Unlocking Quercetin's Therapeutic Potential: The Use of Innovative Drug Delivery Strategies to Remedy Neurodegenerative Disorders

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Abstract

Neurodegenerative disorders are a class of diseases characterized by the degeneration of certain parts of the central and peripheral nervous system, affecting millions of people worldwide. The use of quercetin for the potential treatment of neurodegenerative disorders has been heavily researched due to the flavonoid's antioxidant, anti-inflammatory, metal-ion chelating, and neuroprotective properties. However, free quercetin struggles to make a significant clinical impact due to low aqueous solubility, chemical instability, and an unfavorable absorption profile, ultimately leading to underwhelming levels of bioavailability. To ameliorate these issues, drug delivery systems have been employed in modern research, including polymer-based nanoparticles, lipid-based nanoparticles, and metallic nanoparticles. This review aims to discuss modern research on quercetin's potential in neurodegenerative disorder treatment, particularly with these drug carriers, and identify the most promising configurations for future investigation. Most notably, studies showed that drug carriers for quercetin's delivery increased the flavonoid's bioavailability, likely due to protective mechanisms against bodily chemical degradation. Additionally, many studies also found that drug carriers significantly extended the duration of quercetin's release within the body, allowing for less frequent administration of the flavonoid during treatment periods. Finally, drug delivery systems illustrated the facilitation effects of quercetin's blood-brain barrier crossing—an essential step in treating neurodegenerative disorders. Though the use of quercetin-loaded drug carriers for neurodegenerative disorder treatment is still a relatively new topic of study, certain configurations have shown tremendous potential. Most notably, liposomal delivery systems are especially promising candidates, and future studies should investigate their use in tandem with PEGylations for quercetin's neurodegenerative applications.

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1 Introduction

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a widely abundant dietary polyphenol and flavonoid found in a wide array of fruits, vegetables, and their respective derivatives. Quercetin is most profusely found in berries, leafy greens, citrus fruits, onions, apples, red wine, and green tea [BL22] [SA07] [ADAP16] [CCE$^+$03] [SNS$^+$13]. Throughout the past few years, quercetin has been heavily researched and implemented in both food products and pharmaceuticals alike due to the wide variety of promising health benefits exhibited [LW22] [PVK$^+$22]. One of quercetin's most prominent properties is a free radical scavenging ability, allowing for unpaired electron neutralization, which is notorious for inducing inflammation and oxidative stress [ADB$^+$89]. These very stressors gradually wear down the body and eventually deteriorate enough to the point where disorders and diseases can either be caused directly by the damage or be predisposed to the body's weakened state. The most common free radical-induced maladies include viral infections [Aka01], neurodegenerative disorders [LBBD17], diabetes [MSWI03], cardiovascular complications [ML97], and various cancers [VRM$^+$06] [DJ96] [RBS$^+$00]. As a result, among other factors, quercetin has been found to most significantly display anti-inflammatory [KVM$^+$11], antioxidant [HCS$^+$18], anticancer [HDFY$^+$17], antidiabetic [SVKP18], antimicrobial [WYZ$^+$18], antiviral [SLL$^+$21], hepatoprotective [EAPA$^+$17], and neuroprotective effects *in vivo* [BGP$^+$20].

In the past decade, quercetin has seen a rise in preclinical and clinical research for potential treatments of neurodegenerative disorders, including Alzheimer's Disease [MPSS$^+$17], Parkinson's Disease [SWM$^+$12], Huntington's Disease [CSD$^+$13], Amyotrophic Lateral Sclerosis (ALS) [BMSD20], and Multiple Sclerosis (MS) [AEG$^+$23]. As a result of quercetin's free radical scavenging and neuroprotective properties, quercetin has exhibited the ability not necessarily to reverse the effects of neurodegenerative disorders but rather to hinder and mitigate their progression within the body. As neurodegenerative disorders are most often characterized by neurological degradation and are closely linked to old age, slowing down their progression can play a tremendous role in increasing the life expectancy of those who suffer. However, despite the myriad of pharmaceutical benefits that quercetin possesses, the flavonoid alone has struggled to make a significant clinical impact due to low aqueous solubility, chemical stability, and an unfavorable absorption profile, ultimately leading to an underwhelming bioavailability [MMD$^+$97]. Quercetin's hydrophobic properties, for one, make absorption into the bloodstream extremely difficult. Additionally, the highly reactive and pH-sensitive nature of quercetin prone it to chemical alterations when passing through the acidic environment of the gastrointestinal tract, undergoing deprotonation, which furthers the flavonoid's lack of solubility and bioavailability [ZZM21]. In attempts to ameliorate this issue, recent studies and developments in quercetin applications encompass a wide range of drug delivery systems for the flavonoid, including lipid-based nanoparticles, polymer-based nanoparticles, and metallic nanoparticles [VM19]. In this review, it will be discussed how the numerous pharmacological properties of quercetin can

be harnessed through the use of novel drug delivery systems for the potential treatment of neurodegenerative disorders.

2 Chemical Structure and Properties of Quercetin

Flavonoids are a class of polyphenolic compounds structurally characterized by three aromatic rings, one of which is usually heterocyclic [SJC+21]. Among them are many subclasses with varying functional groups, including Flavones, Flavonols, Isoflavones, Flavanones, Anthocyanins, and Flavan-3-ols. Quercetin, a flavonol, distinguishes itself from the other flavonoids through its unique chemical structure, boasting five hydroxyl groups (circled in red) in addition to a ketone group (circled in green) (Fig. 1) [MS19]. This unique structure provides quercetin with an expansive set of chemical properties fit to combat neurodegenerative disorders.

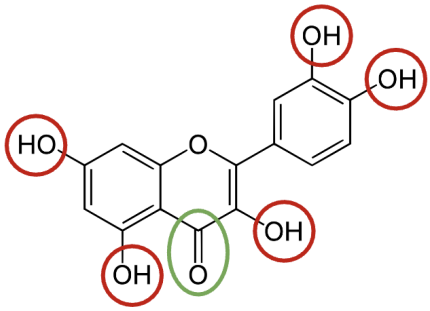

Figure 1: Chemical structure of quercetin ($C_{15}H_{10}O_7$). Hydroxyl groups (OH^-) circled in red. Ketone group (C=O) circled in green.

2.1 Antioxidant Activity

The antioxidative properties of quercetin stem directly from the flavonoid's free radical scavenging ability [MCM+98]. Free radicals, most commonly found in the form of reactive oxygen species (ROS) and reactive nitrogen species (RNS), are molecules containing one or more unpaired electrons [PKVP10]. As highly unstable species that seek stability, free radicals readily attack cells and tissues in search of additional electrons to pair with their lone electron. As a result, new free radicals are formed, setting off a chain reaction that creates a system of oxidative stress [Aru98]. Over time, these unpaired electrons can induce detrimental cellular and tissue damage, leading to a variety of different complications [Ril94]. However, this accumulation of oxidative stress within the body can easily be mitigated and even prevented through the effects of antioxidants [Aru98]. Quercetin, with its five hydroxyl groups, targets these free radicals, neutralizing them by donating hydrogen ions [PHH99]. Additionally,

the creation of new free radicals is eliminated as the double bonds and ketone groups present in quercetin's chemical structure establish a delocalization of electrons, allowing for the loss of charge to be evenly distributed throughout the molecule [WSRE04]. As a result, oxidative stress is unable to amass within the body, lowering the risk of free radical-induced maladies.

2.2 Anti-inflammatory Activity

Quercetin's anti-inflammatory strength can be attributed to a combination of the flavonoid's free radical scavenging abilities and inhibitory capacities. Inflammation within the body is a necessary defense mechanism against harmful stimuli, including pathogens, toxins, damaged cells, and irradiation. However, inflammation that continues over an extended period of time can become detrimental. Paradoxically, prolonged inflammation can lead to severe cell and tissue damage, ultimately aiding in the development of various maladies [AUID$^+$07] [MKMH15]. However, such states of inflammation can be combated through the use of anti-inflammatory agents such as quercetin. As free radicals play a significant role in the induction of damage to cells and tissues through oxidative stress, quercetin's free radical scavenging ability can play a tremendous role in the flavonoid's anti-inflammatory prowess [LBS$^+$18]. Additionally, quercetin possesses the ability to inhibit several inflammatory enzymes and mediators, as well as block inflammatory receptor sites, furthering its anti-inflammatory strength [GBS$^+$15] [Chi10]. In order for inflammation to form, a series of events must occur. To begin, upon detection of harmful stimuli, immune cell receptors will initiate intracellular signaling pathways in attempts to activate transcription factors such as nuclear factor-kappa B (NF-κB) [LZJS17]. These transcription factors enter the nucleus of immune cells and bind to specific DNA sequences, creating pro-inflammatory genes encoding specific enzymes, including cyclooxygenases (COX) and lipoxygenases (LOX). Upon synthesis, these enzymes are released from the immune cell and produce inflammatory mediators, including prostaglandins and leukotrienes [BBW80]. These inflammatory mediators are responsible for recruiting new immune cells. By binding to surrounding immune cells, the mediators can restart the process, making the production of inflammation cyclic [AAA$^+$18]. However, quercetin can inhibit the signaling pathway of this cycle through two main methods: the downregulation of a specific gene's expression and the direct binding to receptor sites. By directly binding to transcription factors such as nuclear factor- kappa B (NF-κB), quercetin can downregulate pro-inflammatory gene expression and minimize enzyme levels in inflamed tissues, decreasing the immune cell count and the overall inflammation in a given area [VHS$^+$11]. Furthermore, by binding directly to specific receptor sites, quercetin can completely block certain events from occurring, including the binding of inflammatory mediators to immune cell receptors, which is the step responsible for restarting the process of inflammation generation [KG99]. It is through these activities that quercetin acts as an anti-inflammatory agent.

2.3 Metal Ion Chelating Activity

Quercetin exhibits a strong metal ion chelating ability due to its unique chemical structure. Metal ions, such as potassium and iron, have shown dietary benefits in trace amounts and are essential for human life. However, an oversupply of these metallic ions and notably even trace amounts of heavy metal ions, such as lead and mercury, can be highly toxic and, in some cases, lethal [KYSO07]. Similar to free radicals, these metallic ions are highly unstable and can catalyze the creation of reactive oxygen species (ROS), generating a system of oxidative stress [Sta90]. To combat the detrimental effects of these metallic ions, metal ion chelators such as quercetin can be employed. Quercetin possesses the ability to act as a ligand and form coordinate covalent bonds with metal ions, creating quercetin-metal complexes [RRD14]. By donating hydrogen ions from hydroxide groups, quercetin is able to neutralize the charge of the metal ion (Fig. 2). Multiple quercetin molecules often contribute to this effort, sequestering the metal ion within the complex, which protects it from the redox reactions that generate reactive oxygen species (ROS) (Fig. 2). Through these chelating mechanisms, quercetin is able to stop the detrimental effects of metal ions.

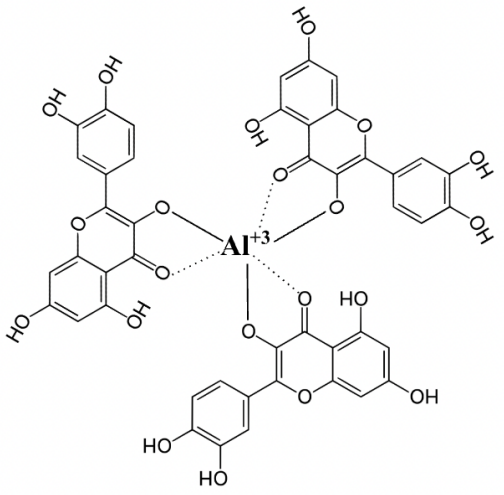

Figure 2: Quercetin-Aluminum Ion Chelation. Three quercetin molecules create a coordination complex with the aluminum ion, which has a charge of +3.

2.4 Other Neuroprotective Activities

In addition to quercetin's antioxidative, anti-inflammatory, and metal ion chelating abilities, the flavonoid possesses a few other neuroprotective properties that make it fit to combat neurodegenerative disorders. For one, quercetin acts as a mitochondrial protective agent, protecting cellular mitochondria from damage.

As mitochondria are the energy-producing organelles in cells, including neurons, mitochondrial dysfunction can be detrimental to neuronal health [FBS+07]. By aiding in the maintenance of mitochondrial membrane potentials through the encouragement of mitochondrial biogenesis-inducing genes, including peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α), in addition to discouraging the buildup of oxidative stress and damage, quercetin can drastically reduce neuronal apoptosis rates, showcasing its neuroprotective prowess [XWG+16]. Another way quercetin can promote neuronal health is by enhancing autophagy, which prevents the buildup of neurotoxic proteins and other harmful cellular components [WLL+11]. The amassing of misfolded proteins within the brain often characterizes neurodegenerative disorders, and by binding to and modulating specific proteins such as AMP-activated protein kinase (AMPK) and Beclin-1, quercetin can stimulate autophagy within neurons, further promoting their health [WLL+11] [KAAS16]. Ultimately, a combination of all of quercetin's neuroprotective properties aids the flavonoid in combating neurodegenerative disorders.

2.5 Bioavailability Struggles

Despite the multitude of pharmaceutically beneficial properties quercetin possesses, the flavonoid has struggled to make a significant impact in the realm of pharmaceutics and dietary supplements for three main reasons: low aqueous solubility, chemical instability, and poor absorption profile [CFD+13]. Quercetin is a hydrophobic compound sparingly soluble in aqueous environments, including the human body. As doses are most frequently administered orally, quercetin is unable to be dissolved, often aggregating to form crystals too large to pass through the intestinal epithelium and be absorbed into the bloodstream. However, even reaching the intestinal epithelium would be a feat for quercetin, as the flavonoid also struggles to cross through the acidic environment of the gastrointestinal tract. Due to the surplus of hydrogen ions that attack quercetin's hydroxyl groups en route to absorption, the flavonoid structurally degrades, further reducing its bioavailability [KTMC22]. Finally, quercetin is transported to the liver upon absorption, where it often undergoes rapid metabolism and further breakdown, preparing it for bodily excretion rather than circulation [HZL+20]. In attempts to ameliorate quercetin's struggles, modern research has turned to drug delivery encapsulation systems, investigating their potential use in improving quercetin's bioavailability without compromising therapeutic potential.

3 Drug Carriers for the Delivery of Quercetin

Modern drug delivery applications encompass a wide variety of methodologies, but in regard to quercetin, research has focused on oral delivery through the use of nanoparticles and nanoformulations. As quercetin's primary struggles are aqueous insolubility and a lack of chemical stability, research has aimed to find carriers that remedy these issues while simultaneously preserving and

enhancing the flavonoid's health benefits [KTMC22]. The most successful delivery systems concerning these efforts include polymer-based, lipid-based, and metallic nanoparticles [VM19].

3.1 Polymer-based Nanoparticles

3.1.1 PLGA & PLA

Polymer-based nanoparticles are among the most widely researched and implemented nanoparticle variations in drug delivery due to the chemical and structural manipulability of polymers in addition to their cell targeting abilities [IZS$^+$20]. The most popular polymers used in nanomedicine, including the delivery of quercetin, are polylactic acid (PLA) and poly(lactic-co-glycolic acid) (PLGA) due to their extreme versatility as drug carriers. Both derivatives of lactic acid, PLA and PLGA share a copious number of properties and abilities, such as their biodegradable and biocompatible natures [LS13]. Notably, PLGA, a copolymer composed of both lactyl and glycolyl groups, can be engineered to improve the polymer's solubility by increasing the ratio of glycolyl to lactyl groups [PWD$^+$04]. However, while PLA and PLGA can differ in solubility profiles, both polymers offer quercetin protection from chemical degradation within the body [LS13]. As the polymers completely encapsulate quercetin as a nanoparticle, the acidic environment of the gastrointestinal tract and other reactive species are no longer a problem for the flavonoid [PQF$^+$12]. Resultantly, the bioavailability of quercetin can be improved. Pool *et al.* used quercetin-encapsulated PLGA nanoparticles, approximately 400 nm in diameter, prepared by solvent displacement to illustrate improvements in quercetin's antioxidative properties when loaded in PLGA compared to its free counterpart. PLGA-quercetin nanoparticles were found to have greater inhibition of nitroblue tetrazolium (NBT) reduction *in vitro* (Fig. 3), which could potentially translate to higher levels of quercetin bioavailability *in vivo* [PQF$^+$12]. In that same study, quercetin-loaded PLGA molecules also showed tremendous improvements in Fe^{2+} ion-chelating activity, albeit taking more time to reach such effects (Fig. 4). While free quercetin's chelating activity diminished quickly after administration, PLGA-quercetin nanoparticle's chelating activity exhibited a gradual increase in intensity over a 32 hour period (Fig. 4), indicative of the controlled release potential of quercetin loaded PLGA nanoparticles [PQF$^+$12]. Similarly, Di Cristo *et al.* used PLA-quercetin nanofibers fabricated through electrospinning in order to depict the controlled release properties that PLA can offer in the delivery of quercetin. PLA-quercetin nanoparticles were found to exhibit free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity up to 48 hours after *in vitro* administration of the drug [DCVDL$^+$22]. Overall, PLA and PLGA nanoparticles have shown tremendous clinical efficacy in their delivery of quercetin.

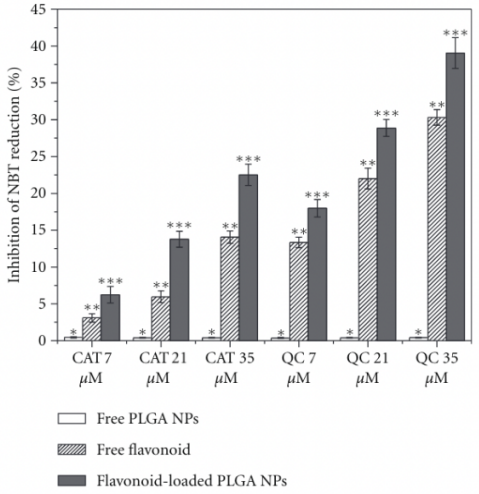

Figure 3: Percentage inhibition of nitroblue tetrazolium (NBT) reduction of free catechin (CAT), free quercetin (QC), catechin-loaded PLGA nanoparticles, and quercetin-loaded PLGA nanoparticles. Measurements taken at three different concentrations: 7 μM, 21 μM, and 35 μM. Free PLGA nanoparticles were used as control [PQF$^+$12].

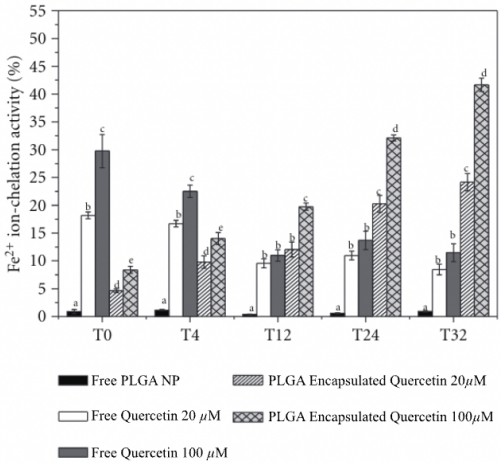

Figure 4: Fe^{2+} ion chelating activity of free quercetin and PLGA encapsulated quercetin at 20 μM and 100 μM. Free PLGA nanoparticles were used as a control. Chelating activity was measured after 0.25 hours, 4 hours, 12 hours, 24 hours, and 32 hours [PQF$^+$12].

3.1.2 Chitosans & Polyethylene Glycols (PEGs)

In addition to PLA and PLGA, a variety of polymer-based nanoparticle delivery systems have shown potential for quercetin delivery, including chitosan nanoparticles and polyethylene glycol conjugations (PEGs) [WSM+16]. Chitosans are natural polysaccharides that share many of the same properties that PLA and PLGA exhibit, such as drug protective and bioavailability enhancing abilities, making the polymer a strong candidate for drug delivery applications [DJ18]. Additionally, due to their chemical structure, chitosans are entirely hydrophilic, resulting in high aqueous solubility through hydrogen bonding from its hydroxyl and amine groups. However, what sets chitosans apart from other polymers as a drug delivery system is its mucoadhesive properties, which can tremendously boost quercetin's bioavailability [SWK08]. As a result of the amine groups' lone electron pair, chitosans possess a positive charge, awarding the polymer an affinity for negatively charged mucosal surfaces (e.g., the lining of the gastrointestinal tract). Through electrostatic attractions, the chitosan nanoparticle becomes tightly bound to the intestinal epithelium, allowing for effective quercetin absorption into the bloodstream, thus increasing the flavonoid's bioavailability [SWK08]. Baksi *et al.* demonstrated this increase, measuring significantly lower IC50 levels in A549 and MDA MB 468 tumor cell lines for quercetin-chitosan nanoparticles, which were prepared by ionic gelation, compared to free quercetin [BSB+18]. Additionally, quercetin-loaded chitosan nanoparticles showed more significant reductions in tumor volume and weight *in vivo* [BSB+18]. In another study, Mukhopadhyay *et al.* showed tremendous drops in blood glucose levels in HT29 cell lines *in vitro* using quercetin-succinylated chitosan-alginate core-shell-corona nanoparticles [MMM+18]. While various particle size groups were tested, the smallest group, approximately 91.58 nanometers in size, was found to be most efficient for quercetin's oral delivery [MMM+18]. On the other hand, polyethylene glycols (PEGs), while sharing many of the same chemical properties as the other polymers, play a unique role in drug delivery applications. PEGs, like chitosans, are hydrophilic polymers that have high water solubility and biocompatibility, making them excellent candidates for drug delivery applications. However, PEGs are non-biodegradable polymers, limiting their use alone as a drug carrier. To remedy this issue, researchers have begun to use novel PEG conjugations where PEG is used in concert with other nanoparticles to improve the polymer's biodegradability while being able to harness PEG's unique chemical properties for drug delivery applications. By attaching PEG chains to the surface of other nanoparticles in a process titled PEGylation, the polymer is further able to protect and stabilize the delivery system, creating a stealth effect for the nanoparticle [LJS+21]. These long PEG chains sterically hinder the nanoparticle due to their large yet flexible nature, physically obstructing anything from binding to the carrier's surface. Likewise, Li *et al.* found that longer attached PEG chains correlate to fewer interactions between the nanocarrier and other cells within the body [LJS+21]. Additionally, due to their hydrophilic nature, these PEG chains create a film-like layer of water that encapsulates the car-

rier, protecting it from protein adsorption and phagocytosis, which ultimately increases the duration of quercetin's bioavailability. Qureshi *et al.* used PEGylated PLGA-quercetin nanoparticles, which were prepared through double emulsion encapsulation, to show cell viability inhibition of cell line MDA-MB-231 *in vitro* [QZW+16]. Additionally, *in vitro* tumor targeting and growth inhibition were shown with tremendous success when doxorubicin was co-delivered with quercetin, illustrating the nanoparticle's potential in targeted drug delivery [QZW+16]. Ultimately, despite their lack of biodegradability, PEGs have shown tremendous promise in the field of targeted and controlled-release drug delivery.

3.2 Lipid-based Nanoparticles

Lipid-based nanoparticles are another widely researched type of nanoparticle for quercetin delivery due to their biocompatibility and versatility as a drug carrier, among the most popular, including liposomes and micelles. These lipid-based nanoparticles structurally differ, exhibiting unique chemical properties resulting in various potentials in drug delivery applications. Liposomes are a variation of lipid-based nanoparticles consisting of a lipid bilayer, that is, two layers of lipid molecules [ARSD+13]. As lipid molecules are amphiphilic, their heads hydrophilic and tails hydrophobic, the outer layer contains lipid molecules with their heads facing outwards, creating a hydrophilic surface for increased nanoparticle dispersion in water, while the inner layer contains inward-facing lipid molecules, creating an aqueous core for encapsulating hydrophilic substances (Fig. 5). Additionally, due to the hydrophilic nature of the lipid molecules' tails, an additional hydrophobic section is created between the two layers for the potential encapsulation of hydrophobic substances (Fig. 5) [ARSD+13]. Due to this unique bilayer structure, liposomes are able to increase the solubility and stability of quercetin. Additionally, the lipid bilayer also awards liposomes high encapsulation efficiency, which can lead to better controlled and sustained release of quercetin over a long period of time [AABM+19]. Patel *et al.* used liposome-quercetin nanoparticles prepared by thin-film hydration to illustrate this potential for sustained release [PTK+20]. While these liposomal quercetin nanoparticles showed significant improvements in breast cancer tumor reduction potentials compared to their free counterpart, they, more importantly, exhibited this behavior consistently over a 30-day period *in vitro* despite only three administrations of the drug throughout the duration [PTK+20]. Priprem *et al.* used a similar method of encapsulation to create liposome-quercetin nanoparticles and experimented with their cognitive-enhancing properties *in vivo* [PWS+08]. Researchers administered these liposomal nanoparticles to rats and had them traverse through a water maze, training them to memorize the location of hidden platforms within the labyrinth repeatedly over a 28-day period. By measuring the time it took the rats to find the platform during each trial, researchers were able to gather data on the cognitive enhancing abilities of quercetin. The rats who had been orally administered quercetin-loaded liposomes exhibited similar acquisition times to other groups, but curiously enough, those who had been ad-

ministered the drug intranasally saw tremendous improvements in their platform acquisition time [PWS+08]. This could potentially be indicative of a blood-brain barrier crossing struggle that the oral administration of liposomes faces, which intranasal delivery can remedy. In addition to liposomes, micelles are another lipid-based nanoparticle that has been heavily researched for quercetin delivery. Micelles are amphiphilic molecules that structurally contain only one layer of lipids. These lipid molecules face outwards, creating a hydrophilic surface like that of liposomes but a hydrophobic core more favorable for quercetin delivery (Fig. 5) [Men79]. Even so, micelles struggle *in vivo* compared to liposomes due to their thinner outer shell, which leads to decreased drug protective properties and stability as a nanoparticle. As such, micelles are sensitive to stimuli, spontaneously dissociating when faced with rapid temperature and pH changes, contributing to their unpredictable drug-release properties [WCZZ09] [GLL13]. However, micelles have shown promise in quercetin delivery when coupled with polyethylene glycols (PEGs) through PEGylations. Lv *et al.* employed thin-film hydration to create PEGylated quercetin-loaded micelles in rats and found that the blood plasma quercetin concentrations of those who had been administered the PEGylated micelle conjugation were significantly greater. Even more notable was that the PEGylated micelle rats also maintained quercetin within their bloodstream for almost 50 hours, quadrupling the duration of those administered free quercetin [LLL+17]. Using a similar formulation technique, Qi *et al.* created and used PEGylated quercetin-loaded micelles and found significant H22 cell line tumor growth inhibition as well as reduction potentials for existing tumors *in vivo* [QGY+22]. These effects lasted up to 15 days after treatment, also illustrating the controlled release potential of PEGylated micelles in quercetin delivery [QGY+22]. Though often outclassed by polymeric nanoparticles in quercetin delivery applications, lipid-based nanoparticles certainly have their place within the field.

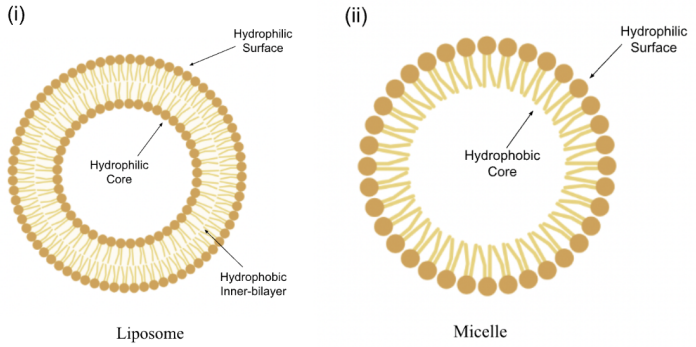

Figure 5: (i) Diagram of a Liposome. Lipid bilayer creates a hydrophilic surface and core in addition to a hydrophobic inner-bilayer area. (ii) Diagram of a Micelle. Lipid monolayer creates a hydrophilic surface and a hydrophobic core.

3.3 Metallic Nanoparticles

Metallic nanoparticles are another form of drug carriers that have been researched for their potential in quercetin delivery. While most metals, particularly heavier transition metals, such as lead and mercury, have exhibited non-biodegradable and cytotoxic properties within the body [KYSO07], certain metals, such as iron and silver, have proven to be more biocompatible, making them viable candidates for drug delivery [BMTC22] [JRM$^+$08]. In addition to increasing the solubility of quercetin through encapsulation, these biocompatible metallic nanoparticles have also exhibited protective effects, increasing the flavonoid's stability [KMZM03]. Unfortunately, due to the high reactivity of metals within the body, these metallic nanoparticles are susceptible to breakdown due to temperature and pH variations [LCK16]. However, this reactivity can work in favor of metallic nanoparticles as the property makes them easy to manipulate and engineer chemically. Most notably, functional groups and other biomolecules, such as antibodies and peptides, can be attached to the nanoparticle's surface for targeted delivery to specific cells and molecules. Additionally, other molecules such as polymers, surfactants, and ligands can be incorporated into the surface of metallic nanoparticles, partially remedying their extreme reactivity and enhancing the overall stability of the nanoparticle [ZLA$^+$11]. Najafabadi *et al.* used a novel iron drug carrier system, quercetin conjugated iron oxide nanoparticles (QT-SPION), for the delivery of quercetin *in vivo* and, using high-performance liquid chromatography (HPLC), which showed tremendous increases in quercetin concentrations within the brain tissue of rats [NKE$^+$18]. Additionally, negligible effects of iron concentrations within the brain and blood plasma were shown. Ultimately, through the use of the quercetin-iron oxide nanoparticle, the crossing of the blood-brain barrier was improved, which was shown by increased quercetin concentrations in the brain [NKE$^+$18]. Metallic nanoparticles have their benefits and downfalls in quercetin delivery, but they have certainly shown promise in targeting neurodegenerative disorders.

4 Applications of Quercetin Delivery for the Treatment of Neurodegenerative Disorders

Neurodegenerative disorders are a class of disorders characterized by neuronal degeneration within the central or peripheral nervous system [ENM$^+$11]. The likelihood of neurodegenerative disease development dramatically increases with respect to age [BK01], and the most common diseases (e.g., Alzheimer's Disease and Parkinson's Disease) plague millions of people across the world [N/A16]. Though modern research has focused on developing treatments for neurodegenerative disorders, there are no cures that currently exist [VLA$^+$18]. However, bioactive flavonoids, such as quercetin, have been found successful in slowing the progression of these disorders within the body. As free radicals and oxidative stress are a large factor of neurodegeneration, quercetin's free radical scavenging and antioxidative properties aid the flavonoid in combating neurodegener-

ative disorders [AAAH86]. Additionally, quercetin's anti-inflammatory, metal ion chelating, and overall neuroprotective abilities play a role in slowing down neurodegeneration [DJM13]. Finally, variations of quercetin-loaded nanoparticles have demonstrated the ability to cross through the blood-brain barrier by improving the bioavailability of the flavonoid [RMS$^+$20]. Ultimately, it is quercetin's unique repertoire of chemical properties that allows it to combat neurodegenerative disorders, including Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Amyotrophic Lateral Sclerosis (ALS), and Multiple Sclerosis (MS).

4.1 Alzheimer's Disease

Alzheimer's Diseases is a disorder characterized by the degeneration and death of neurons within the brain, often leading to cognitive impairments and memory loss [LHS18]. In addition to free radicals and oxidative stress, the onset of Alzheimer's can be attributed to the accumulation of protein aggregates, including amyloid-β plaques and tau tangles [SS11] [WBM21]. The former, amyloid-β, is a peptide that can clump together with other biomaterials to create deposits that can disrupt neuronal communication, inducing a cytotoxic effect on the cells [SS11]. Tau, on the other hand, is a protein responsible for nutrient transport in neurons. However, when these tau proteins misfold into abnormal shapes, they create neurofibrillary tangles, which can disrupt the transport of essential nutrients within neurons, causing their dysfunction and ultimate death [WBM21]. To remedy these protein aggregates, quercetin's neuroprotective properties can be employed. By binding to and modulating proteins such as AMPK-activated protein kinase, quercetin can activate and enhance autophagy-related pathways, working to clear and prevent the amassing of amyloid-β peptides and tau proteins, which ultimately hinders the progression of Alzheimer's disease [WLL$^+$11]. Additionally, as metal ions, such as copper, zinc, and iron, have been found to contribute to the formation of amyloid-β plaques and tau tangles, quercetin's metal ion chelating ability can also be useful in preventing these formations [ADB$^+$89]. Sun *et al.* showed significant and consistent amyloid-β_{42} aggregation inhibition over the course of 60 hours *in vitro* using PLGA-quercetin nanoparticles prepared through double emulsion-solvent evaporation. In that same study, an MTT assay showed that the PLGA-quercetin nanoparticles had an inhibitory effect on amyloid-β_{42}-induced cytotoxicity, which was most significant from concentrations 5-40μg/mL [SLZ$^+$16]. Pinheiro *et al.* used quercetin-loaded solid lipid nanoparticles to show a similar inhibitory effect of the aggregation of amyloid-β(1-42) even just 24 hours after administration *in vitro* [PGL$^+$20]. Though little quercetin drug delivery research has been done *in vivo*, it certainly has potential, and considering that the drug delivery of quercetin for therapeutic purposes is a relatively new concept, its use for the treatment of Alzheimer's is extremely promising.

4.2 Parkinson's Disease

Parkinson's Disease is a disorder characterized by a neurological undersupply of dopamine, most often due to the degeneration of dopamine-producing neurons located in the brain's substantia nigra [DP03]. As dopamine is responsible for facilitating smooth and coordinated motor movements, an undersupply of the neurotransmitter can cause difficulties in executing simple motor movements, leading to bradykinesia, involuntary tremors, muscle rigidity, and a variety of other symptoms [DP03]. While free radical-induced oxidative stress can play a role in dopamine-producing neuronal death, the aggregation of misfolded protein α-Synuclein within the brain can also be a monumental factor in the pathogenesis of Parkinson's Disease [BWU12]. By enhancing the autophagy of misfolded α-Synuclein proteins and aiding in the maintenance of mitochondrial membrane potentials, quercetin can prevent the death of dopamine-producing neurons and mitigate the onset of Parkinson's. Wang *et al.* administered quercetin *in vitro* in 6-hydroxydopamine-treated PC12 cells and showed increased levels of dysfunctional mitochondria and α-Synuclein autophagy [WHH$^+$21]. In that same study, *in vivo* oral administrations of quercetin over 14 days to 6-hydroxydopamine-lesioned parkinsonian rats showed inhibitory effects of reactive oxygen species (ROS) levels and free radical generator malondialdehyde (MDA) levels in addition to improvements in ROS metabolizer superoxide dismutase (SOD) levels (Fig. 6), exhibiting promise for Parkinson's treatment [WHH$^+$21]. Karuppagounder *et al.* orally administered quercetin to rotenone-induced hemi-parkinsonian rats over a period of 4 days and found significant and consistent increases in dopamine levels within the brain [KMP$^+$13]. However, though free quercetin showed promise in rat models of Parkinson's Disease, the flavonoid's effectiveness would likely not be as pronounced in human administrations, resulting in large excess doses of quercetin having to be administered in order to attain the desired effect. Through the use of drug delivery, quercetin's properties can be more efficiently harnessed, enhancing the treatment potential of Parkinson's Disease.

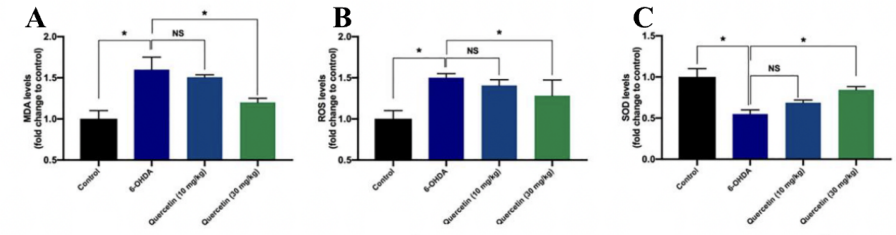

Figure 6: Effects of quercetin administrations at concentrations 10 and 30 mg/kg on 6-hydroxydopamine-lesioned parkinsonian rats. (A) Malondialdehyde (MDA) levels. (B) Reactive oxygen species (ROS) levels. (C) Superoxide dismutase (SOD) levels [WHH$^+$21].

4.3 Huntington's Disease

Huntington's Disease is a disorder characterized by the degeneration of nerve cells in a part of the brain known as the basal ganglia, leading to a decline of motor control and cognitive ability [ABF+00]. Symptomatically, Huntington's Disease shares similarities with Parkinson's Disease as they both hinder smooth, coordinated movements, but while Parkinson's is associated with the undersupply of dopamine, the pathogenesis of Huntington's has been found to be genetic. Huntington's Disease is caused by a mutation in the HTT gene, which is responsible for encoding the huntingtin protein [PRY+19]. The resultant protein is significantly longer as a result of the mutations, proning the protein to misfolding and aggregation. Encouraging the buildup of oxidative stress and mitochondrial dysfunction, the accumulation of mutated huntingtin proteins can become cytotoxic to neurons [PRY+19]. However, quercetin has shown potential in combating Huntington's Disease. By enhancing mutated huntingtin protein autophagy and anti-inflammatory activity within the brain, quercetin can slow the onset of Huntington's. Additionally, the flavonoid can encourage the biogenesis of mitochondria, helping to mitigate previously inflicted neuronal damage [DMCD09]. Sandhir *et al.* orally administered quercetin to 3-nitropropionic acid-induced models of Huntington's diseased rats over the course of 21 days and tested their motor movement and control by measuring their performance on a balance beam test. Researchers found that quercetin administration overtime led to improved motor movement control and balance, as measured by faster balance beam completion times as well as fewer paw slips during the test [SM13]. Chakraborty *et al.* found that oral quercetin administration over four days showed similar increases in motor movements in 3-nitropropionic acid-induced rat models of Huntington's, which was measured by increases in stride as well as higher rates of success in completing an obstacle course compared to their untreated counterparts [CSD+13]. Still, quercetin administration for the treatment of Huntington's can be improved. Though both studies showed improvements in Huntington's symptoms as a result of quercetin administration, the rate of administration was high—every day for 21 days for the former study, while twice a day for four days for the latter. By employing drug delivery systems, the amount of administrations could be reduced for similar or even greater results in the realm of Huntington's treatment.

4.4 Amyotrophic Lateral Sclerosis & Multiple Sclerosis

In addition to Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease, quercetin has been researched for its potential in treating other neurodegenerative disorders, including Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS). ALS, also known as Lou Gehrig's Disease, is characterized by the degeneration of motor neurons throughout both the central and peripheral nervous systems, which can lead to muscle atrophy and overall bodily weakness [HACC+17]. The pathogenesis of ALS roots from a various factors: oxidative stress, neuroinflammation, mitochondrial dysfunction, metal ion ac-

cumulation due to excitotoxicity, and even gene mutations that can lead to misfolded protein aggregations [TRM$^+$15] [TSA18]. On the other hand, MS is characterized by the degeneration of the neuronal myelin sheath, which is responsible for protecting electrical impulses during transmission within the central nervous system and, as a result of slowed transmission, can lead to difficulties in simple movements and coordination [LH11]. The pathogenesis of MS is primarily autoimmune, degeneration mistakenly inflicted by the immune system, but oxidative stress and neuroinflammation can play a role in furthering the progression of the disorder [FBDB$^+$09]. In attempts to treat ALS and MS, quercetin has been employed for its free-radical scavenging, anti-inflammatory, metal ion chelating, and neuroprotective properties. Bhatia *et al.* administered quercetin *in vitro* and measured significant inhibitory effects of SOD1 fibril aggregations with increasing concentrations of quercetin over a 30-hour period. Inhibitory effects were measured visually using TEM imagery and numerically by ThT Fluoresence [BMSD20]. As SOD1 fibril aggregation can be a genetic factor in the pathogenesis of ALS, the shown inhibitory effects can be useful in treating the disorder. Hendriks *et al.* administered quercetin *in vitro* to isolated myelin taken from the brain tissue of adult mice and let RAW 264.7 cells phagocytose the myelin for 90 minutes before adding dihydrorhodamine 123 (DHR). As DHR can be used for the detection of reactive oxygen species (ROS) formation, researchers were able to measure that the myelin treated with quercetin showed significant reductions in reactive oxygen species production during myelin phagocytosis compared to their untreated counterparts [HDVVDP$^+$03]. However, while there have been *in vitro* studies for quercetin-based treatments of ALS and MS, few *in vivo* studies have been executed potentially due to bioavailability struggles and underwhelming results. While quercetin's potential for ALS and MS treatment is evident, the use of drug delivery systems could enhance quercetin's bioavailability and potential for ALS and MS treatments *in vivo*.

5 Discussion

Quercetin, a dietary flavonoid, has been heavily researched for its potential in the treatment of neurodegenerative disorders due to its antioxidative, anti-inflammatory, metal-ion chelating, and neuroprotective properties. However, quercetin struggles in bioavailability due to the flavonoid's lack of aqueous solubility, poor chemical stability, and an unfavorable absorption profile. As a result, free quercetin struggles to pass through the blood-brain barrier and reach neurons and other biomolecules, preventing the flavonoid from having any effect on the progression of neurodegenerative disorders. However, the rise of targeted and controlled-release drug delivery applications provides a remedy for the struggles quercetin faces. Through the use of polymer-based nanoparticles, lipid-based nanoparticles, and metallic nanoparticles, among other drug delivery systems, the bioavailability struggles of quercetin are resolved, allowing the flavonoid to reach and have an impact on neuronal degradation within

the nervous system. Additionally, the targeting properties of drug carriers, in concert with their controlled release manipulability, further enhance quercetin's abilities, ultimately allowing for more efficient treatments of neurodegenerative disorders.

The two most significant benefits that quercetin gains from drug delivery encapsulations are improved bioavailability and controlled release properties. Modern research has focused primarily on polymer-based nanoparticles, including PLA and PLGA nanoparticles, as well as chitosans for quercetin's neurodegenerative applications. However, while polymer-based nanoparticles, particularly PLA and PLGA, can be easily engineered chemically by attaching ligands and other biomolecules for targeted release quercetin delivery, their hydrophobicity leads to challenges with surface interactions in aqueous environments, resulting in difficulties getting the nanoparticle to release the drug at the desired rate. While notably, PLGA can be engineered specifically to increase the nanoparticle's hydrophilicity by increasing the ratio of glycolyl groups to lactyl groups, the polymeric nanoparticle still falls short of the level of surface interactions that lipid-based nanoparticles possess. On the other hand, liposomes and micelles, which only began to rise in popularity recently after they were implemented in the creation of COVID-19 vaccinations, have shown more promise in quercetin delivery for the treatment of neurodegenerative disorders. Despite prior research being much more limited compared to polymer-based nanoparticles, lipid-based nanoparticles are the better candidate due to their hydrophilic surfaces in addition to their surface engineerability through the attachment of biomolecules for targeting applications. Though they struggle to solve quercetin's chemical instability, the problem can easily be remedied by implementing PEGylations, which, in turn, can also further enhance the nanoparticle's bioavailability and controlled release applications. Furthermore, the use of PEGylations can also improve the likelihood of lipid-based nanoparticles crossing the blood-brain barrier—an essential step in facilitating quercetin's interactions with neurons and other biomolecules. Ultimately, future research should investigate the use of PEGylated nanoparticles, particularly for micelles and liposomes, to deliver quercetin. Additionally, while the drug delivery of quercetin for the treatment of neurodegenerative disorders is still a relatively new concept with a very limited research base, especially *in vivo*, the topic has shown tremendous potential and will certainly become an emerging field in the coming years.

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