

# Quercetin As A Natural Antiviral Agent Against Covid-19: Bioavailability Challenges And Nanoformulation Approches

Vinotha.D<sup>1</sup>, Dr.J.Karthi<sup>2</sup>

<sup>1,2</sup>Dept Of Pharmacognosy

<sup>1,2</sup>Pallavan Pharmacy College, Iyyangarkulam  
Kancheepuram, 631 502

**Abstract-** *The urgent search for potent antiviral drugs has been spurred by the worldwide effects of COVID-19. A powerful natural substance with antiviral, anti-inflammatory, and immunomodulatory qualities is quercetin, a polyphenol obtained from plants. Research indicates that quercetin supports host immune response while interfering with several aspects of the SARS-CoV-2 life cycle, such as viral entry and multiplication. Despite its potential for treatment, quercetin's limited bioavailability and poor water solubility prevent it from being used in clinical settings. Nanoformulation technologies have been developed to improve its targeted distribution, stability, and absorption in order to address these issues. In preclinical models, tactics such polymeric nanoparticles, nanoemulsions, and liposomes loaded with quercetin have shown better pharmacokinetic profiles and antiviral results. This abstract emphasizes the two main areas of current research: comprehending the antiviral mechanisms of quercetin and using nanotechnology to get beyond its delivery restrictions for possible use in COVID-19 treatment.*

**Keywords-** Quercetin, COVID-19, SARS-CoV-2, Antiviral agents Bioavailability, Nanoformulation, Liposomes, Nanoemulsions, Polymeric nanoparticles, Nanotechnology

## I. INTRODUCTION

Coronaviruses are positive-sense RNA viruses that are members of the Nidovirales order and the Coronaviridae family. Coronaviruses have been responsible for some of the world's deadliest outbreaks since the turn of the twenty-first century. For instance, coronaviruses with a fatality rate of 10% and 37%, respectively, were responsible for the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak and the SARS outbreak of 2002–2003 [1]. COVID-19, a highly contagious disease that affects the respiratory system and can be fatal in severe cases, is caused by SARS-CoV-2, a novel member of the coronavirus family. Despite having a significantly lower fatality rate (~3.4%) than SARS and MERS, COVID-19 is one of the most deadline illnesses due to its extremely contagious global pandemic.

Numerous research teams worldwide have been investigating different natural compounds for the treatment of COVID-19. Quercetin (QR), a flavonoid molecule present in a wide variety of natural goods, including fruits, vegetables, herbs, and bee products, is one example of a tiny molecule of this type. Both MERS and SARS have been successfully treated with the antiviral drug QR.

Quercetin's antiviral action against coronaviruses, such as SARS-CoV-2, is mediated via its antioxidant properties, cytokine response modulation, and inhibition of viral entrance and reproduction. Because to its significant first-pass metabolism, poor water solubility, and instability at physiological pH, quercetin has a low bioavailability (~2%) despite its therapeutic potential. By boosting quercetin's pharmacokinetics and distribution to target tissues like the lungs and immune cells, delivery methods based on nanotechnology offer a solution. The hunt for potent antiviral drugs, particularly those made from natural sources, has accelerated due to the global COVID-19 pandemic. Fruits and vegetables include quercetin, a plant-based flavonoid that has drawn interest because of its broad-spectrum antiviral, anti-inflammatory, and antioxidant qualities. Quercetin disrupt several phases of the SARS-CoV-2 virus life cycle, including as viral entrance, replication, and host immunological regulation, according to a number of in vitro and in silico investigations. However, its quick metabolism, low bioavailability, and poor water solubility limit its therapeutic use. Nanoformulation techniques like liposomes, nanoparticles, and nanoemulsions have been investigated to improve quercetin's stability, distribution, and therapeutic effectiveness in order to get over these obstacles. This review highlights recent advances in quercetin nanoformulations and their potential role in the prevention and treatment of COVID-19

## QUERCETIN SOURCE AND ITS PROPERTIES:

Quercetin is an antioxidant derived from plants that is a member of the flavonoid family, a class of substances that are well-known for their anti-inflammatory and antioxidant

qualities. It is prevalent in a variety of foods high in nutrients, such as:

Fruits: Citrus fruits, blueberries, cranberries, and raspberries, as well as apples.

Vegetables: asparagus, kale, broccoli, and red and white onions.

Buckwheat and capers are the grains and seeds.  
Drinks: Red wine, black tea, and green tea.

Quercetin originating from the Latin word quercetum, which means "oak forest," quercetin is a flavonol that the human body does not manufacture. One of the most significant plant compounds is quercetin, which has pharmacological action including anti-inflammatory, pro-metabolic, antiviral, and anti-atopic properties. Additionally, it has been shown to possess a variety of anticancer qualities, and multiple investigations suggest that it is an effective cancer-preventive agent. In addition to its psychostimulant qualities, quercetin has been shown to improve mitochondrial biogenesis and inhibit lipid peroxidation, capillary permeability, and platelet aggregation.

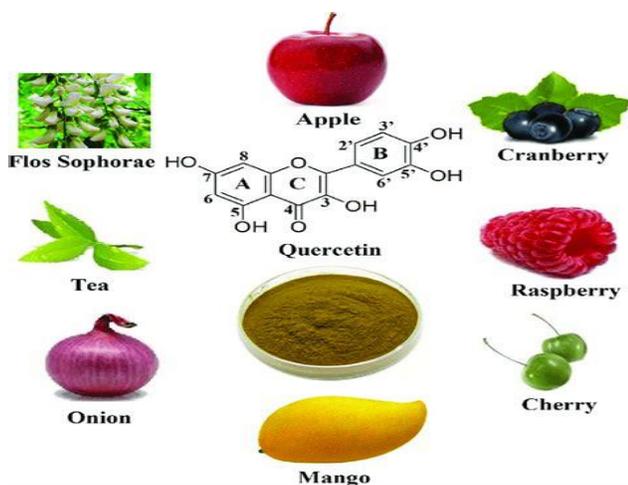


Figure 1. Sources of Quercetin.

Naturally occurring plant phytochemicals are typically less expensive and have less side effects than synthesized medications, there has been an increase in interest in using them to treat a variety of disorders in recent years. As antioxidants and scavengers of ROS and other free radicals, QR and a number of other natural polyphenols also trigger phase II detoxification enzymes. A hydrophobic citron-yellow crystal generated from plants, QR has undergone experimental validation to assess its biological features and attributes. One of the most common flavonoid compounds is QR. The presence of five hydroxyl groups with electron-donating

activity at positions 3, 5, 7, 3', and 4' is what distinguishes QR (Figure 2).

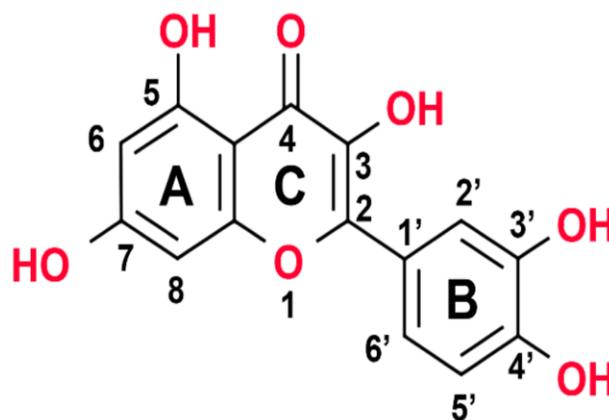


Figure 2. The structural formula of quercetin.

#### QUERCETIN IN IMMUNOMODULATION:

QR directly modulates a number of immune cells, cytokines, and other immune chemicals, it is a powerful immunomodulatory molecule. For example, QR therapy decreases the expression of chemicals that activate dendritic cells (DCs), such as major histocompatibility complex (MHC) class II. When given LPS, DCs obtained from mouse bone marrow exhibit decreased activation. Additionally, QR reduces DC migration brought on by LPS. The body's antigen-specific T-cell activation is decreased when DC activity is decreased. Targeting several intracellular signaling kinases and phosphatases, enzymes, and membrane proteins, QR predominantly acts on leukocytes to influence inflammation and immunity.

Flavonoids have a wide range of biological impacts. Hepatoprotective and antiallergic qualities have also been shown, in addition to antiviral, anti-inflammatory, and antioxidant qualities. One of the primary features of severe viral infections, such as SARS and COVID-19 illness, is the "cytokine storm," which is an enhanced production of cytokines such as interleukins, interferon-gamma (IFN- $\gamma$ ), and tumor necrosis factor (TNF). Due to several investigations on their in vitro inhibitory effect towards different inflammatory mediators, including cytokines, flavonoids are regarded as prospective anti-inflammatory therapeutic agents. By suppressing the expression of multiple proinflammatory cytokines and signaling pathways, QR has strong immunomodulatory effects. Additionally, a decrease in the levels of specific immunoglobulin E (sIgE) was noted, which resulted in a less severe anaphylactic reaction. Asthma symptoms can be reduced by using QR's immunomodulatory qualities. In vaccinated mice, QR therapy boosted the quantity of IgM-producing cells and B-cell proliferation in ex vivo

settings. Inflammatory reactions brought on by the influenza A virus also demonstrated QR's immunomodulatory qualities. In these situations, QR therapy decreased TNF- $\alpha$  expression and enhanced IL-27 release. By lowering the expression of immunoglobulin E responses, QR is also helpful in treating peanut-induced food allergies. By lowering IL-4 expression, eosinophil activity inhibition, Th1/Th2 balance improvement, and leukotriene and prostaglandin levels, QR also regulates the immune system.

#### QUERCETIN IN ANTI-MICROBIAL EFFECTS:

Numerous investigations into QR's antimicrobial properties have revealed that it prevents the growth of a number of bacterial species. According to Jaisinghani et al., for instance, QR prevents the growth of a number of bacterial species, including *Pseudomonas aeruginosa*, *Shigella flexneri*, *Proteus vulgaris*, *Escherichia coli*, and *Staphylococcus aureus*. QR's inhibitory concentration, which was 20 g/mL for *S. aureus* and *P. aeruginosa*, varied, nevertheless. Higher concentrations of QR inhibited other bacterial strains, including *Lactobacillus casei* (500 g/mL), *E. coli* (400 g/mL), *S. flexneri* (500 g/mL), and *P. vulgaris* (300 /mL). Wang et al. also showed that it has bacteriostatic effects on *Salmonella enterica* Typhimurium, *E. coli*, *S. aureus*, and *P. aeruginosa*. At the molecular level, QR inhibits the growth of *E. coli* and *S. aureus* by damaging the cell wall and cell membrane; this increased cell wall/membrane damage is reflected in the increased activity of extracellular enzymes, such as alkaline phosphatase and-galactosidase. QR also exhibited antibacterial action against periodontal pathogens, such as *Actinobacillus actinomycetemcomitans* (Aa) and *Porphyromonas gingivalis* (Pg). A study by Geoghegan et al. revealed that QR inhibits the growth of Aa and Pg in a dose-dependent manner, which suggests that it has potential to prevent bone loss. Nevertheless, Aa only shown growth inhibition for 12 hours, after which QR's antibacterial activity diminished. However, following a 24-hour treatment period, Pg displayed growth inhibition. In An intriguing finding was that Siriwong et al. demonstrated QR's antibacterial activity against a strain of *Staphylococcus epidermidis* that is resistant to multiple drugs. Amoxicillin-resistant *S. epidermidis* (ARSE) was the strain employed in the investigation. Amoxicillin and QR together were found to have synergistic effects on the suppression of bacterial growth. The combination decreased the amount of fatty acids in the bacterial cells, caused damage to the cytoplasmic membrane, increased cell membrane permeability, and prevented the formation of peptidoglycans. Additionally, the main enzyme responsible for the breakdown of lactamases, lactamase, was blocked by QR. According to Hirai et al., QR exhibited antibacterial activity against

*S. aureus* resistant to methicillin. Additionally, when used with other antibiotics as erythromycin, vancomycin, ampicillin, oxacillin, and gentamicin, QR shown synergistic effectiveness against MRSA. Additionally, QR caused *S. aureus* cells to aggregate and impacted the bacteria's capacity to spread colonies.

#### ANTIVIRAL ACTIVITY OF QUERCETIN:

Inhibiting viral infections may require focusing on the viral proteins that allow the virus to enter the host cells. By preventing viruses from entering host cells, QR has demonstrated antiviral qualities. For instance, QR suppressed the early phases of infection in a number of influenza virus strains, including A/FM-1/47/1 (H1N1), A/Puerto Rico/8/34 (H1N1), and A/Aichi/2/68 (H3N2). It has been noted that QR inhibits viral entry by interacting with hemagglutinin (HA2 subunit), a glycoprotein that allows the virus to enter. Targeting different phases of the virus life cycle, such as the assembly and release of mature virus particles from the cells, is another method to prevent or reduce virus infection.

It was demonstrated that QR decreased the copy counts of the M2 and NP proteins, which code for channel proteins and influenza viral nucleoproteins, respectively. QR also decreased virus progeny production and stopped virus-induced cellular death. Additionally, QR was successful in preventing viral infection throughout the post attachment phases. QR suppressed viral replication and decreased lung inflammation in a mouse model of rhinovirus-induced chronic obstructive pulmonary disease. Additionally, QR increased the expression of IL-10 while decreasing the mRNA levels of IL-13 and types I and II interferons. The authors came to the conclusion that QR could be utilized to lessen a variety of respiratory distress symptoms and enhance lung function. QR may be a useful tool to lessen health issues because COVID-19 patients also exhibit significant lung inflammation and breathing difficulties. Additionally, QR promotes mitochondrial antiviral signaling, enhancing the body's defenses against illness.

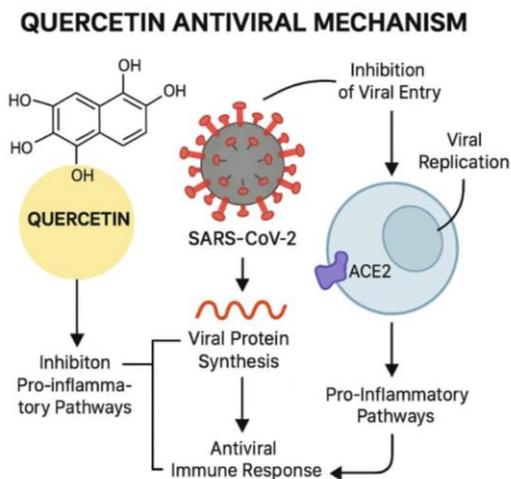


Figure 3. Antiviral mechanism of Quercetin.

**QUERCETIN DELIVERY NANOSYSTEMS:**

A powerful flavonoid with many advantageous qualities, quercetin is frequently made into nanosystems to improve its low bioavailability, which is hampered by its high first-pass metabolism and poor water solubility. These nanocarriers improve quercetin's targeting, absorption, and prolonged release, increasing its therapeutic efficacy in a variety of applications, including bone regeneration, cancer treatment, and anti-inflammatory and antioxidant therapies.

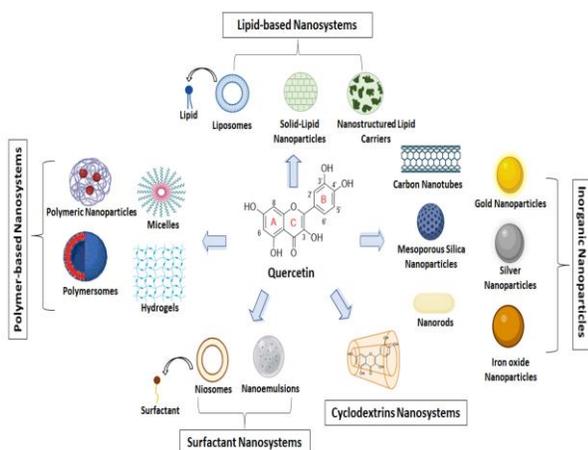


Figure 4. Types of Nanosystem.

**Polymeric-Based Nanosystems:**

Polymers are appealing instruments for the pharmaceutical sector. These materials are made by joining high MW repeating monomers to form a long chain structure. Polymers that are created by joining two or more distinct kinds of Copolymers are monomers with entirely different characteristics. Homopolymers are those made from the same

monomer. Platforms made of polymer nanoparticulates have been acknowledged as cutting-edge delivery methods for the movement of nucleic acids, APIs, and other bioactive substances. Numerous distinct forms of polymer-based systems, such as micelles, vehicles, core-shell structures, nanospheres, polymersomes, and hydrogels, have been thoroughly detailed in the literature. Our study concentrated on the most recent research on polymer-based formulations for quercetin encapsulation, which made reference to a number of structures.

a) polymeric micelles:

Micelles are colloidal nanoparticles (NPs) with a core-shell structure that are nanoscale (less than 100 nm) and comprise a hydrophilic outer layer encircling a hydrophobic center. They are created spontaneously when amphiphilic molecules self-assemble in an water-based solution. They may hold a variety of molecules in their inner core thanks to their form. While the hydrophilic shell helps to stabilize the colloidal structure in a liquid media, they can also serve as delivery platforms for the transportation of genetic material and hydrophobic APIs. The micelles loaded with QUE showed a homogeneous population with a mean particle size of roughly 55 n and a surface charge of 1.41 mV, which is nearly neutral. The QUE encapsulation ratio increased in proportion to the weight ratio of Soluplus to QUE, reaching a maximum value of nearly 100% at a weight ratio of 16:1. The QUE-loaded system's stability at 4 C, 25 C, and 37 C is demonstrated by the findings obtained. For nine months, the system can also sustain a QUE encapsulation efficiency (EE) of greater than 90%. Comparing QUE-loaded Soluplus micelles versus free QUE, this study showed a number of benefits. It has been proposed that QUE's low bioavailability can be improved by incorporating it into Soluplus polymeric micelles while Poloxamer 407 is present. The ideal formulation produced an outstanding EE up to 95% and 7% drug loading.

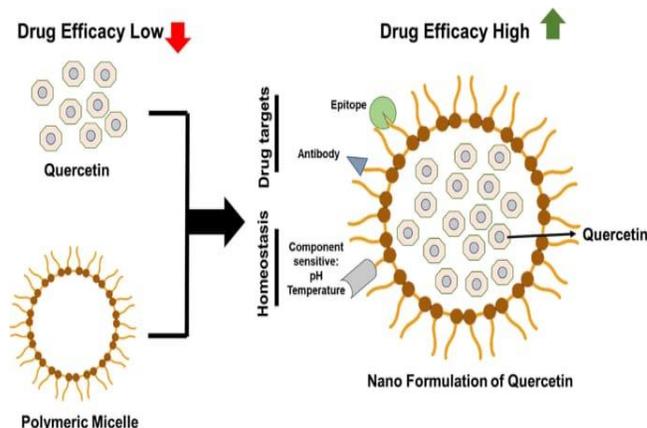


Figure 5. formulation of polymeric micelle.

The micelles' consistent 80 nm particle size and high negative zeta-potential values indicated that they were physically stable. These properties enable it to better absorb from the gut, avoid the reticuloendothelial system, and exhibit an extended half-life ( $t_{1/2}$ ). Studies on *in vitro* release demonstrated a prolonged release of the material for a maximum of ten days. Lastly, QUE's systemic bioavailability and absorption were considerably higher in the beagle dog animal model in the *in-vivo* investigation than in the pure form.

#### b) Polymeric nanoparticles:

NPs may consist of several biomaterials, including polymers and lipids. The scientific community has shown a great deal of interest in polymeric nanoparticles. Their size, which ranges from 10 nm to 10 micrometer and their distinct physicochemical characteristics set them apart from other particles. Numerous bioactive substances, such as proteins, APIs, and genetic material, can be included onto NPs' interior or external surfaces. NPs can transport the substance to the intended site of action because of their small size and ability to achieve a sustained molecule release. Altering the external stimuli, such as pH, temperature, irradiation, etc., can provide the controlled release.

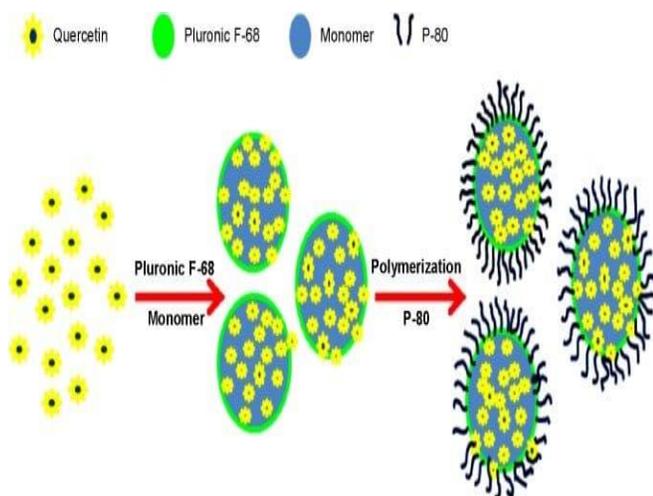


Figure 6. ration of encapsulation of QUE-poly(n-butylcyanoacrylate) NPs by emulsion polymerization.

#### LIPID BASED NANOPARTICLES:

Lipid-based NPs are now commonly administered through a variety of methods because to their high EE, ease of surface modification, and structure resembling that of cell membranes. Specifically, their usefulness has been shown in the distribution of low molecular weight APIs, in addition to the gene transfer industry. This section presents the liposomal

forms of QUE together with liposome-based NPs of the chemical, including as phytosomes and polymer-grafted liposomes. The characteristics of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLC), particularly in the oral delivery of QUE, will also be covered.

#### a) Liposomes:

Phospholipids make up the majority of the vesicular systems known as liposomes. The lipid bilayer's structural alteration is frequently employed to improve the encapsulated APIs' physicochemical characteristics and increase their release profile. Surface modification of liposomes employing different structural features, biological function, and a varying release profile of the encapsulated APIs are caused by various biomaterials, such as polysaccharides.

The effectiveness of QUE liposomes in solid tumors in mice models and their ability to prevent radiation-induced acute pneumonitis and late fibrosis by lowering oxidative damage have already been assessed.

QUE was made into liposomes that were "twins." Specifically, magnetoporation—which entails creating holes in the liposome's surface or membrane—was used to successfully integrate the enzyme laccase and QUE into liposomes. The QUE- and laccase-containing Liposomes were connected and loaded pH-sensitive substances into the pores. It was shown that this method caused tumor cells to die and increased the release of QUE and laccase at an acidic pH. In RBL-2H3 cells, QUE liposomes made using a green thin-film dispersion technique shown more potent anti-allergic effects, such as a reduction in histamine and hexosaminidase release, calcium influx, and inflammatory factor expression. For a period of two months, rats with diabetic nephropathy were given either a placebo, free QUE, PEGylated liposomes without API, or PEGylated QUE liposomes. PEG 4000, cholesterol, and soybean lecithin made up the liposomes. In diabetic nephropathy, the liposomal form of QUE was reported to improve the biochemical/pathological abnormalities. Furthermore, the liposomal version increased the amount of QUE in plasma.

#### b) Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLC):

Solid lipids make up SLN and NLC are lipid-based nanosystems, which are typically biocompatible and biodegradable. They are made using a variety of techniques, but high-pressure homogenization is the most often utilized because of its speed and repeatability. Hydrophobic APIs are encapsulated using SLN and NLC are primarily for topical and

oral delivery. A coacervation process was used to create QUE-loaded SLN with a negative charge. The particles were identified using a variety of physicochemical characterisation techniques and were made up of stearic acid and arabic gum. A steady distribution of the API within the particles was shown by the 26-hour QUE release from the SLNs across a controlled exponential plateau pattern. When compared to the non-encapsulated version, the encapsulated QUE retained a high degree of antioxidant activity (81% of that of free QUE).

QUE-loaded SLNs coated with chitosan were created using the ultrasonication technique to treat bladder cancer. The SLNs had a sustained release of around six days, a size of about 250 nm, and an EE of QUE more than 97%. The profile of cytotoxicity showed found the toxicity of QUE varied with concentration, having an IC<sub>50</sub> between 1.6 and 8.9 g/mL. QUE-loaded SLNs using a volatile oil—rosemary oil—were created using the phase-inversion temperature approach. The solid lipid trilaurin self-assembled into the smallest, most stable particles. QUE may be loaded with an entrapment efficiency of more than 60% in SLNs made with a rosemary oil-to-trilaurin ratio of 1:3. Depending on the concentration, polyoxyethylene hydrogenated castor oil RH40 generated the tiniest particles. Cell survival was more than 75% in the QUE-trilaurin SLNs, which had a prolonged biphasic release profile for over 24 hours.

#### SURFACTANT BASED NANOPARTICLES:

##### a) Niosomes

Microscopic vesicles called niosomes are made up of lipid substances including cholesterol and L-soya phosphatidylcholine as well as non-ionic surfactants of the alkyl or dialkylpolyglycerol. Non-ionic surfactants self-assemble to create a bilayer structure in aqueous media, with the hydrophobic tails pointed in the direction of one another and the hydrophilic heads seeking contact with the solution. The aqueous compartment that forms in the center of the structure as a result of these niosome component movements can accommodate hydrophilic medications, while the hydrophobic ones can be integrated into the lipophilic bilayer. The size of niosomes or the quantity of bilayers in their structure can be used to categorize them. These characteristics allow for the description of five different types of vesicles: bola-niosomes, proniosomes, large unilamellar vesicles (LUV, 100–3000 nm diameter), small unilamellar vesicles (SUV, 10–100 nm diameter), and multilamellar vesicles (MLV, 0.5–10 m diameter). The slurry, the slow spray coating, and the coacervation phase separation method are the three recognized preparation techniques. Niosomes behave similarly to liposomes *in vivo*, which increases the entrapped drug's

stability and bioavailability and facilitates more effective organ distribution. Because of their shape and function, niosomes are biocompatible, non-immunogenic, and biodegradable drug carriers that offer a number of benefits. Since their amphiphile nature promotes a wide range of solubility and the preservation of the most vulnerable structural elements, they are especially thought to be suitable for the encapsulation of low-solubility compounds or labile molecules.

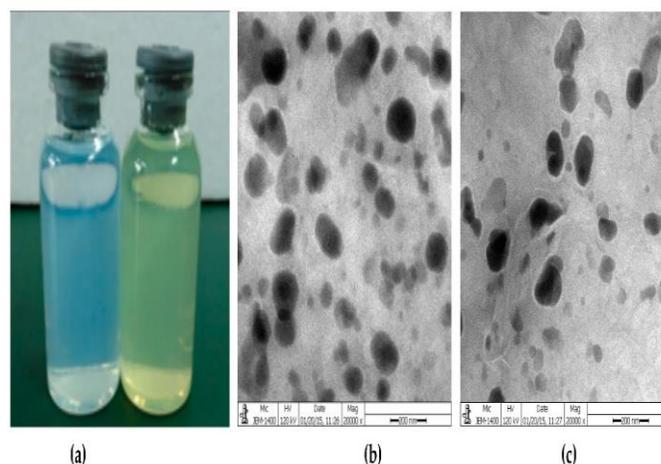


Figure 7. (a) Appearance of empty niosomes and quercetin-niosomes; (b) Transmission electron microscopy (TEM) image of blank niosomes; (c) TEM image of quercetin-niosomes.

##### b) Nanoemulsions

Nanoemulsions are colloidal systems with nanosized droplets scattered throughout the continuous phase and two immiscible phases (continuous and dispersed). The literature reports droplet sizes ranging from 10 to 1000 nm, with 20–200 nm being the most common. These systems are also known as miniemulsions, fine-dispersed emulsions, or submicron emulsions. O/W (oil in water) and W/O (water in oil) nanoemulsions are both possible, and the proportion of oil in O/W typically ranges from 5 to 20% w/w. Additionally, bicontinuous nanoemulsions, in which the continuous and dispersed phases are both liquid and stabilized by a surfactant, as well as double emulsions, W/O/W (water in oil in water) and O/W/O (oil in water in oil), respectively, can be made. Three different kinds of surfactants—cationic, anionic, and nonionic—are employed to stabilize nanoemulsions. To strengthen the stabilizing process, co-surfactants such as glycerin, ethylene glycol, propylene glycol, etc., can be added. There have been several documented techniques for creating nanoemulsions, which can be broadly divided into two categories: high and low energy emulsification. The first one involves microfluidization, high-pressure homogenization, and

ultrasonic emulsification; the second one involves temperature inversion and spontaneous emulsification.

Nanoemulsion delivery methods have been created for a variety of administration routes, including topical or systemic. Increased medication solubility and improved in-vitro dissolution during oral delivery can improve absorption in the gastrointestinal (GI) tract. Both hydrophilic and lipophilic molecules' characteristics can be modulated by W/O and O/W nanoemulsions. The parental administration of insoluble medications may also be made possible by solubility augmentation. Additionally, the capacity of these systems to stop penetrating through membranes and the continuous release of medications from nanoemulsions make them amenable to topical and ophthalmic delivery.

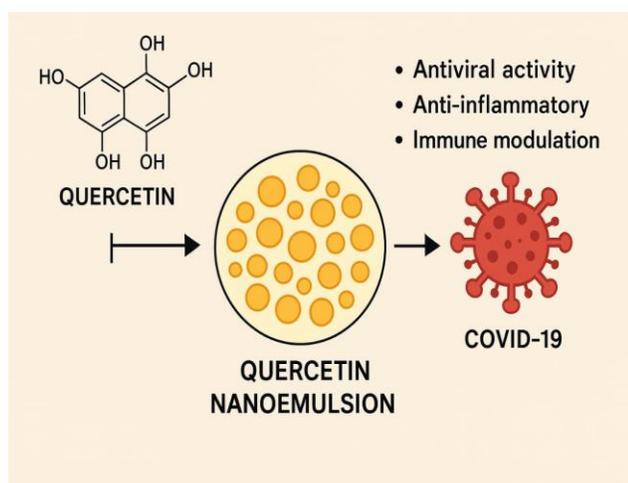


Figure 8. Quercetin Nanoemulsion.

## II. RESULT AND DISCUSSION

Quercetin may prove to be a useful adjuvant treatment for viral infections such as COVID-19 in the future, particularly if its bioavailability is increased by sophisticated delivery methods. Further investigation into nanoformulations, including polymeric carriers, solid lipid nanoparticles, and nanoemulsions, is expected to improve its clinical efficacy. These developments could enable continuous drug release, better patient compliance, and targeted delivery to lung tissue. It may be possible to increase quercetin's therapeutic potential by combining it with additional antiviral or immune-boosting substances. Future clinical studies are necessary to ascertain the best dosage, level of safety, and long-term effectiveness in people. If quercetin nanoformulation proves effective, it might be incorporated into conventional antiviral therapy regimens.

## III. CONCLUSION

A naturally occurring flavonoid in fruits and vegetables, quercetin has a wide range of antiviral properties, including encouraging results against the COVID-19 virus, SARS-CoV-2. Its therapeutic promise is highlighted by its modes of action, which include modulating inflammatory responses, blocking viral entrance, and interfering with replication enzymes. Furthermore, quercetin has immunomodulatory and antioxidant qualities that could aid in controlling the cytokine storm linked to severe COVID-19 instances. Despite its pharmacological advantages, quercetin's low bioavailability severely restricts its therapeutic use. Its fast metabolism, poor intestinal absorption, and low water solubility limit its systemic presence and therapeutic efficacy. This has led scientists to investigate cutting-edge delivery methods that can improve the stability, absorption, and biological activity of quercetin.

In order to get around these restrictions, nanoformulation techniques such polymeric carriers, solid lipid nanoparticles, liposomes, and nanoemulsions have showed a lot of promise. In addition to enhancing quercetin's pharmacokinetic profile, these technologies allow for tailored administration to affected tissues, which may increase therapeutic results while reducing adverse effects. To sum up, combining nanotechnology with organic substances like quercetin may provide a potent and long-lasting approach to creating antiviral medications in the future, particularly for newly emerging infectious disorders like COVID-19. To confirm these results and guarantee human safety and effectiveness, more in vivo research and clinical trials are necessary.

## REFERENCES

- [1] Björklund, G.; Dadar, M.; Chirumbolo, S.; Lysiuk, R. Flavonoids as detoxifying and pro-survival agents: What's new? *Food Chem. Toxicol.* 2017, 110, 240–250. [CrossRef]
- [2] Chirumbolo, S.; Björklund, G.; Lysiuk, R.; Vella, A.; Lenchyk, L.; Upyr, T. Targeting Cancer with Phytochemicals via Their Fine Tuning of the Cell Survival Signaling Pathways. *Int. J. Mol. Sci.* 2018, 19, 3568. [CrossRef]
- [3] Davis, J.M.; Murphy, E.A.; Carmichael, M.D. Effects of the dietary flavonoid quercetin upon performance and health. *Curr. Sports Med. Rep.* 2009, 8, 206–213. [CrossRef]
- [4] Verna, G.; Liso, M.; Cavalcanti, E.; Bianco, G.; Di Sarno, V.; Santino, A.; Campiglia, P.; Chieppa, M. Quercetin Administration Suppresses the Cytokine Storm in

- Myeloid and Plasmacytoid Dendritic Cells. *Int. J. Mol. Sci.* 2021, 22, 8349. [CrossRef] [PubMed]
- [5] Delvecchio, F.R.; Vadrucchi, E.; Cavalcanti, E.; De Santis, S.; Kunde, D.; Vacca, M.; Myers, J.; Allen, F.; Bianco, G.; Huang, A.Y.; et al. Polyphenol administration impairs T-cell proliferation by imprinting a distinct dendritic cell maturational profile. *Eur. J. Immunol.* 2015, 45, 2638–2649. [CrossRef]
- [6] Chirumbolo, S. The role of quercetin, flavonols and flavones in modulating inflammatory cell function. *Inflamm. Allergy Drug Targets* 2010, 9, 263–285. [CrossRef]
- [7] Lysiuk, R.; Hudz, N. Differential spectrophotometry: Application for quantification of flavonoids in herbal drugs and nutraceuticals. *Int. J. Trends Food Nutr.* 2017, 1, e102.
- [8] Rogerio, A.P.; Dora, C.L.; Andrade, E.L.; Chaves, J.S.; Silva, L.F.; Lemos-Senna, E.; Calixto, J.B. Anti-inflammatory effect of quercetin-loaded microemulsion in the airways allergic inflammatory model in mice. *Pharmacol. Res.* 2010, 61, 288–297. [CrossRef]
- [9] Maturu, P.; Wei-Liang, Y.; Androutsopoulos, V.P.; Jiang, W.; Wang, L.; Tsatsakis, A.M.; Couroucli, X.I. Quercetin attenuates the hyperoxic lung injury in neonatal mice: Implications for Bronchopulmonary dysplasia (BPD). *Food Chem. Toxicol.* 2018, 114, 23–33. [CrossRef]
- [10] Sternberg, Z.; Chadha, K.; Lieberman, A.; Hojnacki, D.; Drake, A.; Zamboni, P.; Rocco, P.; Grazioli, E.; Weinstock-Guttman, B.; Munschauer, F. Quercetin and interferon-modulate immune response(s) in peripheral blood mononuclear cells isolated from multiple sclerosis patients. *J. Neuroimmunol.* 2008, 205, 142–147. [CrossRef]
- [11] Gupta, K.; Kumar, S.; Gupta, R.K.; Sharma, A.; Verma, A.K.; Stalin, K.; Chaudhari, B.P.; Das, M.; Singh, S.P.; Dwivedi, P.D. Reversion of Asthmatic Complications and Mast Cell Signalling Pathways in BALB/c Mice Model Using Quercetin Nanocrystals. *J. Biomed. Nanotechnol.* 2016, 12, 717–731. [CrossRef]
- [12] Valentova, K.; Sima, P.; Rybkova, Z.; Krizan, J.; Malachova, K.; Kren, V. (Anti)mutagenic and immunomodulatory properties of quercetin glycosides. *J. Sci. Food Agric.* 2016, 96, 1492–1499. [CrossRef]
- [13] Mehrbod, P.; Abdalla, M.A.; Fotouhi, F.; Heidarzadeh, M.; Aro, A.O.; Eloff, J.N.; McGaw, L.J.; Fasina, F.O. Immunomodulatory properties of quercetin-3-O-alpha-L-rhamnopyranoside from *Rapanea melanophloeos* against influenza A virus. *BMC Complement Altern. Med.* 2018, 18, 184. [CrossRef]
- [14] Zhang, W.-q. Evaluation of anti-fatigue and immunomodulating effects of quercetin in strenuous exercise mice. *IOP Conf. Ser. Earth Environ. Sci.* 2017, 61, 012046. [CrossRef]
- [15] Mlcek, J.; Jurikova, T.; Skrovankova, S.; Sochor, J. Quercetin and Its Anti-Allergic Immune Response. *Molecules* 2016, 21, 623. [CrossRef]
- [16] Jaisinghani, R.N. Antibacterial properties of quercetin. *Microbiol. Res.* 2017, 8, 6877. [CrossRef]
- [17] Chroni, A.; Mavromoustakos, T.; Pispas, S. Biocompatible PEO-b-PCL Nanosized Micelles as Drug Carriers: Structure and Drug-Polymer Interactions. *Nanomaterials* 2020, 10, 1872. [CrossRef]
- [18] Pippa, N.; Pispas, S.; Demetzos, C. Polymer Self-Assembled Nanostructures as Innovative Drug Nanocarrier Platforms. *Curr. Pharm. Des.* 2016, 22, 2788–2795. [CrossRef] [PubMed]
- [19] Patel, H.S.; Shaikh, S.J.; Ray, D.; Aswal, V.K.; Vaidya, F.; Pathak, C.; Sharma, R.K. Formulation, Solubilization, and In Vitro Characterization of Quercetin-Incorporated Mixed Micelles of PEO-PPO-PEO Block Copolymers. *Appl. Biochem. Biotechnol.* 2022, 194, 445–463. [CrossRef]
- [20] Qi, X.; Gao, C.; Yin, C.; Fan, J.; Wu, X.; Di, G.; Wang, J.; Guo, C. Development of quercetin-loaded PVCL-PVA-PEG micelles and application in inhibiting tumor angiogenesis through the PI3K/Akt/VEGF pathway. *Toxicol. Appl. Pharmacol.* 2022, 437, 115889. [CrossRef]
- [21] Paranthaman, S.; Uthaiyah, C.A.; Osmani, R.A.M.; Hani, U.; Ghazwani, M.; Alamri, A.H.; Fatease, A.A.; Madhunapantula, S.V.; Gowda, D.V. Anti-Proliferative Potential of Quercetin Loaded Polymeric Mixed Micelles on Rat C6 and Human U87MG Glioma Cells. *Pharmaceutics* 2022, 14, 1643. [CrossRef]
- [22] Elsabahy, M.; Wooley, K.L. Design of polymeric nanoparticles for biomedical delivery applications. *Chem. Soc. Rev.* 2012, 41, 2545–2561. [CrossRef]
- [23] Sun, L.; Wu, Q.; Peng, F.; Liu, L.; Gong, C. Strategies of polymeric nanoparticles for enhanced internalization in cancer therapy. *Colloids Surf. B Biointerfaces* 2015, 135, 56–72. [CrossRef]
- [24] Sunoqrot, S.; Abujamous, L. pH-sensitive polymeric nanoparticles of quercetin as a potential colon cancer-targeted nanomedicine. *J. Drug Deliv. Sci. Technol.* 2019, 52, 670–676. [CrossRef]
- [25] Bagad, M.; Khan, Z.A. Poly(n-butylcyanoacrylate) nanoparticles for oral delivery of quercetin: Preparation, characterization, and pharmacokinetics and biodistribution studies in Wistar rats. *Int. J. Nanomed.* 2015, 10, 3921–3935. 62. Huang, K.T.; Wu, C.T.; Chang, Y.; Ho, F.M.; Chiang, C.K.; Liu, S.H. Therapeutic effect of quercetin polymeric nanoparticles on ischemia/reperfusion-induced acute kidney injury in mice.

- Biochem. Biophys. Res. Commun. 2022, 608, 122–127. [CrossRef] [PubMed]
- [26] Zhou, Y.; Chen, D.; Xue, G.; Yu, S.; Yuan, C.; Huang, M.; Jiang, L. Improved therapeutic efficacy of quercetin-loaded polymeric nanoparticles on triple-negative breast cancer by inhibiting uPA. *RSC Adv.* 2020, 10, 34517–34526. [CrossRef] [PubMed]
- [27] Doosti, M.; SeyedDorraj, M.S.; Mousavi, S.N.; Rasoulifard, M.H.; Hosseini, S.H. Enhancing quercetin bioavailability by super paramagnetic starch-based hydrogel grafted with fumaric acid: An in vitro and in vivo study. *Colloids Surf. B Biointerfaces* 2019, 183, 110487. [CrossRef] [PubMed]
- [28] Pippa, N.; Pispas, S.; Demetzos, C. Recent advances in micellar-like polyelectrolyte/protein complexes. In *Design and Development of New Nanocarriers*; Grumezescu, A.M., Ed.; Elsevier: Amsterdam, The Netherlands, 2018; pp. 57–88. ISBN 978-0-12-813627-0.
- [29] Bashir, S.; Teo, Y.Y.; Ramesh, S.; Ramesh, K. Synthesis and characterization of karaya gum-g- poly (acrylic acid) hydrogels and in vitro release of hydrophobic quercetin. *Polymer* 2018, 147, 108–120. [CrossRef]
- [30] Esposito, L.; Barbosa, A.I.; Moniz, T.; Costa Lima, S.; Costa, P.; Celia, C.; Reis, S. Design and Characterization of Sodium Alginate and Poly(vinyl) Alcohol Hydrogels for Enhanced Skin Delivery of Quercetin. *Pharmaceutics* 2020, 12, 1149. [CrossRef]
- [31] Mok, S.W.; Fu, S.C.; Cheuk, Y.C.; Chu, I.M.; Chan, K.M.; Qin, L.; Yung, S.H.; Kevin Ho, K.W. Intra-Articular Delivery of Quercetin Using Thermosensitive Hydrogel Attenuate Cartilage Degradation in an Osteoarthritis Rat Model. *Cartilage* 2020, 11, 490–499. [CrossRef]
- [32] SafarSajadi, S.M.; Khoee, S. The simultaneous role of porphyrins' H- and J- aggregates and host-guest chemistry on the fabrication of reversible Dextran-PMMA polymersome. *Sci. Rep.* 2021, 11, 2832. [CrossRef]
- [33] Gomes, C.P.; Dias, R.C.S.; Costa, M.R.P.F.N. Design of RAFT synthesized amphiphilic and stimuli-responsive block copolymers for encapsulation of polyphenols in polymersomes. *CHEMPOR* 2018, P-IM02, 579–580.
- [34] Chavda, V.P.; Vihol, D.; Mehta, B.; Shah, D.; Patel, M.; Vora, L.K.; Pereira-Silva, M.; Paiva-Santos, A.C. Phytochemical-loaded liposomes for anticancer therapy: An updated review. *Nanomedicine* 2022, 17, 547–568. [CrossRef]
- [35] Liu, H.; Xue, J.X.; Li, X.; Ao, R.; Lu, Y. Quercetin liposomes protect against radiation-induced pulmonary injury in a murine model. *Oncol. Lett.* 2013, 6, 453–459. [CrossRef]
- [36] Kim, Y.; Oh, K.T.; Youn, Y.S.; Lee, E.S. pH-Sensitive Twin Liposomes Containing Quercetin and Laccase for Tumor Therapy. *Biomacromolecules* 2022, 23, 3688–3697. [CrossRef] [PubMed]
- [37] Abdel-Mageed, H.M.; Abd El Aziz, A.E.; Mohamed, S.A.; AbuelEzz, N.Z. The tiny big world of solid lipid nanoparticles and nanostructured lipid carriers: An updated review. *J. Microencapsul.* 2022, 39, 72–94. [CrossRef]
- [38] Akbari, J.; Saeedi, M.; Ahmadi, F.; Hashemi, S.M.H.; Babaei, A.; Yaddollahi, S.; Rostamkalaei, S.S.; Asare-Addo, K.; Nokhodchi, A. Solid lipid nanoparticles and nanostructured lipid carriers: A review of the methods of manufacture and routes of administration. *Pharm. Dev. Technol.* 2022, 27, 525–544. [CrossRef]
- [39] Salah, E.; Abouelfetouh, M.M.; Pan, Y.; Chen, D.; Xie, S. Solid lipid nanoparticles for enhanced oral absorption: A review. *Colloids Surf. B Biointerfaces.* 2020, 196, 111305. [CrossRef]
- [40] Khoee, S.; Yaghoobian, M. Niosomes: A novel approach in modern drug delivery systems. In *Nanostructures for Drug Delivery*; Elsevier: Amsterdam, The Netherlands, 2017; pp. 207–237.
- [41] Kauslya, A.; Borawake, P.D.; Shinde, J.V.; Chavan, R.S. Niosomes: A Novel Carrier Drug Delivery System. *J. Drug Deliv. Ther.* 2021, 11, 162–170. [CrossRef]
- [42] Sadeghi-Ghadi, Z.; Ebrahimnejad, P.; TalebpourAmiri, F.; Nokhodchi, A. Improved oral delivery of quercetin with hyaluronic acid containing niosomes as a promising formulation. *J. Drug Target.* 2021, 29, 225–234. [CrossRef] [PubMed]
- [43] Tayeb, H.H.; Sainsbury, F. Nanoemulsions in drug delivery: Formulation to medical application. *Nanomedicine* 2018, 13, 2507–2525. [CrossRef]
- [44] Wilson, R.J.; Li, Y.; Yang, G.; Zhao, C.-X. Nanoemulsions for drug delivery. *Particology* 2021, 64, 85–97. [CrossRef]
- [45] Ashaolu, T.J. Nanoemulsions for health, food, and cosmetics: A review. *Env. Chem. Lett.* 2021, 19, 3381–3395. [CrossRef] [PubMed]