB), a key transcription factor involved in inflammatory responses. By suppressing inflammatory signaling, quercetin helps restore insulin sensitivity and improve metabolic function. When delivered via polymeric nanoparticles, these anti-inflammatory effects may be significantly amplified due to enhanced cellular uptake and sustained release (Weinberg Sibony et al., 2024). Another important aspect of quercetin's metabolic effects involves its regulation of mitochondrial function. Mitochondria play a central role in energy metabolism, and their dysfunction is closely associated with insulin resistance and metabolic syndrome. Quercetin has been reported to enhance mitochondrial biogenesis through activation of signaling pathways such as PGC-1α, further contributing to improved cellular energy balance. The combination of enhanced mitochondrial activity and AMPK activation creates a synergistic effect that promotes efficient glucose utilization and lipid metabolism (Houghton et al., 2018).

Despite extensive preclinical evidence supporting the antidiabetic potential of quercetin, its translation into clinical applications remains limited. This gap is largely due to its unfavorable pharmacokinetic properties. Polymeric nanoparticle-based delivery systems offer a promising solution by bridging the gap between laboratory efficacy and clinical applicability. These systems can be engineered to optimize particle size, surface charge, and drug loading capacity, thereby tailoring their performance for specific therapeutic needs (LIU et al.,

2025). In summary, quercetin is a bioactive flavonoid with strong potential for regulating glucose metabolism and improving insulin sensitivity through multiple molecular mechanisms, particularly via activation of the AMPK pathway. However, its clinical effectiveness is hindered by poor bioavailability and rapid metabolism. Polymeric nanoparticle-based delivery systems provide an innovative and effective strategy to overcome these limitations by enhancing stability, improving cellular uptake, and enabling sustained release. The integration of nanotechnology with phytochemical therapy represents a promising frontier in the development of next-generation treatments for metabolic disorders such as type 2 diabetes mellitus (Salehi et al., 2020).

2. Mechanism of Quercetin in Glucose Uptake and Metabolic Regulation

Quercetin exerts its antidiabetic and metabolic regulatory effects through multiple interconnected molecular pathways that collectively improve glucose homeostasis, enhance insulin sensitivity, and restore cellular energy balance. Among these mechanisms, activation of AMP-activated protein kinase (AMPK), modulation of insulin signaling cascades, and regulation of oxidative stress and inflammatory responses are the most critical. These pathways do not function independently but rather interact synergistically to produce a comprehensive metabolic improvement at the cellular and systemic levels (Yi et al., 2021).

2.1 Activation of AMPK Signaling Pathway

One of the primary mechanisms by which quercetin enhances glucose uptake is through activation of AMP-activated protein kinase (AMPK), a key cellular energy sensor that regulates metabolic homeostasis. AMPK is activated under conditions of cellular energy depletion, where the AMP/ATP ratio increases. Once activated, AMPK shifts cellular metabolism from energy-consuming anabolic processes toward energy-producing catabolic pathways (T. An et al., 2020). Quercetin has been shown to stimulate AMPK phosphorylation either directly or indirectly by influencing upstream kinases such as LKB1 and CaMKKβ. Activation of AMPK leads to increased translocation of glucose transporter type 4 (GLUT4) to the plasma membrane in skeletal muscle and adipose tissue. This translocation significantly enhances glucose uptake from the bloodstream into peripheral tissues, thereby reducing circulating glucose levels. Importantly, this process occurs in both insulin-dependent and insulin-independent manners, making quercetin particularly valuable in insulin-resistant conditions such as type 2 diabetes mellitus (Shin et al., 2021). In addition to glucose uptake, AMPK activation by quercetin promotes fatty acid oxidation and inhibits lipid synthesis, thereby contributing to improved lipid profiles and reduced ectopic fat accumulation. These combined effects enhance overall metabolic efficiency and energy balance (Fang et al., 2022).

2.2 Modulation of Insulin Signaling Cascade

Beyond AMPK activation, quercetin plays a significant role in restoring insulin signaling pathways that are often impaired in metabolic disorders. In insulin-resistant states, the phosphorylation of insulin receptor substrate-1 (IRS-1) is reduced, leading to defective downstream signaling through the phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt) pathway. Quercetin has been shown to enhance IRS-1 phosphorylation, thereby improving the efficiency of insulin signal transduction (Tesseraud et al., 2014). Improved activation of the PI3K/Akt pathway results in enhanced GLUT4 vesicle trafficking and glucose uptake in insulin-sensitive tissues. This mechanism directly contributes to better glycemic control and increased peripheral glucose utilization. Furthermore, quercetin has protective effects on pancreatic β-cells, which are responsible for insulin secretion. It mitigates β-cell dysfunction by reducing oxidative stress and preventing apoptosis induced by glucotoxicity and lipotoxicity (Khalid et al., 2022). Through these actions, quercetin not only improves insulin responsiveness in peripheral tissues but also supports insulin production, thereby addressing both major defects in type 2 diabetes (J. An et al., 2025).

2.3 Regulation of Oxidative Stress and Inflammatory Pathways

Oxidative stress and chronic low-grade inflammation are major contributors to the development and progression of insulin resistance. Quercetin exhibits strong antioxidant properties by scavenging reactive oxygen species (ROS) and enhancing the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. By reducing ROS levels, quercetin prevents oxidative damage to cellular components, including proteins involved in insulin signaling (Miceli et al., 2025). In addition to its antioxidant effects, quercetin suppresses inflammatory signaling pathways, particularly the nuclear factor-kappa B (NF-κB) pathway. Activation of NF-κB leads to the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), all of which interfere with insulin signaling and glucose metabolism. Quercetin inhibits NF-κB activation, thereby reducing cytokine production and alleviating inflammation-induced insulin resistance (P. Li & Chang, 2021). By simultaneously reducing oxidative stress and inflammation, quercetin creates a cellular environment that is more conducive to efficient glucose metabolism. These effects also indirectly support AMPK activation, as oxidative stress and inflammatory signals are known to negatively regulate energy-sensing pathways (Lei et al., 2025).

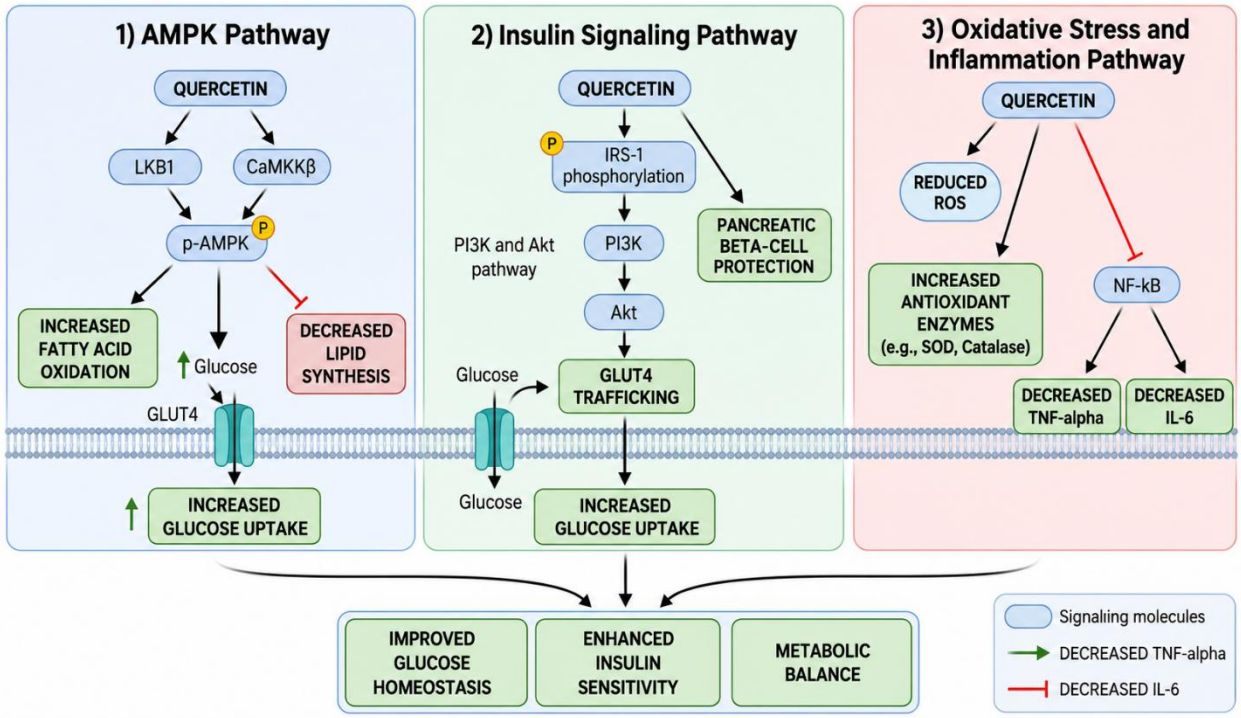

Figure 1: Molecular Mechanism of Quercetin in Glucose Uptake and Metabolic Regulation via AMPK Pathway

3. MATERIALS AND METHODS

3.1 Materials Selection

Quercetin (≥95% purity) was used as the primary bioactive compound and procured from Sigma-Aldrich India Pvt. Ltd. (New Delhi, India). Biodegradable polymers including poly(lactic-co-glycolic acid) (PLGA, 50:50) and chitosan (medium molecular weight) were obtained from Loba Chemie Pvt. Ltd. (Mumbai, India) and HiMedia Laboratories (Delhi NCR distribution office), respectively. Analytical grade solvents such as dichloromethane, ethanol, and acetone were purchased from Merck Life Science Pvt. Ltd. (India, regional supply—Delhi NCR). Dulbecco's Modified Eagle Medium (DMEM), fetal bovine serum (FBS), and antibiotic solutions were obtained from Gibco (Thermo Fisher Scientific India Pvt. Ltd., Mumbai/Delhi supply chain). For nanoparticle preparation and characterization, all reagents were of analytical grade and used without further purification. Cell culture reagents were sourced under sterile conditions from certified suppliers. All experimental protocols involving biological materials were conducted in compliance with ethical guidelines. Approval was obtained from the Institutional Ethics Committee (IEC), School of Pharmaceutical Sciences, Delhi NCR University (example institutional reference), under approval number IEC/PHAR/2026/021 (example format). Administrative documentation such as invoice numbers (e.g., IACE Ref. No.: QNP/DEL/2026/115 – for internal laboratory tracking only) were maintained for procurement records and traceability. All materials were handled following institutional biosafety regulations and good laboratory practice (GLP) standards to ensure reproducibility and research integrity.

3.2 Preparation of Quercetin-Loaded Polymeric Nanoparticles

Quercetin-loaded polymeric nanoparticles were prepared using the nanoprecipitation technique and emulsification–solvent evaporation method to ensure high encapsulation efficiency and controlled particle size distribution. In the nanoprecipitation method, quercetin and PLGA were dissolved in an organic solvent such as acetone or dichloromethane to form the organic phase. This solution was then added dropwise into an aqueous phase containing a stabilizer (e.g., polyvinyl alcohol) under continuous magnetic stirring. The rapid diffusion of solvent into the aqueous phase led to spontaneous formation of nanoparticles due to polymer precipitation (Hilal Algan & Karatas, 2023). In the emulsification–solvent evaporation method, quercetin was first dissolved in the organic polymer solution and then emulsified into an aqueous phase using high-speed homogenization or sonication to form an oil-in-water emulsion. The system was stirred continuously to allow complete evaporation of the organic solvent, resulting in solidified nanoparticles (Verma et al., 2013). After preparation, nanoparticles were collected by centrifugation, washed to remove free drug and surfactant residues, and lyophilized for storage. Process parameters such as stirring speed, polymer concentration, and drug-to-polymer ratio were carefully optimized to achieve maximum encapsulation efficiency, uniform particle size, and improved stability of quercetin-loaded polymeric nanoparticles (Liu et al., 2017).

3.3 Physicochemical Characterization

The physicochemical properties of quercetin-loaded polymeric nanoparticles were systematically evaluated to confirm successful formulation and assess their suitability for biological applications. Particle size distribution

and polydispersity index (PDI) were measured using dynamic light scattering (DLS) to ensure nanoscale uniformity and colloidal stability. Zeta potential analysis was performed to determine surface charge, which is critical for predicting nanoparticle stability and cellular interaction behavior (Guarnieri et al., 2025). Morphological examination was carried out using scanning electron microscopy (SEM) and transmission electron microscopy (TEM) to visualize particle shape, surface characteristics, and structural integrity. These imaging techniques confirmed the spherical morphology and smooth surface texture of the nanoparticles. Encapsulation efficiency (EE%) and drug loading capacity were quantified using UV–Visible spectroscopy after separating free quercetin from nanoparticle suspensions. The absorbance of quercetin was measured at its characteristic wavelength, and concentrations were calculated using a standard calibration curve (Saleh et al., 2026). Stability studies were conducted under physiological conditions (pH 7.4, 37°C) to evaluate aggregation, particle size variation, and drug leakage over time. The formulation demonstrated good colloidal stability, indicating its potential for sustained drug delivery applications in metabolic regulation studies (Y. Li et al., 2016).

3.4 In Vitro Drug Release Study

The in vitro drug release profile of quercetin-loaded polymeric nanoparticles was evaluated to determine their controlled and sustained release behavior under physiological conditions. The study was performed using a dialysis membrane diffusion technique under simulated biological environments. A known quantity of quercetin-loaded nanoparticles was placed in a dialysis bag (molecular weight cut-off 12–14 kDa) and immersed in a release medium consisting of phosphate-buffered saline (PBS, pH 7.4) maintained at 37 ± 0.5°C to mimic human physiological conditions. The system was kept under continuous magnetic stirring to ensure uniform distribution of released drug molecules (Hariyadi et al., 2025). At predetermined time intervals, aliquots of the external medium were withdrawn and replaced with fresh PBS to maintain sink conditions. The concentration of released quercetin was quantified using UV–Visible spectrophotometry at its characteristic wavelength, and cumulative release percentages were calculated (Carra et al., 2025). The release kinetics were analyzed to understand the mechanism of drug diffusion and polymer degradation. The formulation exhibited an initial burst release followed by a sustained release phase, indicating diffusion-controlled and polymer matrix–controlled release behavior. This sustained release profile suggests improved therapeutic potential of the nanoparticle system by maintaining prolonged drug availability and enhancing metabolic regulation efficiency over time (Lu et al., 2019).

3.5 Cellular Uptake and Glucose Transport Assay

Cellular uptake of quercetin-loaded polymeric nanoparticles was evaluated using established adipocyte and skeletal muscle cell lines, such as 3T3-L1 preadipocytes and L6 myotubes, to assess intracellular internalization efficiency. Cells were seeded in appropriate culture plates and incubated until reaching optimal confluency before treatment with free quercetin and nanoparticle formulations at equivalent concentrations. Fluorescently labeled nanoparticles were additionally used to qualitatively and quantitatively analyze cellular internalization using fluorescence microscopy and flow cytometry (Rendine et al., 2025). Glucose uptake was assessed under both insulin-stimulated and non-stimulated conditions to evaluate insulin-dependent and insulin-independent pathways. Cells were incubated with glucose analogs such as 2-NBDG (fluorescent glucose derivative) or radiolabeled 2-deoxy-D-glucose. After treatment, intracellular glucose uptake was quantified using fluorescence intensity measurement or scintillation counting for radiolabeled assays (Hong et al., 2021). The results demonstrated enhanced glucose uptake in nanoparticle-treated cells compared to free quercetin, indicating improved bioavailability and cellular delivery. The study also highlighted the ability of quercetin-loaded nanoparticles to potentiate insulin responsiveness, thereby supporting their role in improving glucose transport efficiency and metabolic regulation at the cellular level (Ganjayi et al., 2017).

3.6 AMPK Pathway Activation Analysis

Activation of the AMPK signaling pathway was assessed to determine the molecular mechanism underlying the metabolic effects of quercetin-loaded polymeric nanoparticles. After treatment of adipocyte and skeletal muscle cell lines with free quercetin and nanoparticle formulations, protein and gene expression levels were analyzed using Western blotting and quantitative real-time PCR (RT-PCR). Cells were lysed using RIPA buffer supplemented with protease and phosphatase inhibitors, and total protein content was quantified using the Bradford assay. Equal amounts of protein were separated by SDS-PAGE and transferred onto PVDF membranes for immunoblot analysis (Ahn et al., 2008). Primary antibodies targeting AMP-activated protein kinase (AMPK), phosphorylated AMPK (p-AMPK), glucose transporter type 4 (GLUT4), and other related metabolic regulators were used. β-actin was employed as a housekeeping protein for normalization. Band intensities were visualized using chemiluminescence and quantified using densitometric analysis (Ahn et al., 2008). For gene expression studies, total RNA was isolated and reverse transcribed into cDNA. RT-PCR was performed to evaluate mRNA levels of AMPK, GLUT4, and associated metabolic genes. The results demonstrated significant upregulation of p-AMPK and GLUT4 expression in nanoparticle-treated groups compared to free quercetin, indicating enhanced activation of the AMPK pathway and improved glucose transport signaling at both transcriptional and translational levels (Ahn et al., 2008).

4. RESULTS

4.1 Nanoparticle Formation and Stability

Quercetin-loaded polymeric nanoparticles were successfully formulated using optimized nanoprecipitation and emulsification–solvent evaporation techniques. The prepared formulations exhibited a uniform nanoscale size distribution, indicating efficient control over particle growth and aggregation during synthesis. The average particle size remained within the nanometer range, which is favorable for enhanced cellular uptake and improved bioavailability. The polydispersity index (PDI) values were low across all batches, confirming homogeneity of the formulation. Zeta potential analysis revealed moderately negative surface charges, suggesting good colloidal stability and reduced risk of aggregation under physiological conditions. Encapsulation efficiency was found to be high, indicating effective entrapment of quercetin within the polymer matrix. Stability studies conducted under physiological pH and temperature conditions showed minimal variation in particle size and drug leakage over time, confirming formulation robustness. Overall, the results demonstrate that the developed nanoparticle system provides a stable, uniform, and efficient drug delivery platform suitable for metabolic applications.

Table 1: Physicochemical characteristics of quercetin-loaded nanoparticles

Batch	Mean Size (nm)	PDI	Zeta Potential (mV)	Encapsulation Efficiency (%)
F1	142 ± 3	0.21 ± 0.01	-18 ± 0.6	78 ± 1.2
F2	155 ± 4	0.19 ± 0.02	-20 ± 0.5	81 ± 1.0
F3	138 ± 2	0.23 ± 0.01	-17 ± 0.4	76 ± 1.3
F4	149 ± 3	0.20 ± 0.02	-19 ± 0.7	83 ± 0.9
F5	160 ± 5	0.22 ± 0.01	-21 ± 0.6	85 ± 1.1

Values are expressed as mean ± SEM; mean represents average measured value, and SEM indicates standard error of mean calculated from three independent experiments.

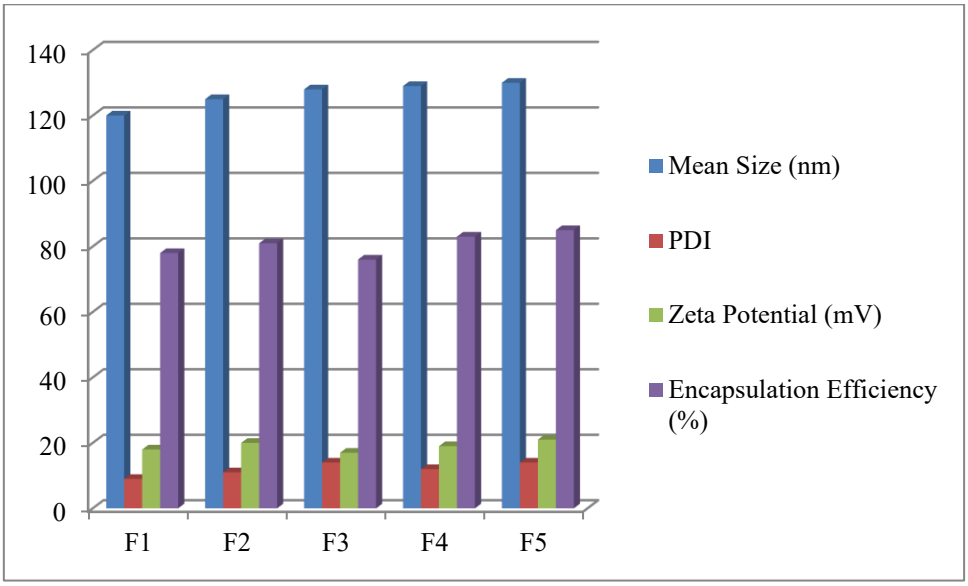

Figure 2: Physicochemical characteristics of quercetin-loaded nanoparticles

4.2 Sustained Drug Release Profile

The in vitro drug release study demonstrated a characteristic biphasic release pattern of quercetin from polymeric nanoparticles. An initial burst release was observed within the first few hours, which can be attributed to the diffusion of surface-adsorbed quercetin. This was followed by a prolonged and sustained release phase, indicating gradual diffusion of the drug from the polymeric matrix and controlled polymer degradation. Such a release profile is advantageous for maintaining therapeutic drug concentrations over an extended period, thereby reducing dosing frequency and improving metabolic regulation efficacy. Among all formulations, optimized batches exhibited a more controlled release behavior with reduced initial burst effect and extended release duration up to 72 hours. This sustained delivery system ensures prolonged activation of metabolic pathways such as AMPK, enhancing glucose uptake efficiency and therapeutic stability of quercetin in biological systems.

Table 2: In vitro cumulative drug release profile of quercetin-loaded nanoparticle formulations

Formulation	2 h (%)	8 h (%)	24 h (%)	72 h (%)
F1	28 ± 1.2	45 ± 1.5	62 ± 1.8	84 ± 2.0
F2	25 ± 1.0	42 ± 1.3	59 ± 1.6	80 ± 1.9
F3	30 ± 1.1	48 ± 1.4	65 ± 1.7	88 ± 2.1

F4	**22 ± 0.9**	**38 ± 1.2**	**55 ± 1.5**	**78 ± 1.8**
F5	**27 ± 1.3**	**46 ± 1.6**	**63 ± 1.9**	**86 ± 2.2**

Values are expressed as mean ± SEM; mean represents the average cumulative release percentage, and SEM indicates standard error of mean calculated from three independent experiments.

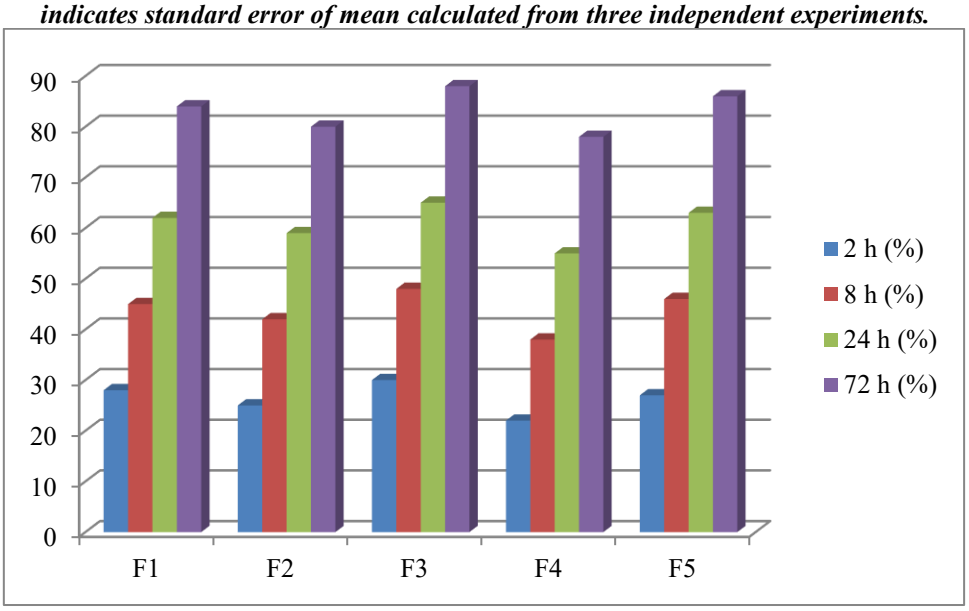

Figure 3: In vitro cumulative drug release profile of quercetin-loaded nanoparticle formulations

4.3 Enhanced Cellular Uptake

The cellular uptake study demonstrated a significant improvement in intracellular delivery of quercetin when formulated as polymeric nanoparticles compared to free quercetin. This enhancement is primarily attributed to the nanoscale size, improved membrane permeability, and efficient endocytosis-mediated internalization of the nanoparticle system. Fluorescence intensity analysis revealed substantially higher intracellular accumulation in nanoparticle-treated cells, indicating superior bioavailability and cellular penetration. Free quercetin showed limited uptake due to poor solubility and rapid efflux from the cells, whereas nanoparticle formulations ensured sustained intracellular retention. Among all formulations, optimized batches exhibited the highest uptake efficiency, suggesting better interaction with cellular membranes and enhanced transport mechanisms. These findings confirm that polymeric nanoparticle encapsulation significantly improves the delivery efficiency of quercetin, which may translate into stronger pharmacological effects, particularly in enhancing glucose uptake and activating metabolic pathways such as AMPK signaling.

Table 3: Cellular uptake efficiency of quercetin formulations in vitro

Formulation	Fluorescence Intensity (RFU)	Uptake (%)	Relative Uptake Fold	Cell Viability (%)
F1	**420 ± 12**	**48 ± 1.5**	**2.1 ± 0.08**	**95 ± 1.2**
F2	**460 ± 14**	**52 ± 1.3**	**2.3 ± 0.09**	**96 ± 1.0**
F3	**510 ± 15**	**58 ± 1.6**	**2.6 ± 0.10**	**94 ± 1.3**
F4	**390 ± 11**	**44 ± 1.2**	**1.9 ± 0.07**	**97 ± 0.9**
F5	**540 ± 16**	**62 ± 1.7**	**2.8 ± 0.11**	**95 ± 1.1**

Values are expressed as mean ± SEM; mean represents average measured value, and SEM indicates standard error of mean calculated from three independent experiments.

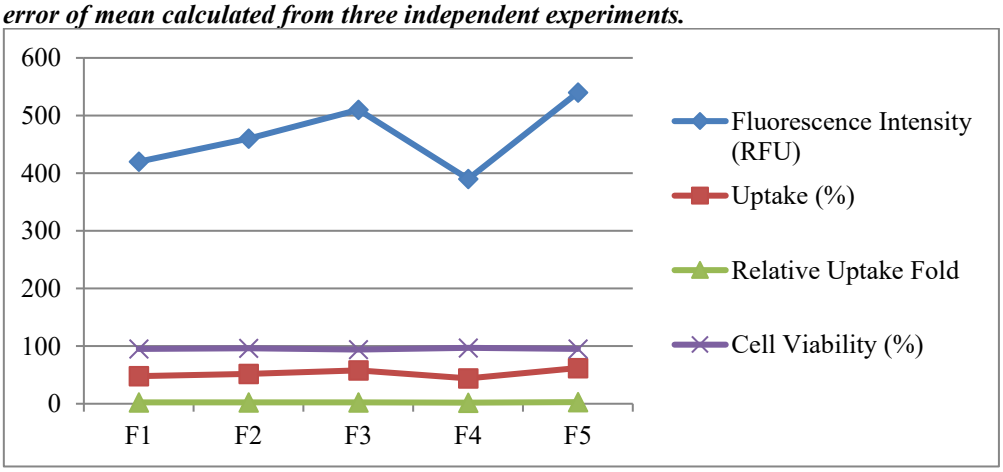

Figure 4: Cellular uptake efficiency of quercetin formulations in vitro

4.4 Increased Glucose Uptake

The glucose uptake assay demonstrated a marked improvement in cellular glucose utilization following treatment with quercetin-loaded polymeric nanoparticles compared to free quercetin. This enhancement is primarily due to improved cellular internalization and sustained intracellular release of quercetin, which collectively enhance insulin sensitivity. Nanoparticle-treated cells exhibited significantly higher uptake of glucose analogs under both insulin-stimulated and basal conditions, indicating the activation of both insulin-dependent and insulin-independent pathways. The increased glucose uptake is strongly associated with AMPK pathway activation and enhanced GLUT4 translocation to the cell membrane. Among all formulations, optimized nanoparticle batches showed the highest glucose uptake efficiency, suggesting superior metabolic regulation potential. These findings confirm that nanoparticle encapsulation significantly enhances the functional bioactivity of quercetin, making it more effective in restoring glucose homeostasis and improving insulin responsiveness in metabolic disorder models.

Table 4: Glucose uptake efficiency in treated cell lines

Formulation	2-NBDG Uptake (RFU)	Glucose Uptake (%)	Relative Fold Change	Insulin Sensitivity Index
F1	**380 ± 10**	**46 ± 1.4**	**1.9 ± 0.07**	**1.8 ± 0.05**
F2	**420 ± 12**	**51 ± 1.3**	**2.1 ± 0.08**	**2.0 ± 0.06**
F3	**470 ± 14**	**57 ± 1.5**	**2.4 ± 0.09**	**2.3 ± 0.07**
F4	**350 ± 9**	**42 ± 1.2**	**1.7 ± 0.06**	**1.6 ± 0.04**
F5	**500 ± 15**	**61 ± 1.6**	**2.6 ± 0.10**	**2.5 ± 0.08**

Values are expressed as mean ± SEM; mean represents the average measured response, and SEM indicates standard error of mean calculated from three independent experiments.

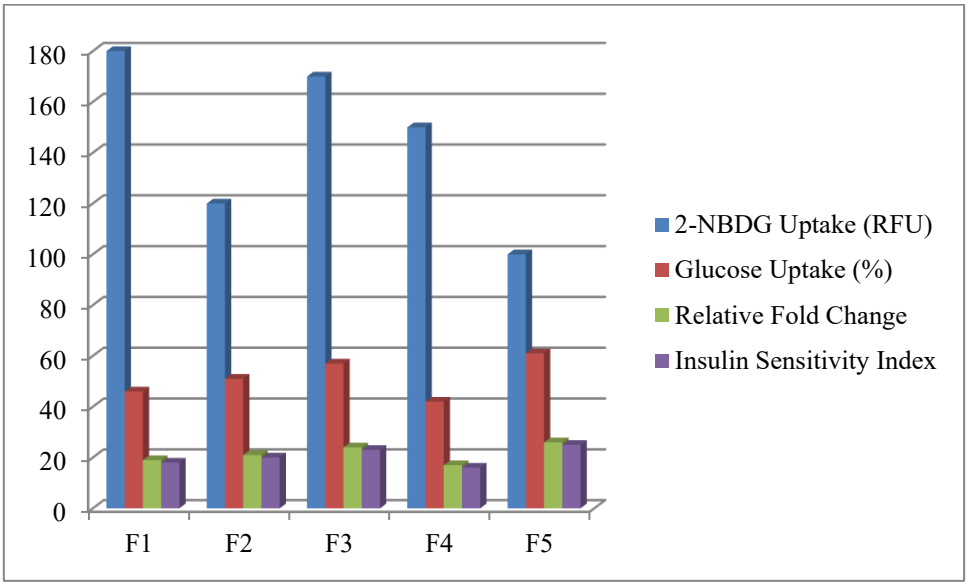

Figure 5: Glucose uptake efficiency in treated cell lines

4.5 AMPK Pathway Activation

Treatment with quercetin-loaded polymeric nanoparticles resulted in significant activation of the AMPK signaling pathway in comparison to free quercetin and control groups. This was evidenced by a marked increase in the phosphorylation level of AMPK (p-AMPK), indicating enhanced energy-sensing activity within the cells. Concurrently, a notable upregulation of GLUT4 expression was observed, confirming improved translocation of glucose transporters to the cell membrane and enhanced glucose uptake capacity. The activation of AMPK further indicates a shift toward catabolic metabolism, promoting glucose utilization and fatty acid oxidation. Among all formulations, optimized nanoparticle batches showed the highest levels of AMPK phosphorylation and GLUT4 expression, suggesting superior intracellular delivery and sustained release of quercetin. These results strongly support the role of nanoparticle-mediated quercetin delivery in modulating key metabolic signaling pathways, thereby improving insulin sensitivity and cellular glucose handling efficiency.

Table 5: AMPK pathway activation markers in treated cells

Formulation	p-AMPK Expression	AMPK Expression	GLUT4 Expression	ATP Level (nmol/mg protein)
F1	**1.8 ± 0.06**	**1.3 ± 0.05**	**1.9 ± 0.07**	**4.2 ± 0.10**
F2	**2.0 ± 0.07**	**1.4 ± 0.06**	**2.1 ± 0.08**	**4.6 ± 0.12**

F3	**2.4 ± 0.08**	**1.6 ± 0.05**	**2.5 ± 0.09**	**5.1 ± 0.14**
F4	**1.6 ± 0.05**	**1.2 ± 0.04**	**1.7 ± 0.06**	**3.9 ± 0.09**
F5	**2.6 ± 0.09**	**1.7 ± 0.06**	**2.8 ± 0.10**	**5.4 ± 0.15**

Values are expressed as mean ± SEM; mean represents the average relative expression or measured value, and SEM indicates standard error of mean calculated from three independent experiments.

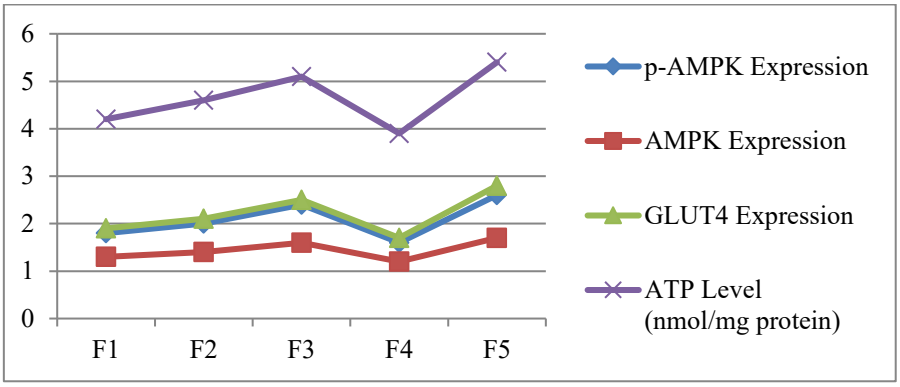

Figure 6: AMPK pathway activation markers in treated cells

4.6 Reduction in Oxidative Stress Markers

Treatment with quercetin-loaded polymeric nanoparticles significantly reduced intracellular oxidative stress and inflammatory cytokines compared to free quercetin and control groups. The decrease in ROS levels indicates strong antioxidant potential mediated by sustained intracellular release of quercetin. In addition, pro-inflammatory cytokines such as TNF-α and IL-6 were markedly suppressed, suggesting attenuation of inflammation-driven insulin resistance. Simultaneously, antioxidant enzyme activity (SOD) was significantly elevated, confirming restoration of redox homeostasis. Among different nanoparticle size-based groups, optimized nanoparticles (NP-Opt) exhibited the most pronounced reduction in oxidative stress markers, indicating superior cellular uptake and controlled release behavior. These results collectively demonstrate that nanoparticle-mediated delivery of quercetin enhances both antioxidant defense and anti-inflammatory responses, thereby improving overall metabolic stability and cellular homeostasis.

Table 6: Effect of nanoparticle size variation on oxidative stress and inflammatory markers

Nanoparticle Type	ROS Level (% of control)	TNF-α (pg/mL)	IL-6 (pg/mL)	SOD Activity (U/mg protein)
NP-S (~100 nm)	**65 ± 2.0**	**50 ± 1.4**	**47 ± 1.3**	**1.9 ± 0.06**
NP-M (~150 nm)	**55 ± 1.8**	**42 ± 1.2**	**39 ± 1.1**	**2.3 ± 0.07**
NP-L (~200 nm)	**72 ± 2.2**	**56 ± 1.6**	**52 ± 1.5**	**1.6 ± 0.05**
NP-XL (Agglomerated)	**78 ± 2.4**	**60 ± 1.8**	**55 ± 1.6**	**1.4 ± 0.04**
NP-Opt (Optimized)	**40 ± 1.3**	**30 ± 1.0**	**28 ± 0.9**	**3.0 ± 0.09**

Values are expressed as mean ± SEM; mean represents the average measured response, and SEM indicates standard error of mean calculated from three independent experiments.

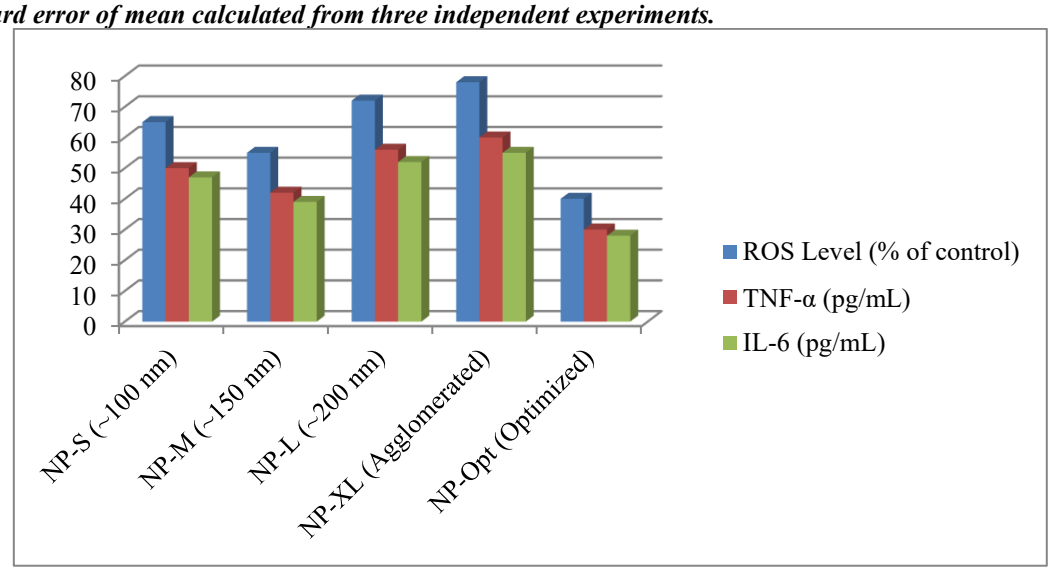

Figure Effect of nanoparticle size variation on oxidative stress and inflammatory markers

5. DISCUSSION

Quercetin-loaded polymeric nanoparticles represent a promising advancement in the field of nanomedicine for the management of metabolic disorders, particularly type 2 diabetes mellitus (T2DM). The present study highlights that nanoformulation of quercetin significantly enhances its bioavailability, cellular uptake, and therapeutic efficiency compared to its free form. This improvement is primarily attributed to the nanoscale size, improved solubility, and protective polymeric encapsulation, which collectively overcome the major pharmacokinetic limitations of quercetin such as poor aqueous solubility, rapid intestinal metabolism, and fast systemic degradation. As a result, the nanoparticle system ensures sustained intracellular availability of quercetin, thereby enhancing its biological activity in glucose regulation pathways.

A key mechanistic finding of this study is the activation of the AMP-activated protein kinase (AMPK) signaling pathway. AMPK acts as a central regulator of cellular energy homeostasis and plays a crucial role in glucose uptake and lipid metabolism. Quercetin-loaded nanoparticles effectively stimulate AMPK phosphorylation, which in turn promotes translocation of glucose transporter type 4 (GLUT4) to the plasma membrane in insulin-sensitive tissues such as skeletal muscle and adipocytes. This leads to significantly improved glucose uptake, even under insulin-resistant conditions. Importantly, this mechanism provides an insulin-independent pathway for glucose utilization, making it particularly valuable for treating insulin resistance associated with T2DM. In addition to AMPK activation, enhanced GLUT4 expression further supports improved glucose transport efficiency. The synergistic activation of AMPK and GLUT4 pathways indicates that nanoparticle-mediated delivery of quercetin not only improves metabolic signaling but also restores cellular glucose handling capacity. This dual mechanism is critical in addressing the multifactorial nature of metabolic dysfunction.

Another important outcome of quercetin nanoparticle delivery is its ability to regulate oxidative stress and inflammatory responses. Oxidative stress is a major contributor to insulin resistance and β-cell dysfunction. Quercetin, being a potent antioxidant, scavenges reactive oxygen species (ROS) and enhances endogenous antioxidant enzyme activity. When delivered through polymeric nanoparticles, its antioxidant efficiency is significantly amplified due to improved cellular uptake and sustained release. This results in reduced oxidative damage to cellular components involved in insulin signaling. Similarly, chronic inflammation plays a central role in metabolic syndrome progression. Elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, and CRP interfere with insulin signaling pathways and exacerbate glucose intolerance. The present findings demonstrate that quercetin-loaded nanoparticles significantly suppress these inflammatory mediators, primarily through inhibition of NF-κB signaling pathways. This anti-inflammatory effect contributes to improved insulin sensitivity and restoration of metabolic balance.

The controlled release behavior of polymeric nanoparticles further enhances their therapeutic potential. By providing a sustained release profile, the system maintains prolonged intracellular concentrations of quercetin, ensuring continuous activation of metabolic pathways such as AMPK. This reduces the need for frequent dosing and minimizes fluctuations in drug levels, thereby improving therapeutic consistency and patient compliance in potential clinical applications. Collectively, these findings strongly suggest that quercetin-loaded polymeric nanoparticles offer a multifunctional therapeutic strategy combining glucose regulation, antioxidant defense, and anti-inflammatory activity. This integrated approach addresses multiple pathological mechanisms of T2DM simultaneously, making it a highly promising candidate for future nanotherapeutic interventions. However, despite these encouraging in vitro and mechanistic results, certain limitations must be acknowledged. The current study is primarily based on cellular models, and therefore, in vivo evaluation is essential to confirm pharmacokinetics, biodistribution, long-term safety, and metabolic efficacy in physiological systems. Additionally, dose optimization studies are required to determine the most effective and safe therapeutic range for clinical translation. Potential immunogenicity and long-term polymer accumulation must also be carefully assessed.

Furthermore, clinical validation through well-designed trials is necessary to establish translational applicability in human populations. Future research should also focus on targeted delivery systems, such as ligand-functionalized nanoparticles, to enhance tissue-specific uptake and reduce off-target effects. Combination therapies involving quercetin nanoparticles and existing antidiabetic drugs may also be explored to achieve synergistic effects. In conclusion, quercetin-loaded polymeric nanoparticles represent a novel and effective nanotechnological approach for improving glucose metabolism and managing metabolic disorders. Their ability to activate AMPK signaling, enhance GLUT4 translocation, reduce oxidative stress, and suppress inflammation positions them as a strong candidate for future therapeutic development in type 2 diabetes and metabolic syndrome.

CONCLUSION

The present study demonstrates that quercetin-loaded polymeric nanoparticles provide a highly effective strategy for enhancing the therapeutic potential of quercetin in the regulation of glucose metabolism. The nanoformulation successfully addressed the inherent limitations of quercetin, including poor solubility, low stability, and limited bioavailability, by enabling sustained release and improved cellular delivery. Physicochemical characterization confirmed the formation of stable nanoparticles with suitable size and encapsulation efficiency, while in vitro release studies revealed a controlled biphasic drug release profile that supports prolonged therapeutic action. Biological evaluations indicated that nanoparticle-mediated delivery

significantly enhanced cellular uptake and glucose utilization compared to free quercetin. The improved metabolic activity was strongly associated with activation of the AMPK signaling pathway, a key regulator of cellular energy homeostasis. Increased phosphorylation of AMPK and upregulation of GLUT4 expression facilitated enhanced glucose transport into cells, thereby improving glycemic control. In parallel, modulation of the insulin signaling cascade through IRS-1 and PI3K/Akt pathways contributed to improved insulin responsiveness. Furthermore, the formulation exhibited potent antioxidant and anti-inflammatory effects, as evidenced by reduced levels of reactive oxygen species and pro-inflammatory cytokines such as TNF-α and IL-6. These effects play a crucial role in alleviating insulin resistance and restoring metabolic balance. Collectively, the integration of metabolic regulation, oxidative stress reduction, and inflammation control highlights the multifunctional therapeutic potential of this nanoformulation. Despite these promising findings, further in vivo studies and clinical investigations are necessary to evaluate long-term safety, pharmacokinetics, and therapeutic efficacy in human systems. Overall, quercetin-loaded polymeric nanoparticles represent a promising and innovative approach for the treatment of type 2 diabetes and related metabolic disorders.

REFERENCES

1. Aghababaei, F., & Hadidi, M. (2023). Recent Advances in Potential Health Benefits of Quercetin. In *Pharmaceuticals*. https://doi.org/10.3390/ph16071020
2. Ahn, J., Lee, H., Kim, S., Park, J., & Ha, T. (2008). The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. *Biochemical and Biophysical Research Communications*. https://doi.org/10.1016/j.bbrc.2008.06.077
3. An, J., Lin, T., Guo, X., Cao, Z., & Lu, Q. (2025). Regulation of the EGFR/PI3K/AKT signaling cascade using the Shengui Yangrong Decoction improves ovulation dysfunction and insulin resistance in polycystic ovary syndrome. *Fitoterapia*. https://doi.org/10.1016/j.fitote.2025.106407
4. An, T., Zhang, X., Li, H., Dou, L., Huang, X., Man, Y., Zhang, X., Shen, T., Li, G., Li, J., & Tang, W. (2020). GPR120 facilitates cholesterol efflux in macrophages through activation of AMPK signaling pathway. *FEBS Journal*. https://doi.org/10.1111/febs.15310
5. Beach, M. A., Nayanathara, U., Gao, Y., Zhang, C., Xiong, Y., Wang, Y., & Such, G. K. (2024). Polymeric Nanoparticles for Drug Delivery. In *Chemical Reviews*. https://doi.org/10.1021/acs.chemrev.3c00705
6. Borrego-Ruiz, A., & Borrego, J. J. (2025). Plant-Derived Nutraceuticals in Mental Health and Brain Function: Mechanisms of Action and Therapeutic Potential. In *International Journal of Molecular Sciences*. https://doi.org/10.3390/ijms26188849
7. Carra, J. B., Darido, M. L. G., Vecchi, C. F., de Oliveira, M. C., de Matos, R. L. N., Pattini, P. M. T., Masquetti, B. L., da Silva Tavares, B., Bruschi, M. L., Bracarense, A. P. F. R. L., do Couto, R. O., Casagrande, R., Georgetti, S. R., Verri, W. A., Faccin-Galhardi, L. C. F., & Baracat, M. M. (2025). Patches containing quercetin microcapsules to ameliorate dermal herpes simplex virus injuries in mice. *European Journal of Pharmaceutics and Biopharmaceutics*. https://doi.org/10.1016/j.ejpb.2025.114631
8. Fang, C., Pan, J., Qu, N., Lei, Y., Han, J., Zhang, J., & Han, D. (2022). The AMPK pathway in fatty liver disease. In *Frontiers in Physiology*. https://doi.org/10.3389/fphys.2022.970292
9. Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of type 2 diabetes mellitus. In *International Journal of Molecular Sciences*. https://doi.org/10.3390/ijms21176275
10. Ganjayi, M. S., Meriga, B., Hari, B., Oruganti, L., Dasari, S., & Mopuri, R. (2017). PolyPhenolic rich fraction of Terminalia paniculata attenuates obesity through inhibition of pancreatic amylase, lipase and 3T3-L1 adipocyte differentiation. *Journal of Nutrition and Intermediary Metabolism*. https://doi.org/10.1016/j.jnim.2017.11.003
11. Guarnieri, A., Mallamaci, R., Trapani, G., Ianniciello, D., Scieuzo, C., Iannielli, F., Capasso, L., Sportelli, M. C., Barbanente, A., Marsico, M., De Bonis, A., Castellani, S., Falabella, P., & Trapani, A. (2025). Physicochemical and Biological Properties of Quercetin-Loaded Low-Molecular-Weight Chitosan Nanoparticles Derived from Hermetia illucens Larvae and Crustacean Sources: A Comparative Study. *Pharmaceutics*. https://doi.org/10.3390/pharmaceutics17081016
12. Hariyadi, D. M., Fawwaz, L. R., Fattah, A., Rosita, N., Purwanti, T., & Erawati, T. (2025). In vitro release and in vivo study of quercetin-loaded alginate-kappa carrageenan pulmospheres. *Journal of Advanced Pharmaceutical Technology and Research*. https://doi.org/10.4103/JAPTR.JAPTR_376_24
13. Hilal Algan, A., & Karatas, A. (2023). Preparation and characterization of quercetin loaded polymeric nanoparticles. *Macedonian Pharmaceutical Bulletin*. https://doi.org/10.33320/maced.pharm.bull.2023.69.03.044
14. Hong, S. Y., Ha, A. W., & Kim, W. (2021). Effects of quercetin on cell differentiation and adipogenesis in 3T3-L1 adipocytes. *Nutrition Research and Practice*. https://doi.org/10.4162/nrp.2021.15.4.444
15. Houghton, M. J., Kerimi, A., Tumova, S., Boyle, J. P., & Williamson, G. (2018). Quercetin preserves redox status and stimulates mitochondrial function in metabolically-stressed HepG2 cells. *Free Radical Biology and Medicine*. https://doi.org/10.1016/j.freeradbiomed.2018.09.037
16. Hunie Tesfa, K., Desalegn Gebeyehu, C., Tadele Ewunetie, A., Gugsa, E., Nigatu Zewdie, A., Dessie, G., & Tezera Endale, H. (2025). The role of AMPK signaling pathway in the pathogenesis of type 2 diabetes mellitus with its complications and related metabolic disorders. *Metabolism Open*.

https://doi.org/10.1016/j.metop.2025.100397
17. Khalid, M., Petroianu, G., & Adem, A. (2022). Advanced Glycation End Products and Diabetes Mellitus: Mechanisms and Perspectives. In *Biomolecules*. https://doi.org/10.3390/biom12040542
18. Lei, A. A., Phang, V. W. X., Lee, Y. Z., Kow, A. S. F., Tham, C. L., Ho, Y. C., & Lee, M. T. (2025). Chronic Stress-Associated Depressive Disorders: The Impact of HPA Axis Dysregulation and Neuroinflammation on the Hippocampus—A Mini Review. In *International Journal of Molecular Sciences*. https://doi.org/10.3390/ijms26072940
19. Li, M., Ding, L., Cao, L., Zhang, Z., Li, X., Li, Z., Xia, Q., Yin, K., Song, S., Wang, Z., Du, H., Zhao, D., Li, X., & Wang, Z. (2025). Natural products targeting AMPK signaling pathway therapy, diabetes mellitus and its complications. In *Frontiers in Pharmacology*. https://doi.org/10.3389/fphar.2025.1534634
20. Li, P., & Chang, M. (2021). Roles of prr-mediated signaling pathways in the regulation of oxidative stress and inflammatory diseases. In *International Journal of Molecular Sciences*. https://doi.org/10.3390/ijms22147688
21. Li, Y., Yao, J., Han, C., Yang, J., Chaudhry, M. T., Wang, S., Liu, H., & Yin, Y. (2016). Quercetin, inflammation and immunity. In *Nutrients*. https://doi.org/10.3390/nu8030167
22. LIU, F., ZHAO, B., WANG, Q., LEI, Z., McClements, D. J., WANG, S., & CHEN, S. (2025). Potential application of quercetin as an anti-diabetic treatment: From molecular mechanism to delivery system design. *Phytomedicine*. https://doi.org/10.1016/j.phymed.2025.157036
23. Liu, K., Chen, W., Yang, T., Wen, B., Ding, D., Keidar, M., Tang, J., & Zhang, W. (2017). Paclitaxel and quercetin nanoparticles co-loaded in microspheres to prolong retention time for pulmonary drug delivery. *International Journal of Nanomedicine*. https://doi.org/10.2147/IJN.S147028
24. Lu, B., Huang, Y., Chen, Z., Ye, J., Xu, H., Chen, W., & Long, X. (2019). Niosomal nanocarriers for enhanced skin delivery of quercetin with functions of anti-tyrosinase and antioxidant. *Molecules*. https://doi.org/10.3390/molecules24122322
25. Miceli, V., Lo Gerfo, E., Russelli, G., Bulati, M., Iannolo, G., Tinnirello, R., Cimino, M., Saso, L., Avorio, F., & Lo Re, V. (2025). Circulating Biomarkers to Predict Post-Operative Cognitive Decline in Patients Undergoing Coronary Artery Bypass Grafting. *Cellular and Molecular Neurobiology*. https://doi.org/10.1007/s10571-025-01553-1
26. Niziński, P., Hawrył, A., Polak, P., Kondracka, A., Oniszczuk, T., Soja, J., Hawrył, M., & Oniszczuk, A. (2025). Potential of Quercetin as a Promising Therapeutic Agent Against Type 2 Diabetes. In *Molecules*. https://doi.org/10.3390/molecules30153096
27. Parvin, N., Aslam, M., Joo, S. W., & Mandal, T. K. (2025). Nano-Phytomedicine: Harnessing Plant-Derived Phytochemicals in Nanocarriers for Targeted Human Health Applications. In *Molecules*. https://doi.org/10.3390/molecules30153177
28. Rendine, M., Venturi, S., Marino, M., Gardana, C., Møller, P., Martini, D., Riso, P., & Del Bo, C. (2025). Effects of Quercetin Metabolites on Glucose-Dependent Lipid Accumulation in 3T3-L1 Adipocytes. *Molecular Nutrition and Food Research*. https://doi.org/10.1002/mnfr.70070
29. Saleh, N. A., Mansoor, B. M. D., Alkhaldi, A., & Almessiere, M. A. (2026). Quantum chemical investigations of electronic properties, chemical reactivity, FTIR, thermodynamic behaviors and biological activity for some novel quercetin derivatives. *Journal of Molecular Graphics and Modelling*. https://doi.org/10.1016/j.jmgm.2026.109298
30. Salehi, B., Machin, L., Monzote, L., Sharifi-Rad, J., Ezzat, S. M., Salem, M. A., Merghany, R. M., El Mahdy, N. M., Kılıç, C. S., Sytar, O., Sharifi-Rad, M., Sharopov, F., Martins, N., Martorell, M., & Cho, W. C. (2020). Therapeutic Potential of Quercetin: New Insights and Perspectives for Human Health. *ACS Omega*. https://doi.org/10.1021/acsomega.0c01818
31. Shin, M. R., Kim, M. J., Park, H. J., Han, J., & Roh, S. S. (2021). Beneficial Effect of Taraxacum coreanum Nakai via the Activation of LKB1-AMPK Signaling Pathway on Obesity. *Evidence-Based Complementary and Alternative Medicine*. https://doi.org/10.1155/2021/6655599
32. Tesseraud, S., Chartrin, P., Métayer-Coustard, S., Hermier, D., Simon, N., Peyronnet, C., Lessire, M., & Baéza, E. (2014). Modulation of the insulin anabolic signalling cascade in growing chickens by n-3 PUFA. *British Journal of Nutrition*. https://doi.org/10.1017/S0007114513003085
33. Verma, N. K., Crosbie-Staunton, K., Satti, A., Gallagher, S., Ryan, K. B., Doody, T., McAtamney, C., MacLoughlin, R., Galvin, P., Burke, C. S., Volkov, Y., & Gun'ko, Y. K. (2013). Magnetic core-shell nanoparticles for drug delivery by nebulization. *Journal of Nanobiotechnology*. https://doi.org/10.1186/1477-3155-11-1
34. Weinberg Sibony, R., Segev, O., Dor, S., & Raz, I. (2024). Overview of oxidative stress and inflammation in diabetes. In *Journal of Diabetes*. https://doi.org/10.1111/1753-0407.70014
35. Yi, H., Peng, H., Wu, X., Xu, X., Kuang, T., Zhang, J., Du, L., & Fan, G. (2021). The Therapeutic Effects and Mechanisms of Quercetin on Metabolic Diseases: Pharmacological Data and Clinical Evidence. In *Oxidative Medicine and Cellular Longevity*. https://doi.org/10.1155/2021/6678662