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NANOTECHNOLOGY-BASED DELIVERY SYSTEMS FOR QUERCETIN: A REVIEW OF ITS APPLICATIONS, CHALLENGES, AND FUTURE DIRECTIONS.

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Abstract: Quercetin, a polyphenolic flavonoid found in plants and plant-based foods, is known for its antioxidant and anti-inflammatory properties. It can protect against cancer, cardiovascular diseases, chronic inflammation, oxidative stress, and neurodegenerative diseases. However, its poor bioavailability limits its potential benefits. Nanocarriers have been developed to improve solubility and design tissue-specific delivery systems. This review discusses the properties, chemical nature, occurrence, source, biosynthesis, biological activity, and nanotechnology's role in quercetin-loaded nanoparticles, its research, challenges, and future directions.

Keywords - Quercetin, flavonoid, poor bioavailability, Nanocarriers, improve solubility, tissue-specific delivery, quercetin-loaded nanoparticles.

INTRODUCTION:

Quercetin, or 3,3',4',5,7-pentahydroxyflavone, is a member of a broad class of polyphenolic flavonoid chemicals that are found in nearly all plants and plant-based foods. Often, quercetin is found as glycosides, which are sugar derivatives; for example, rutin, where a disaccharide has taken the place of the hydrogen atom in the R 4 hydroxyl group. Quercetin is known as the sugarless version of rutin, or aglycone. Much of the biological and medicinal information regarding quercetin was provided in two comprehensive volumes that were the outcomes of significant symposia on plant flavonoids in 1985 and 1987 [(1)].

Quercetin is a naturally occurring flavonoid found in many fruits, vegetables, and plants, such as onions, apples, berries, and tea. This compound can protect against cancer, cardiovascular diseases, chronic inflammation, oxidative stress, and neurodegenerative diseases due to its radical scavenging and anti-inflammatory properties. However, its poor bioavailability dampens the potential beneficial effects of this flavonoid. In that sense, many types of nanocarriers have been developed to improve quercetin solubility, as well as to design tissue-specific delivery systems. Collectively, quercetin can become a promising compound if nanotechnology is employed as a tool to enhance its therapeutic efficacy. In this review We are going to discuss about the Properties, chemical nature, Occurrence, Source, Biosynthesis, Biological activity and also how nanotechnology plays a crucial role in the quercetin loaded nanoparticles and its Research, Challenges, and Future Directions [(2)].

PROPERTIES:

A yellow, crystalline substance with a bitter flavor, quercetin is soluble in glacial acetic acid and aqueous alkaline solutions but insoluble in water and only weakly soluble in alcohol [(3,4)].

CHEMICAL STRUCTURE: Quercetin belongs to the class of naturally occurring substances known as flavonoids, which share a flavone nucleus made up of two benzene rings connected by a heterocyclic pyrone ring [(5,6)].

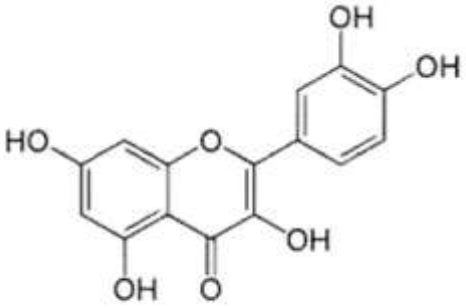

Fig-1: 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one

Quercetin and over 2,000 other flavonoids are condensation products of p-glycosides, and because animals cannot synthesis the flavone nucleus, flavonoids are only found in plants[7,8].

OCCURENCE:

Quercetin is present in various food products and plants, including fruits, seeds, vegetables, tea, coffee, bracken fern, and natural colors. Quercetin is usually derived via the hydrolysis of rutin (quercetin-3 rutinoside), a naturally occurring flavonoid glycoside although it can also be synthesized [9].Quercetin's bioavailability varies depending on the source and how it is consumed. While it is naturally present in many foods, its absorption can be enhanced when taken with healthy fats or in combination with other flavonoids, such as vitamin C. Some studies suggest that quercetin may help improve exercise performance, reduce oxidative stress, and support brain health by protecting neurons from damage [10].

SOURCES OF QUERCETIN [11]:
Here are some common sources of quercetin

1. Fruits:
   - ❖ Apples (especially with skin)
   - ❖ Berries (blue berries, cranberries, blackberries)
   - ❖ Grapes (red and purple varieties)
   - ❖ Citrus fruits (oranges, lemons)
   - ❖ Cherries
2. Vegetables:
   - ❖ Onions (red and yellow varieties have the highest amounts)
   - ❖ Kale
   - ❖ Broccoli
   - ❖ Spinach
   - ❖ Peppers (especially hot peppers)
3. Beverages:
   - ❖ Greeen tea
   - ❖ Red wine
   - ❖ Black tea
4. Other sources:
   - ❖ Capers (one of the richest source)
   - ❖ Cocoa
   - ❖ Dark chocolate
   - ❖ Buck wheat

BIOSYNTHESIS:

After exposing cuttings of the Fagopyrum tataricum plant to light for 24 hours, pentamethyl ether was hydrolyzed alkalinely to produce precursors of quercetin, and veratric acid was then separated. Furthermore, phenylalanine, cinnamic acid, and shikimic acid were used to create quercetin precursors. Additionally, the phenylpropanoid metabolic route is used in the production of coumarin. The extremely significant enzyme phenylalanine ammonia-lyase catalyzes the first step in the production of cinnamic acid from phenylalanine. Larger quercetin glycosides are created when glucose moieties bind to the 3, 5, 7, 3', and 4 hydroxyl groups of quercetin during the glycosylation process. Quercetin 3-O-galactoside is created when quercetin binds to galactose at position 3-OH. Conversely, quercetin 3-O-rhamnoside and quercetin 7-O-rhamnoside are created when the rhamnosyl group binds to positions 3-OH and 7-OH, respectively. Furthermore, α-L-rhamnopyranosyl-(1 → 6)-β D-glucopyranose attaches itself to quercetin's position 3-OH. Methylation of the compound quercetin results in the formation of numerous derivatives, including ramnetin 7-O-methyl quercetin,dimethyl quercetin, isorhamnetin, 3-methyl quercetin, isorhamnetol, isorhamnetin 3-O-rutinoside, isorhamnetin 3-O-rutinoside-7-O-glucoside, and isorhamnetin 3-O-rutinoside-4'-O-glucoside. Furthermore, tamarixetin 3-O-β-D-glucoside derivatives are created when a glucose molecule is joined to the third position of the quercetin structure [12,13,14].

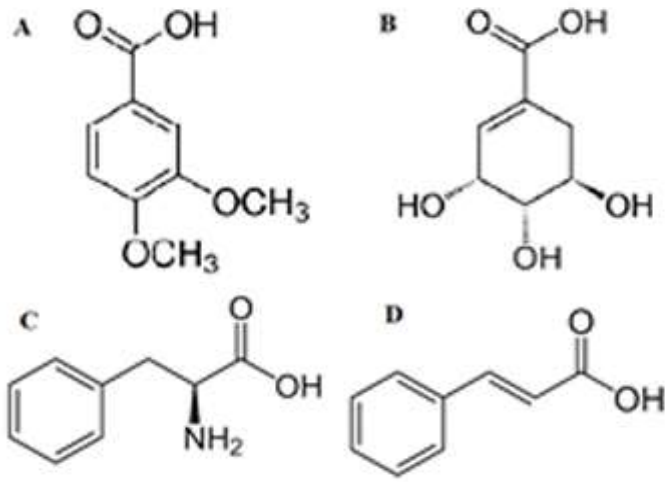

Fig 2. Molecular formulas of veratric, shikimic, cinnamic acids and phenylalanine

BIOLOGICAL ACTIVITY [15,16]**:**

S No	Bioactivity
01	Anti oxidant
02	Anti viral, Anti bacterial,
03	Anti microbial,
04	Anti inflammatory
05	Anti cancer
06	hepatoprotective,
07	cytotoxic

Table 1: Biological Activity

QUERCETIN NANOTECHNOLOGY APPLICATIONS:

Nanoparticles for Quercetin Delivery: Today, the challenge in the drug delivery field is to transport drugs to their intended locations, allowing to increase compound bioavailability,

There by reducing the amount of administered substances and, as a result, minimizing side effects while increasing therapeutic efficacy. This subject is especially essential when working with hydrophobic compounds, as it is critical to create the appropriate carriers to boost their solubility and bioavailability so that they can reach their intended targets.

Quercetin is one of these instances, and multiple research in the literature have focused on the development of various nanotechnological techniques to determine the optimal strategy for encapsulating and delivering quercetin for various uses [17].

NPs Type	Composition	Morphology	Zeta Potential (mV)	Administration Route
Liposomes	PC/Chol; EPC/Chol/PEG; lecithin/Chol/PEG; ESM/Chol/PEG P90G/STA/Eudragit S100	spherical	+7to 30	oral, intranasal, intravenous, topical
Lipid nanoparticles	GMS/soya lecithin/PEG; GMS/SA/MCT/soya lecithin; Compritol;	spherical	-10to-35	oral, intravenous, topical, intraperitoneal
Polymeric nanoparticles	PLGA; PLGA/PEG/AEMA; PLGA/PEG/FA; PCL/TPGS;	bean-like shape	+42to 40	intravenous, topical
Biopolymeric nanoparticles	Zein-Dextran sulfate sodium; Skin Fibroin; Chitosan	spherical	-16to 39; +14to+30	oral, intravenous
Mesoporous silica nanoparticles	TEOS/APTS; TEOS/FA	spherical	-25to+13	N I.

Table 2: Properties of different quercetin-loaded carriers.

1. Liposomes:

An inventive method to improve the effectiveness and distribution of quercetin, a naturally occurring antioxidant, is liposome-loaded quercetin nanotechnology. Its stability, solubility, and bioavailability are all enhanced when quercetin is encapsulated in liposomes. **Applications of this technology in wound healing, cancer therapy,** and other medical therapies are being investigated. It minimizes adverse effects by enabling focused distribution and controlled release. These developments could lead to better treatment outcomes for a number of illnesses [18-21].

2. Lipid nanoparticles:

A state-of-the-art nanotechnology called lipid-loaded quercetin nanoparticles was created to improve the transport of the powerful antioxidant quercetin. The solubility, stability, and bioavailability of quercetin are enhanced by these nanoparticles, increasing its efficacy in medicinal applications. With their controlled release and fewer adverse effects, **they are especially helpful in treating conditions like cancer and inflammation.** Quercetin is protected by the lipid matrix, which guarantees its continuous release. The potential of this technology in biomedical applications and drug delivery systems is being investigated. It is a promising development in the field of nanomedicine [22-25].

3. Polymeric nanoparticles:

A cutting-edge medication delivery method created to maximize quercetin's therapeutic potential is polymeric-loaded quercetin nanoparticles. By enhancing quercetin's solubility, stability, and bioavailability, **these nanoparticles increase its efficacy in the treatment of conditions like diabetes and cancer.** By providing focused distribution and controlled release, they lessen adverse effects. Quercetin is shielded from deterioration by the polymeric matrix, guaranteeing a prolonged release. **Applications of this technique in antibacterial and anti-inflammatory therapies are being investigated.** It is a potential advancement in nanomedicine [26-28].

4. Biopolymeric nanoparticles:

Using biodegradable and biocompatible polymers, biopolymeric-loaded quercetin nanoparticles are a novel medication delivery method. The potent antioxidant quercetin's solubility, stability, and bioavailability are all improved by these nanoparticles. They provide focused distribution and controlled release, reducing adverse effects and enhancing therapeutic results. Because biopolymeric carriers shield quercetin from deterioration, its release is sustained. **Applications of this technique in anti-inflammatory therapies, cancer therapy,** and other biomedical domains are being investigated. It is a promising and long-lasting development in nanomedicine [29-32].

5. Mesoporous silica nanoparticles:

Mesoporous silica quercetin-loaded nanoparticles are a novel drug delivery system designed to enhance the therapeutic potential of quercetin. These nanoparticles improve quercetin's solubility, stability, and bioavailability, addressing its poor water solubility. The mesoporous silica structure allows for high drug loading and controlled release, ensuring sustained therapeutic effects. **This technology is being explored for applications in cancer therapy, anti-inflammatory treatments,** and other biomedical fields. It minimizes side effects by enabling targeted delivery. Such advancements hold promise for improving drug efficacy and patient outcomes [33,34].

LIST OF RESEARCH ON QUERCETIN NANOTECHNOLOGY:

1. **Quercetin-Imprinted Nanospheres as Novel Drug Delivery Devices:(2012)** [35,36]

In this study, methacrylic acid and ethylene glycoldymethacrylate were used as functional monomers and crosslinking agents, respectively, to create molecularly imprinted nanospheres for the controlled/sustained release of quercetin. Precipitation from one pot.

In order to produce spherically shaped nanoscale materials, polymerization was selected as the polymerization approach. Using the template quercetin and its structural equivalent, the flavonoid catechin, the recognition and selectivity features of the imprinted materials were evaluated, along with their morphological and hydrophilic characteristics as assessed by scanning electron microscopy and water content assays. Lastly, cytotoxicity tests on HeLa cells and in vitro release studies in plasma mimicking fluids were used to assess the suitability of the produced materials as drug delivery systems.

2. **Improved therapeutic efficacy of quercetin-loaded polymeric nanoparticles on triple-negative breast cancer by inhibiting uPA. (2020)** [37,38]

One type of breast cancer that exhibits extremely aggressive tumor biology is triple negative breast cancer (TNBC). Due to its significant heterogeneity, TNBC has very limited and blind individual clinical treatment, which further complicates illness detection and treatment. Urokinase-type plasminogen activator (uPA), which promotes tumor growth and metastasis, is a high-level indicator of breast cancer. Many plants contain quercetin, a flavonoid that inhibits uPA. It has a low bioavailability and moderate pharmacological effectiveness. Thus, we herein developed polymeric nanoparticulate systems from PLGA-TPGS (Qu-NPs) for quercetin oral delivery and evaluated the anticancer effect of this formulation on TNBC in vitro and in vivo. Qu-NPs have a uniform spherical morphology with a mean diameter of 198.4 7.8 nm and good drug loading capacity (8.1 0.4%). Moreover, Qu-NPs showed noticeably better suppression of TNBC cell proliferation and metastasis. Qu-NPs demonstrated a strong anticancer impact on 4T1-bearing mice after oral gavage, as evidenced by a tumor inhibition ratio of 67.88% and a decrease in lung metastatic colonies. Additionally, the Quercetin significantly reduced the inhibitory effect of uPA knockdown MDA-MB231 cells on their migration. Together, Qu-NPs improved the significant antitumor and antimetastatic effects by inhibiting uPA, which provides a new strategy for the treatment of TNBC.

3. **Quercetin and Its Nano-Scale Delivery Systems in Prostate Cancer Therapy: Paving the Way for Cancer Elimination and Reversing Chemoresistance (2023)** [39,40]

After lung cancer, prostate cancer is the second most common and deadly cancer worldwide. The unchecked proliferation of cells in the prostate gland is a hallmark of prostate cancer. Morbidity and mortality rates from prostate cancer have sharply increased, and Treatment for prostate cancer is unlikely to yield satisfactory results. In practical practice, synthetic medications used to treat prostate cancer encounter a number of difficulties. Fruits and vegetables naturally contain quercetin, a flavonoid. In addition to its positive properties, it is an important anti-cancer agent. Both by itself and in combination, quercetin has demonstrated anticancer potential. In order to gather data from the literature about its therapeutic importance in the treatment of prostate cancer, the current study was created. Through many underlying mechanisms, quercetin effectively protects prostate cancer, according to studies conducted both in vitro and in vivo. Clinical research on quercetin's pharmacokinetics and potential uses in humans have also produced encouraging results. Meanwhile, epidemiological research has pointed to a chemo preventive impact of quercetin on prostate cancer in animal models and a negative association between quercetin consumption and the incidence of prostate cancer. The two main problems with quercetin—its high metabolism and low bioavailability—need to be addressed first. Another significant drawback with regard to the treatment of prostate cancer is chemoresistance. This review emphasizes quercetin's ability to eradicate chemoresistance in prostate cancer as well as its chemotherapeutic and chemo preventive effects. The underlying mechanisms for elimination of prostate cancer and eradication of resistance, either alone or in combination with other agents, are also discussed. In addition, the nanoscale delivery of quercetin is underpinned along with possible directions for future study.

4. **Synthesis of Quercetin-Loaded Silver Nanoparticles and Assessing Their Anti-Bacterial Potential: (2023)** [41,42]

The study explores the diverse potential of silver nanoparticles (AgNPs) in conjunction with quercetin (Qu), a phytoconstituent present in a variety of fruits, vegetables, and medicinal plants. The study investigates the production and description of AgNPs loaded with Qu and examines its use in medicine, paying special attention to their antibacterial qualities. Qu's identity and physicochemical characteristics are carefully assessed in the study, which confirms that it is suitable for usage in pharmaceuticals. The creation of Qu-loaded AgNPs indicates improved therapeutic efficacy and fewer adverse effects due to their high drug entrapment efficiency, optimal particle properties, and regulated drug release kinetics. Additionally, the study looks into Qu's antibacterial activity in various solvents, showing varying results. Qu has antibacterial action against Escherichia coli in both methanol and water formulations, with the methanol formulation showing a marginally higher level of effectiveness. To sum up, our work effectively creates AgNPs loaded with Qu and demonstrates their promise as a strong antibacterial solution. The findings underscore the influence of solvent choice on Qu's antibacterial properties and have the way for further research and development in drug delivery systems and antimicrobial agents.

CHALLENGES OF QUERCETIN LOADED NANOPARTICLES [42]

Formulation Challenges:

1.Poor solubility: Quercetin's low water solubility limits its effectiveness in the biological systems.

2.Instability: Quercetin is prone to degradation, which affects the stability of the nanocarriers.

Biocompatibility and Toxicity Challenges:

1.Nanoparticle Toxicity: The toxicity of nanoparticles can be a concern, and particularly if they are not biocompatible or biodegradable.

2. Immunogenicity: Nanoparticles can trigger an immune response, which affects their efficacy and safety.

Targeting and Delivery Challenges:

1. Targeting Specific Cells or Tissues: Quercetin-loaded nanocarriers may not specifically target the desired cells or tissues, reducing their efficacy.

2. Maintaining Therapeutic Levels: Quercetin-loaded nanocarriers may not maintain therapeutic levels of quercetin at the target site, reducing their efficacy.

FUTURE DIRECTIONS [20]

1. Optimizing Formulation: Optimizing the formulation of quercetin-loaded nanocarriers that improves their stability, biocompatibility, and targeting efficiency.

2. Developing New Nanocarrier Systems: Developing new nanocarrier systems, such as liposomes, polymeric nanoparticles, or nanocrystals, to improves delivery system of quercetin.

3. Investigating Combination Therapies: Investigating combination therapies involving quercetin-loaded nanocarriers and the other therapeutic agents that enhance their efficacy.

CONCLUSION:

An important development in medication delivery methods is the creation of nanoparticles loaded with quercetin. By improving quercetin's solubility, stability, and bioavailability, these nanoparticles overcome some of its intrinsic drawbacks. They provide focused distribution and controlled release, reducing adverse effects and enhancing therapeutic results. Applications of this technique in anti-inflammatory therapies, cancer therapy, and other scientific domains appear promising. However, challenges such as scalability, Poor solubility, Nanoparticle Toxicity, Targeting Specific Cells or Tissues. Overall, quercetin-loaded nanoparticles are a promising innovation in nanomedicine, paving the way for more effective and sustainable therapeutic solutions.

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