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Recent Developments in Quercetin-Loaded Nanoparticles for Cancer Targeting

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ABSTRACT

Quercetin, a dietary polyphenol, has demonstrated anticancer properties across several malignancies, including pancreatic cancer, breast cancer, and melanoma. Quercetin is a naturally occurring bioflavonoid found in fruits, vegetables, seeds, berries, and tea. The cancer-preventive properties of quercetin are well established, attributed to its anti-inflammatory, anti-proliferative, and anti-angiogenic effects. Nonetheless, the inadequate water solubility and transport, chemical instability, brief half-life, and low bioavailability of quercetin restrict its therapeutic use in cancer chemoprevention. A comprehensive understanding of the molecular mechanisms governing controlled and regulated drug delivery is crucial for developing innovative and effective therapeutics. To surmount the accessibility constraints of quercetin, it may be administered as nano-conjugated quercetin. Nano-conjugated quercetin has garnered significant interest owing to its regulated drug release, prolonged retention in tumors, improved anticancer efficacy, and potential for therapeutic application. This paper presents an overview of quercetin's effects on cancer cells and the mechanisms behind these actions. We also examine the prospective usage of nanoparticles as nanocarriers in medicine delivery systems. This review can summarize the recent developments in quercetin-loaded Nanoparticles for Cancer treatment.

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Abbreviations

QCN: Quercetin
PNPs: Polymeric Nanoparticles
PACA: Poly Alkyl Cyanoacrylate
PCL: Polycaprolactone
PEI: Polyethyleneimine
PLA: Polylactic Acid
FA: Folic Acid
BSA: Modified Bovine Serum Albumin
(FA-Rg5-BSA NPs): Nanoparticles
SLN: Solid Lipid Nanoparticles
ZMSLN: Zataria Multiflora
QCN-LNPs: QCN Liposome Nanoparticles
MPA-LNPs: MPA Liposome Nanoparticles
QDs: Quantum Dots
EXOs: Exosomes
ROS: Reactive Oxygen Species
ADR: Agents Adriamycin
MTX: Mitoxantrone
MDR: Multi-Drug Resistance

Introduction

Quercetin is a flavonol, a subclass of flavonoids frequently found in diverse foods such as onions, fruits, and vegetables. Quercetin, at safe doses, is recognized for its numerous biological impacts, although many of its processes remain enigmatic. Although the majority of knowledge regarding quercetin is derived from in vitro and mouse studies, substantial evidence indicates that quercetin possesses numerous medically advantageous qualities. These qualities substantiate quercetin's efficacy in addressing oxidative damage, cancer, inflammation, bacterial and viral infections, cardiovascular disease, and diabetes. The extent of investigation for each of these groups differs. To our knowledge, definitive evidence of quercetin's advantages has not undergone the full spectrum of pharmacological research trials. This research will concentrate solely on quercetin and its established mechanisms and capabilities in cancer treatment as nanoparticles, despite the existence of several quercetin analogs and dietary flavonoids with differing levels of supporting data. Quercetin is named after quercetum, signifying an oak grove. It is a flavonoid named from the Latin term 'flavus', signifying yellow. The structure of quercetin is derived from 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one or (3,3′,4′,5,7-pentahydroxyflavone), which is likewise categorized as a flavone. Numerous suggested attributes of quercetin may exist in plant biology. This encompasses the protection of plants from UV radiation, and its effects on bacterial, viral, and fungal infections, as well as serving as an enzyme inhibitor, a possible attractant for pollinators, and regulators of plant hormones. Cancer is a life-threatening disease that impacts global human health. Recent advancements in drug discovery infrastructure and molecular methodologies have significantly facilitated the identification of novel drug targets for therapeutic intervention. Nonetheless, the morbidity and mortality rates associated with this disease continue to increase at an alarming rate. The recent application of natural and synthetic molecules as therapeutic agents has facilitated advancements in cancer chemoprevention. Cancer chemoprevention is a preventive

approach that entails the long-term use of one or more natural or synthetic agents to obstruct, inhibit, or suppress the progression of cancer before its advancement to an invasive stage. Quercetin, a dietary bioflavonoid, specifically inhibits the proliferation of cancer cells and functions as an effective chemopreventive agent against cancer. Quercetin exhibits various intracellular targets within cancer cells. Consequently, numerous mechanisms have been proposed to elucidate its chemopreventive effects. The chemo-preventive effects of this natural molecule in various model systems include antioxidant and pro-oxidant actions, regulation of redox homeostasis, apoptosis, cell cycle arrest, anti-inflammatory effects, modulation of drug-metabolizing enzymes, changes in gene expression patterns, inhibition of Ras gene expression, and modulation of signal transduction pathways. Over the past two decades, initiatives have focused on developing drugs that can selectively modulate aberrant signaling pathways. Substantial progress has been made in the creation of tyrosine kinase inhibitors in the last five years. Quercetin (QCN) is significant among structurally defined compounds for its function as a protein tyrosine kinase inhibitor. QCN is a dietary flavonoid attracting increased attention as a novel medical biomolecule with diverse therapeutic properties. Among the discovered flavonoids, QCN is recognized for its significant antioxidant properties, attributed to its capacity to neutralize highly reactive oxygen species (O2 and ONOO). Consequently, the enhancement of mutant cell death through the modulation of cell signaling pathways is documented, potentially leading to the suppression of cancer proliferation [1]. The biochemical activity of quercetin arises from its hydroxyl groups, which demonstrate antioxidant properties by scavenging free radicals. Quercetin contains several structural features indicative of its antioxidant properties, including (i) an ortho-dihydroxy or catechol group in ring B, (ii) a 2,3-double bond, and (iii) hydroxyl groups at positions 3 and 5, along with a 4-oxo group. Various factors such as pH, temperature, and metal ions influence the chemical stability of quercetin. Quercetin is a lipophilic compound with a log P value of 1.82 ± 0.32. It exhibits moderate solubility in ethanol and high solubility in DMSO. Its solubility in water is approximately 0.01 mg/mL at room temperature. The half-life of quercetin ranges from approximately 11 to 24 hours. Incorporating high levels of quercetin into a water-based food matrix presents challenges, necessitating improvements in its solubility, bioaccumulation, and delivery to target specific diseases such as cancer [2].

Bioavailability

Initial investigations of quercetin's bioavailability following a single oral administration indicated that the bioavailability was roughly 2%. The bioavailability of radiolabeled quercetin was approximately 44.8%, as shown by mouse blood plasma tests. Nonetheless, given that the half-life of radiolabeled carbon varies from 11 to 28 hours, the bioavailability of quercetin may exceed previous estimations, particularly with continued supplementation of quercetin. Quercetin is widely recognized for its low toxicity as a natural compound, despite the scarcity of knowledge regarding dose regimens [3]. QCN is a phytochemical prevalent in various ethnic plants, particularly onions, and tea, therefore allowing for enough daily consumption. It holds significance in ethnopharmacology for its applications as an antioxidant, anticancer agent, and neuroprotective substance. It has been identified as an effective free radical scavenger (antioxidant). In phase-I clinical studies, QCN has demonstrated an inhibitory action on tyrosine kinase, indicating its promise as an anticancer therapy. QCN therapy has been demonstrated to induce cell cycle arrests, including G2/M arrest and G1 arrest, in many cell types. Additionally, QCN-induced apoptosis may stem from the activation of stress proteins, breakdown of microtubules and mitochondria, release of cytochrome c, and subsequent activation of caspases. It exhibits a broad range of biopharmacological properties and may provide promising new avenues for the advancement of more efficient chemopreventive and chemotherapeutic treatments due to its potent antioxidant and free radical scavenging capabilities. The QCN therapy has demonstrated selective antiproliferative effects and the induction of cell death, likely via an apoptotic mechanism, in breast and other cancer cell lines, while sparing normal cells [4]. Recently, NF-κB has emerged as a promising target for novel drug discovery, hence increasing interest in molecules derived from natural sources. NF-κB plays a significant role in carcinogenesis and cancer progression. The principal variant of NF-κB, known as RelA (the heterodimer p50/p65), is preserved in an inactive state by the NF-κB inhibitor IκB. NF-κB is activated by the phosphorylation of IκB by IκB kinase (IKK), which comprises the IKKα, IKKβ, and IKKγ subunits. IKKβ is the principal kinase that phosphorylates the amino terminus of IκB in vivo, while IKKγ, sometimes referred to as NF-κB essential modulator or NEMO, serves as a vital regulatory subunit.

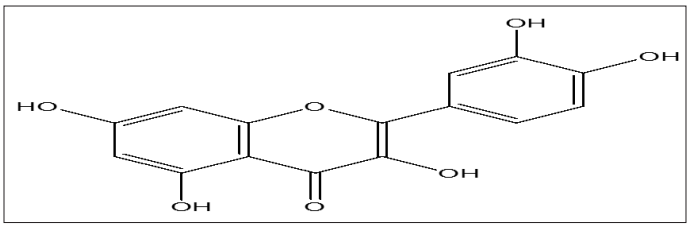

Figure 1: Structure of Quercetin

Quercetin has demonstrated considerable anticancer properties both in vitro and in vivo, with many of these effects associated with its direct or indirect interactions with molecular entities involved in carcinogenesis. Numerous research evaluate the pro-apoptotic effects of quercetin in cancer cells, which enhance the chemopreventive properties of diet, akin to various other flavonoids. This flavonoid can inhibit the PI3K/Akt/IKKα/NF-κB pathway in human salivary adenoid cystic carcinoma, resulting in the induction of cell death via a mitochondria-dependent mechanism [5]. Nanotechnology is described as the development, characterization, and application of systems at the nanoscale. Nanoscale often refers to dimensions between 1 and 100 nm, with nanomaterials being organized and/or sized within that spectrum [6]. Quercetin has been shown to inhibit the STAT3 and PI3K/AKT/mTOR pathways in primary effusion lymphoma (PEL) cells, resulting in the downregulation of prosurvival protein expression, including cMyc, cyclin D1, and c-FLIP. Moreover, quercetin decreased the secretion of IL-6 and IL-10, leading to the apoptosis of PEL cells. Quercetin also facilitated prosurvival autophagy, enhancing the cytotoxic effects of bortezomib, a proteasomal inhibitor. Recent research indicates that quercetin may augment the efficacy of radiation-induced cytotoxicity in tumor treatment. The conjunction of quercetin therapy and X-irradiation augmented DNA damage and induced typical apoptotic cell death, while also elevating Bax levels and diminishing Bcl-2 levels in ovarian cancer cell lines (OV2008 and SKOV3) relative to cells exposed to quercetin or X-rays independently. Furthermore, the conjunction of quercetin administration with radiation significantly inhibited tumor proliferation, subsequently leading to the activation of p53, CCAAT/enhancer-binding protein homologous protein (CHOP), an endoplasmic reticulum stress biomarker, and γ-H2AX. Inhibits cellular proliferation and triggers apoptosis by decreasing Bcl-2 and Bcl-xL while elevating the expression levels of caspase-3,

caspase-9, cytochrome c, Bid, Bad, and Bax in the PA-1 cell line. Regulate proliferation, apoptosis, and the secretion of steroid and peptide hormones in ovarian cells by decreasing PCNA and increasing BAX in porcine cells, resulting in reduced T production and IGF-I secretion. Conversely, in bovine cells, T release increased at lower concentrations (1 or 10 ng/mL) while IGF-I secretion was promoted at lower concentrations and diminished at higher concentrations (100 ng/mL) [7]. Nanoparticles (NPs) are defined as particles with at least one dimension measuring fewer than 100 nanometers, exhibiting unique properties often missing in bulk samples of identical material. Nanoparticles can be classified as 0D, 1D, 2D, or 3D based on their overall morphology [8]. Quercetin has been documented to be advantageous against U2OS/MTX300 human osteosarcoma cells by suppressing proliferation and inducing apoptosis. Inhibition of parathyroid hormone receptor 1 also diminishes the invasion, adhesion, proliferation, and migration of osteosarcoma cells. The impact of quercetin on pancreatic cancer shown that it reversed resistance to apoptosis and diminished proliferation, angiogenesis, and the expression of cancer stem cell markers with quercetin therapy, a dietary polyphenol. Quercetin, present in various foods along with β-glycosides like rutin, has been documented to suppress the G1 phase in human gastric cancer cells [9].

Types of Nanoparticles Utilized With Phytoconstituents for Oncological Therapy

Organic NPs

Polymeric Nanoparticles (PNPs) are well recognized as colloidal macromolecules characterized by a specific structural architecture composed of several monomers. Synthetic and natural polymers are employed to create polymer nanoparticles, which represent a significant category of drug-delivery systems. Polymeric Nanoparticles (PNPs) are well recognized as colloidal macromolecules characterized by a distinct structural architecture composed of several monomers. Polymer nanoparticles serve as a diverse delivery mechanism for various materials, including small molecules, proteins, genes, and chemotherapeutic agents. Poly (alkyl cyanoacrylate) (PACA), Polycaprolactone (PCL), polyanhydrides, Polyethyleneimine (PEI), chitosan, gelatin, and Polylactic Acid (PLA) represent a selection of polymer nanoparticles now under investigation in the laboratory. To achieve targeted medication release, the drug is either encapsulated or attached to the surface of nanoparticles, resulting in a nano-sphere or nano-capsule. Recent studies indicate that Ginsenoside Rg5, a triterpene saponin extracted from the ginseng plant, is one of the most efficacious anticancer agents against various carcinoma cell types. Rg5's inadequate bioavailability, untargeted delivery, and low aqueous solubility, however, constrain its therapeutic efficacy. To enhance the therapeutic efficacy and tumor targeting of Rg5, researchers developed Folic Acid (FA) modified Bovine Serum Albumin (BSA) nanoparticles (FA-Rg5-BSA NPs) [8]. Quercetin has been documented to diminish the CYP450 enzyme family, which is crucial in the activation of certain probable human carcinogens. Quercetin can demethylate the promoter of the p16INK4a gene, which is hypermethylated in human colon cancer cells. Quercetin modulates the expression of tumor suppressor genes, suppresses the expression of cell cycle genes, and regulates the expression of oncogenes in the prostate cancer cell line. Quercetin stimulates the enzymatic activity of histone deacetylase, leading to reduced histone H3 acetylation, which may restrict viable expression and increase vulnerability to TRAIL-induced death. Research has demonstrated that quercetin enhances the stability of the p53 gene and facilitates its apoptotic effects by phosphorylating and stabilizing the gene.

Solid Lipid Nanoparticles (SLN)

These consist of phospholipid monolayers, emulsifiers, and water-based colloidal nanocarriers, with dimensions ranging from 1 to 100 nm. These are designated as zero-dimensional nanomaterials. Triglycerides, fatty acids, waxes, steroids, and Polyethylene Glycol (PEG) exemplify lipid constituents. Lipids have been suggested as an alternative carrier to address the limitations of polymeric nanoparticles, particularly for lipophilic medications. Solid Lipid Nanoparticles (SLNs) are a kind of lipid nanoparticles that are attracting significant interest from formulators globally. The global cancer burden is increasing swiftly, resulting in around 8.8 million fatalities per year. The negative effects of chemical medications and the establishment of resistance have prompted significant interest in the creation of novel green pharmaceuticals. We sought to examine if solid-lipid nanoparticles containing the essential oil of Zataria Multiflora (ZMSLN) augmented the anticancer activity of the essential oil against breast cancer (MDA-MB-468) and melanoma (A-375) cells. Research on podophyllotoxin-based solid lipid nanoparticles with epidermal targeting mechanisms has also been described. The results indicated that podophyllotoxin-based SLN formulations facilitated drug permeation across the stratum corneum and hair follicle pathways. Research on podophyllotoxin-based solid lipid nanoparticles with epidermal targeting mechanisms has also been described. The results indicated that podophyllotoxin-based SLN formulations facilitated drug permeation across the stratum corneum and hair follicle pathways. To specifically target HT-29 cells for colon cancer treatment, the synthesized SLNs were further conjugated with folic acid. Despite the application of chitosan on the surface of SLN, the optimization approach results in a minimal particle size of 174 ± 5 nm. The chitosan-coated formulation exhibits enhanced cytotoxicity against HT-29 cells at a concentration of 10 μg mL–1, in contrast to the uncoated formulation (25 μg mL–1). The drug is administered via folate receptor-mediated endocytosis, perhaps resulting in heightened cytotoxicity due to FA conjugation. Western blot and fluorescent labeling techniques were utilized to confirm the high-affinity binding of the folate receptor. The improved medication absorption and mortality in Ht29 cells are reexamined using flow cytometry [8].

Liposomes

Spherical vesicles encapsulating pharmacological molecules in phospholipids can be classified as either uni-lamellar or multilamellar. Liposomes exhibit unique characteristics, such as low intrinsic toxicity, low immunogenicity, and biological inertness. After their description in 1965, the initial closed bilayer phospholipid structures, termed liposomes, were promptly proposed as drug delivery methods. Numerous technological advancements have been achieved in the field of liposomes over the past five decades. These include remote drug loading, extrusion for uniform size, long-circulating (PEGylated) liposomes, triggered release liposomes, liposomes with nucleic acid polymers, ligand-targeted liposomes, and liposomes containing drug combinations, all stemming from the pioneering efforts of countless researchers. Liposomes provide an effective vehicle for drug administration, including Doxorubicin (Dox), PTX, and nucleic acids, due to their enhanced anti-tumor efficacy and improved absorption. Liposomal phytochemical formulations have gained increasing popularity in recent years. Deshmukh et al. utilized chitosan and lecithin in an electrostatic deposition-assisted film hydration method to create a liposomal nanosystem that encapsulated the flavone chrysin, also known as 5,7-dihydroxyflavone, found in passion flowers, honey, propolis, Passiflora caerulea, Passiflora incarnata, and Oroxylum indicum, within the nano-lipoidal shell. This study examines the impact of liposomal NP-delivered

QCN on the metabolism of Mycophenolic Acid (MPA) during combination therapy, specifically focusing on the inhibition of MPA metabolic rate. QCN liposome nanoparticles (QCN-LNPs) and MPA liposome nanoparticles (MPA-LNPs) were produced independently and comprehensively characterized. The sizes of the produced MPA-LNPs and QCNLNPs were measured at 183 ± 13 and 157 ± 09.8, respectively [8].

Dendrimers

Dendrimers are highly branched, tree-like macromolecules characterized by a central core, multiple branching units, and terminal functional groups. Their unique structure enables diverse applications in drug delivery, imaging, and nanotechnology. Dendrimers are spherical polymeric macromolecules characterized by a well-defined hyperbranched topology. Dendrimers exhibit highly branched architectures. Dendrimers generally range in size from 1 nm to 10 nm. The size may reach up to 15 nm. The dendrimer chemistry described offers a method for synthesizing target molecules characterized by spherical shapes, unique surface chemistries, and dimensions analogous to virus particles. The primary objective is to develop a generation 13 dendrimer composed of triazines linked by diamines, exhibiting stability in the presence of additives across various concentrations, pH levels, temperatures, and solvent polarities. Dendrimers are a class of structurally defined macromolecules characterized by a central core, a high-density exterior with surface functional groups, and a low-density interior composed of repeating branching units. Dendrimers, in contrast to polymeric counterparts, exhibit symmetrical structures and are nanoscale particles that can be produced en masse with reproducibility through mono-dispersity technology. Ursolic acid and FA were conjugated with PAMAM dendrimer for specific applications. The FA enhances cellular uptake by specifically targeting the folate receptor in HepG2 cells. The PAMAM dendrimer enhances the cytotoxic effects of ursolic acid and demonstrates electrostatic absorptive properties that aid in attracting HepG2 cells. PAMAM dendrimer serves as a promising carrier for the targeted delivery of phytochemicals [8].

Nano-Emulsions

Nano-emulsions are colloidal systems consisting of two immiscible liquids, typically oil and water, stabilized by surfactants. They exhibit unique properties due to their small droplet size, which enhances stability and bioavailability. Applications span pharmaceuticals, and cosmetics, Colloidal nanoparticles containing heterogeneous mixtures of oil droplets in aqueous media, with diameters ranging from 10 nm to 1,000 nm, are referred to as nanoemulsions. Advanced melanoma may be treated using a nanoemulsion comprising rapamycin, bevacizumab, and temozolomide. Compared to liposomes, nanoemulsions demonstrate enhanced properties such as stability, optical clarity, and biodegradability. The selected medication combination administered in IL demonstrated promising outcomes in both cellular and animal models, likely by affecting multiple mechanisms related to tumor proliferation, dissemination, and angiogenesis. Future research will investigate the effects of altering the chemical composition of the nanoemulsion. Nanosystems have been employed in the co-delivery of various anticancer drugs to enhance their therapeutic efficacy and bioavailability. Mice with SKOV3 cancer received a combination of PTX and curcumin delivered as a nanoemulsion, as reported by Ganta S and Amiji M. Administration of PTX to mice receiving curcumin in nanoemulsion form resulted in a 4.1-fold. Increase in AUC. The relative bioavailability of PTX was 5.2-fold greater, resulting in a 3.2-fold increase in drug accumulation within cancer tissues [8].

Inorganic Nanoparticles

Carbon Nanoparticles

Carbon nanoparticles are fundamentally derived from the element carbon. Due to their biocompatibility and advantageous optical, mechanical, and electrical properties, these materials have found extensive applications in the medical field. The graphene family of nanomaterials presents the most promising options for various applications due to their unique intrinsic properties, which are appreciated for their simple molecular design and ability to integrate effectively with existing nanomaterials. Graphene oxide, through differentiation-based nano-therapy, presents a promising non-toxic method for the eradication of cancer stem cells. A new class of carbon compounds, termed fullerenes (previously known as buckminsterfullerenes), was initially discovered in 1985. If fullerene (Cm) is introduced into tumor tissue, it is expected to exert a photodynamic effect due to its efficient production of singlet oxygen upon light exposure. Curcumin, a widely utilized natural compound in anticancer therapy, is limited in its efficacy due to low bioavailability. We evaluated the in vivo performance and in vitro properties of SWCNT-Cur, expanding upon our previous research on a novel curcumin delivery system that employs functionalized single-walled carbon nanotubes in conjunction with phosphatidylcholine and poly-vinyl-pyrrolidone (SWCNT-Cur). In mice, SWCNT-Cur significantly elevated the blood levels of curcumin, achieving an increase of up to eighteen times [8].

Metallic Nanoparticles

Metallic nanoparticles exhibit remarkable optical, magnetic, and photothermal properties, making them a subject of extensive research in biological imaging and targeted drug delivery systems. The most commonly used metallic nanoparticles are copper, silver, iron-based, and gold nanoparticles. The size and surface characteristics of gold nanoparticles can be easily manipulated, making them suitable for use as intracellular targeted drug carriers.

Nanotechnology is a multidisciplinary field focused on the engineering and design of materials and devices with dimensions smaller than 500 nanometers (nm). The majority of cancer-related fatalities result from metastases. Treatment of metastases poses unique challenges due to their small size, high multiplicity, and distribution across various organ systems. Ginseng (Panax ginseng) root is widely utilized as a traditional medicine in Asia. Prior consumption of ginseng was associated with an increased overall survival rate in patients diagnosed with breast cancer. The consumption of P. ginseng enhanced various aspects of physical and mental functioning in patients with gynecologic or hepatobiliary cancer, as demonstrated in a randomized placebo-controlled study. European mistletoe, or Viscum album, is frequently suggested as a cancer treatment. By 2003, this plant extract had been the focus of approximately 23 clinical studies, with 19 yielding positive results related to quality of life, survival rates, and tumor suppression in cancer patients [8].

Quantum Dots

Semiconductors are nanocrystals that exhibit unique optical and electronic properties due to their size and shape. They have applications in various fields, including optoelectronics, biomedical imaging, and solar energy conversion. Semiconductor Quantum Dots (QDs) are nanoscale particles that exhibit unique optical and electronic properties, enabling light emission. The capabilities encompass the simultaneous excitation of multiple fluorescent colors, enhanced signal brightness, and the stability of the fluorescent signal. In cultured HeLa cells, quantum dots conjugated with the protein transferrin participated in

receptor-mediated endocytosis, whereas dots labeled with immuno-molecules identified specific antibodies or antigens. The characteristics of semiconducting quantum dots are notably unique; these entities exist within the nanometer scale. A novel family of inorganic fluorophores, referred to as QDs, is gaining recognition for its exceptional photophysical properties. A targeted system for cancer imaging, treatment, and sensing employing QD-aptamer (Apt)Dox conjugate [QD-Apt(Dox)]. C-dots (aqueous fluorescent) derived from turmeric, black pepper, cinnamon, and red chili were synthesized through a one-pot green process and subsequently analyzed in vitro. Human kidney cells (HK-2) and human glioblastoma cells (LN-229) demonstrated increased cytotoxicity in cytotoxicity assays [8].

Magnetic Nanoparticles

Magnetic NPs MRI imaging frequently employs magnetic nanoparticles, while drug delivery typically incorporates metals or metal oxides. Lipid-based gene transfection methods and magnetic nanoparticles were employed to promote active Fas expression in breast cancer cells. Plasmid DNA (pDNA) expressing human Fas and GFP was transfected into MCF-7 breast cancer cells. The injection of LHRH-SPIONs into the tissues resulted in a significantly greater contrast enhancement in conventional T2 images of tumor tissue compared to saline controls in mice with breast cancer xenografts. Improved MRI contrast in magnetic anisotropy multi-CRAZED images was observed in breast cancer xenografts and lung metastases from animals treated with SPIONs. The combination of thermal ablation and antibody-targeting magnetic nanoparticles presents a viable treatment option for oral squamous cell carcinoma. Curcumin-loaded folate-grafted magnetic nanoparticles exhibit significant inhibitory effects on MCF-7 breast cancer cells and KB nasopharyngeal carcinoma cells. The nanoparticles exhibited targeted thermo-chemotherapy, inducing apoptosis through selective interaction with the folate receptor, which is overexpressed in cancer cells, as indicated by the magnetic effect [8].

Exosomes

Exosomes are small extracellular vesicles that play a crucial role in intercellular communication and the transport of biomolecules. Recent literature emphasizes the importance of Exosomes (EXOs) in cancer biology. Researchers are investigating plant-derived EXO-like nanoparticles (PENs) as a potential alternative to exosomes produced by mammalian cells. This enables the resolution of technical limitations linked to mammalian vesicles. Polymer-based nanoparticles (PENs) exhibit significant potential as nanocarriers in drug delivery systems, attributed to their physiological, chemical, and biological properties. They demonstrate significant efficacy in administering varying drug doses, particularly in contexts requiring extensive repeatability. Extracellular vesicles, known as EXOs, are the smallest vesicles found in bodily fluids and function as carriers of biomolecules, enabling intercellular communication. This attribute renders them valuable as conveyors. The similarity between the membranes of these nanoparticles and cell membranes facilitates their transport for the conveyance of various components. EXOs may serve as an effective method for loading chemotherapeutic agents due to their limited solubility in liquid. This cancer therapy may eliminate the necessity for large doses of medications administered through injections, providing a more appropriate method for drug release. Researchers have developed a new method to selectively trigger programmed cell death in breast cancer cells and inhibit their metastasis to the lungs. This was accomplished through the utilization of natural nano-vehicles derived from tea flowers, referred to as TFENs. The nano-vehicles demonstrated particle sizes of 131 nm, shapes akin to EXOs, and negative zeta potentials. Cellular assays indicated that TFENs exert significant cytotoxic effects on cancer cells through the induction of Reactive Oxygen Species (ROS) proliferation. Increased intracellular levels of Reactive Oxygen Species (ROS) cause mitochondrial damage and disrupt the cell cycle, resulting in the inhibition of cell proliferation, migration, and invasion in breast cancer cells under laboratory conditions. Subsequent studies in mice indicated that TFENs, administered either intravenously or orally, may localize in breast tumors and lung metastatic sites. They may impede the progression and dissemination of breast cancer and also affect the composition of gut microbiota [8]. Fig. 2 shows the potential of nano-conjugated Quercetin [2].

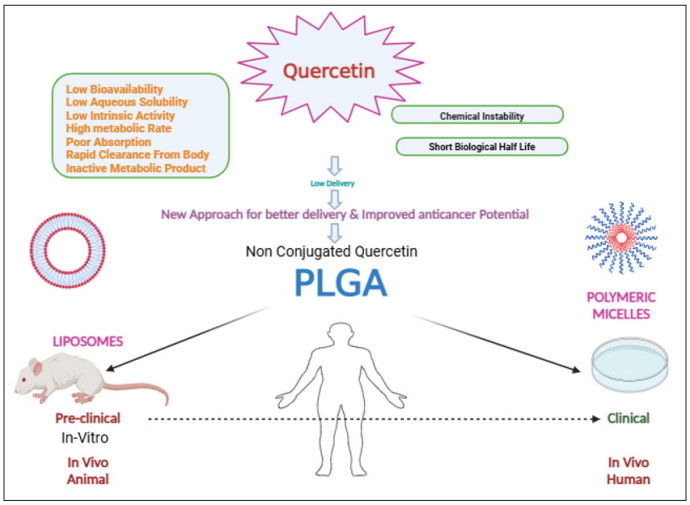

Figure 2: Nano Conjugated Quercetin.

Here, PLGA-(Poly lactic-co-glycolic acid) 1

Quercetin's Role in Cancer

Quercetin's ability to influence epigenetics, thereby regulating miRNA expression and DNA methylation levels, may contribute to cancer treatment efficacy and enhance the susceptibility of tumor cells to therapeutic interventions. Quercetin can inhibit or halt cancer growth through alterations in epigenetics. Researchers discovered that nano-quercetin induces apoptosis in MCF7 cells and inhibits their progression from the G1 phase to the S phase of the cell cycle. Another study examined the effects of inhibiting the epidermal growth factor receptor (EGFR)/VEGFR-2-mediated pathway on epithelial-mesenchymal transition (EMT), angiogenesis, and invasiveness in breast cancer. Quercetin has been demonstrated to utilize the p-STAT3/Bcl-2 pathway to induce ER stress, apoptosis, and autophagy in cells. Numerous studies indicate that quercetin induces apoptosis in ovarian cancer cells that have metastasized to other organs, thereby reducing their potential for growth and dissemination. The levels of anti-apoptotic molecules, such as Bcl-2 and Bcl-xL, as well as pro-apoptotic molecules, including caspase-3, caspase-9, Bid, Bax, and Bad, are increasing. Quercetin can inhibit cytochrome c activity. Quercetin induces mitochondrial-mediated apoptosis in metastatic cancer cells, thereby inhibiting the proliferation of ovarian cancer cells. Quercetin influences the angiogenic pathway and inhibits the growth of P70S6K, a regulatory factor for the AKT/mTOR/ribosomal protein S6 kinase signaling cascade. VEGFR-2 regulates the angiogenic system. Numerous studies indicate that this intervention slows or halts tumor growth in men diagnosed with prostate cancer. Quercetin significantly inhibited the proliferation and invasion of lung cancer cells. The intervention reduced the levels of N-cadherin, vimentin, and ADAM9 while

increasing the levels of E-cadherin and MMP-related proteins [10]. Researchers have increasingly considered conventional therapies, such as natural components and other therapeutic methods, due to their lower cost and reduced side effects. Quercetin demonstrates an anti-cancer effect on prostate cancer cells through the induction of apoptosis. Recent studies further suggest that quercetin influences multiple signal transduction pathways, contributing to the attenuation of cancer progression. Quercetin inhibits the expression of N-cadherin, MMP-9, and the STAT-3 signaling pathways, potentially suppressing Epithelial-Mesenchymal Transition (EMT), invasion, and metastasis. Quercetin increases the sensitivity of pancreatic cancer cells to gemcitabine by inhibiting RAGE expression. It demonstrates broad accessibility, efficacy, and low toxicity relative to other examined compounds, rendering it a compelling option in cancer therapy. Quercetin has recently emerged as a promising agent for the treatment of various cancers, either alone or in combination with other chemotherapeutic agents [11]. Quercetin (QCN) has demonstrated safety with no recorded side effects in the treatment of human cancer. Considering the various advantages linked to QCN and its derivatives, it is imperative to further explore the impact of these molecules on cancer prevention and treatment. Currently, there is inadequate data concerning its specific mechanism of action to substantiate its clinical application in human cancer treatment. Consequently, additional research should aim to clarify the specific mechanisms of action of QCN. Further clinical trials are necessary to evaluate the efficacy and bioavailability of QCN for potential application in human biological systems, particularly in cancer treatment. The examination of QCN conversion into its metabolites is essential for assessing the effectiveness and pharmacokinetics of QCN for potential pharmaceutical applications. The interaction between xenobiotics and QCN influences the reactivity of QCN; nonetheless, various metabolic byproducts formed in conjugation exhibit beneficial bioactivity. Continued investigation into the mechanisms of action of QCN is crucial, especially regarding its capacity to inhibit carcinogenicity in rabbits [12]. Quercetin is a naturally occurring flavonol compound found in various commonly consumed foods. Quercetin exhibits notable inhibitory effects on tumor progression through multiple mechanisms of action. These encompass the induction of cell cycle arrest and/or apoptosis, along with exhibiting antioxidant properties [13].

The impact of quercetin on tumor growth in vivo is also evident through graft angiogenesis and metastasis. Thrombospondin-1 (TSP-1) is a well-established anti-angiogenic factor known to inhibit tumor growth. A recent study indicates that quercetin inhibits tumor growth in prostate cancer model mice through the up-regulation of TSP-1 expression. In the BALB/c mice model of breast cancer, Zhao et al. demonstrated that treatment with 34 mg/kg quercetin inhibits angiogenesis through the inhibition of the calcineurin/NFAT pathway. In vivo experiments confirmed quercetin's inhibitory effect on tumor metastasis. Treatment with 50 mg/kg quercetin significantly reduced colorectal lung metastasis. The administration of quercetin inhibits Epithelial-Mesenchymal Transition (EMT) by modulating the EGFR signaling pathway and suppressing VEGF expression. Quercetin exhibits an inhibitory effect on allogeneic tumor growth, as demonstrated in tumor cell models including lung and pancreatic cancers. Furthermore, quercetin can coordinate anti-tumor activity with additional compounds [14].

Nano-Conjugated Quercetin

Nanoparticles have been thoroughly studied for their ability to deliver anticancer drugs, demonstrating increased anticancer efficacy and potential for clinical application. Recent studies on nanoconjugated quercetin aim to address its challenges related to low bioavailability, chemical instability, and short biological half-life. The pharmacological effect of quercetin-conjugated nanoparticles primarily relies on the drug carriers employed. Quercetin-conjugated polymeric micelles, liposomes, silver nanoparticles, and PLGA (Poly Lactic-co-Glycolic Acid) demonstrate enhanced inhibition of tumor growth in vivo. Controlled drug release, prolonged retention in tumors, and enhanced efficiency in invagination and extravasation through the pores of tumor capillary endothelium by nanoconjugated drugs present promising prospects for their clinical application in metastatic cancer. The delivery of quercetin nanoparticles and their anticancer efficacy are primarily limited to laboratory animals and in vitro systems. However, other nanoconjugated anticancer drugs are currently undergoing clinical trials. Although there have been many in vitro and in vivo studies on the anti-cancer effects of quercetin formulations, clinical translation faces limitations related to cost, safety, and side effects. The primary objectives of optimal cancer treatment include identifying key target molecules, developing safe and stable delivery systems, and implementing superior strategies to overcome resistance while minimizing the side effects of chemotherapeutic agents. The incorporation of cancer cell-specific targeting moieties onto nanoparticles has advanced to improve the targeted delivery of nano-formulations while minimizing interactions with normal cells, thereby reducing drug side effects [2]. Nanoformulations of quercetin demonstrate significant potential for improved uptake by the epithelial system and enhanced delivery to target sites [15]. The nano-biomaterials of solid lipids, including Stearic Acid (SA) and Tripalmitin (TpN), along with the surfactants Tween 80 and Span 80, were utilized to develop novel Quercetin (QuR)-loaded solid lipid nanoparticles (QuR-SLNs) for medical applications in Colorectal Cancer (CRC). The mean Entrapment Efficiency (EE) and Particle Size (PS) of the bio-nano Solid Lipid Nanoparticles (SLNs) were optimized using the Box–Behnken Design (BBD) by Response Surface Methodology (RSM). The variables consist of lipid ratio (X1), surfactant ratio (X2), QuR-to-lipid ratio (X3), sonication time (X4), and homogenization time (X5). The maximum EE (%) and minimum PS (nm) requirements were optimized for QuR SLN preparation. Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD) analysis, and Scanning Electron Microscopy (SEM) were employed to analyze the optimized Solid Lipid Nanoparticles (SLN) and to investigate the crystalline state of QuR about lipids. Furthermore, in Caco-2 cells, in vitro cytotoxicity was achieved at the IC50 of 49 μM/mL [16]. Another study focuses on the synthesis and characterization of Nanoformulations (NFs) derived from Q-loaded PLGA (Poly Lactic-co-Glycolic Acid) Nanoparticles (NPs) through surface modification. The surface of Q-loaded nanoparticles is modified through the application of biopolymer coatings such as bovine serum albumin or histones. Conventional chemotherapeutic agents Adriamycin (ADR) and Mitoxantrone (MTX) are conjugated to BSA and His, respectively, before their application on Q-loaded nanoparticles for the nanoformulation of NF1 and NF2. The dimensions of these NFs range from 400 to 500 nm, as determined by SEM and DLS measurements. The encapsulation of Q in polymer nanoparticles is evidenced by shifts observed in the FT-IR, TGA, and DSC traces of Q-loaded nanoparticles in comparison to native PLGA and Q. Surface modification in nanofibers is indicated by three distinct regions observed in their transmission electron microscopy images: the core, polymer capsule, and coated surface. The negative zeta potential of Q-loaded nanoparticles transitioned to a positive potential following surface modification in NF1 and NF2. The in vitro release of Q from the NFs extended for twenty days, characterized by an initial burst release. NF2 demonstrates superior formulation characteristics, achieving an

MTX loading of 85% in contrast to the 23% loading of ADR [17]. The synthesis and characterization of Nanoformulations (NFs) from Q-loaded PLGA (Poly Lactic-co-Glycolic Acid) Nanoparticles (NPs) through surface modification. The surface of Q-loaded nanoparticles is modified through the application of biopolymers such as bovine serum albumin or histones. Conventional chemotherapeutic agents Adriamycin (ADR) and Mitoxantrone (MTX) are conjugated to BSA and His, respectively, before their application on Q-loaded nanoparticles for the nanoformulation of NF1 and NF2. The dimensions of these NFs range from 400 to 500 nm, as determined by SEM and DLS measurements. The encapsulation of Q in polymer nanoparticles is evidenced by shifts observed in the FT-IR, TGA, and DSC traces of Q-loaded nanoparticles in comparison to native PLGA and Q. Surface modification in nanofibers is demonstrated by three distinct regions observed in their transmission electron microscopy images: the core, polymer capsule, and coated surface. The negative zeta potential of Q-loaded nanoparticles transitioned to a positive potential following surface modification in NF1 and NF2. The in vitro release of Q from the NFs extended for twenty days, characterized by an initial burst release. NF2 demonstrates superior formulation characteristics, achieving an MTX loading of 85% in contrast to the 23% loading of ADR. These nanofibers are anticipated to address Multi-Drug Resistance (MDR) by effectively targeting and treating cancerous cells due to their size, charge, and retention properties [17]. The potential anti-tumor effects of quercetin are attributed to its antioxidant properties. Quercetin nanoparticles are synthesized with precision using the nanoprecipitation method, employing poly(caprolactone) as the polymer matrix. After synthesis, the nanoparticles are extracted for subsequent analysis. Additional efforts are made to improve the drug loading process, and the resulting nanoparticles are subjected to comprehensive analysis, which includes morphological examination via scanning electron microscopy and assessment of drug-polymer interactions through Fourier transform infrared spectroscopy and differential scanning calorimetry. The efficacy of quercetin's envelopment is significantly influenced by its lipophilic nature, achieving a maximum of 81%. Scanning electron microscopy enables the observation of nanoparticles in diverse shapes. The lack of significant interactions observed in Fourier-transform infrared analysis suggests the stability of poly(caprolactone) nanoparticles containing quercetin [18]. A group of researchers examined the therapeutic efficacy of novel nano micelles containing QCT (M-QCTs) in the treatment of refractory prostate cancer. Research indicated that QCT was successfully encapsulated in micelles, enhancing the drug's solubility in aqueous environments. Nonetheless, their research indicated that the semi-maximal inhibitory concentration value of M-QCT was significantly lower than that of free QCT. MQCT demonstrated a significantly greater potency than free QCT in inhibiting the proliferation of human androgen-independent PC3 cells and inducing apoptosis [19].

Conclusion and Future Aspects

Nanoparticles have been thoroughly studied for the delivery of anticancer medications due to their superior anticancer efficacy and promise for clinical application. Recent studies on nanoconjugated quercetin aim to address its challenges of limited bioavailability, chemical instability, and brief biological half-life. The pharmacological efficacy of quercetin-conjugated nanoparticles primarily relies on the used drug carriers. Quercetin-conjugated polymeric micelles, liposomes, silver nanoparticles, and PLGA (Poly Lactic-co-Glycolic Acid) have demonstrated superior suppression of tumor growth in vivo. The controlled release of medications, prolonged retention in tumors, and enhanced efficacy in invagination and extravasation through the pores of tumor capillary endothelium by nanoconjugated pharmaceuticals have established promising prospects for their therapeutic application in metastatic cancer. The delivery of quercetin nanoparticles and their anticancer effectiveness are primarily limited to laboratory animals and in vitro systems. Nonetheless, various additional nanoconjugated anticancer agents are currently undergoing clinical testing. Despite extensive in vitro and in vivo anti-cancer research on quercetin formulations, there are notable constraints for clinical application, including cost, safety, and adverse effects. The primary objectives of optimal cancer treatment are the identification of critical target molecules, the development of secure and reliable delivery methods, and the implementation of advanced strategies to surmount resistance and minimize the adverse effects of chemotherapeutic medicines. The incorporation of cancer cell-specific targeting moieties onto nanoparticles has developed to improve the targeted distribution of nano-formulations while minimizing their interaction with normal cells, hence mitigating drug-related side effects.

Ethics Approval and Consent to Participate

Not applicable.

Human and Animals Rights

Not applicable.

Consent for Publication

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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