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Quercetin Therapeutic Potential for Neurodegenerative Diseases and its Nano-Technological Perspectives

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Research Article

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ABSTRACT

Quercetin (Que) and its derivatives are naturally occurring phytochemicals with promising bioactive effects. The anti-diabetic, anti-inflammatory, anti-oxidant, anti-microbial, anti-Alzheimer's, anti-arthritic, cardiovascular, and wound healing effects of Que have been extensively investigated, as well as its anticancer activity against different cancer cell lines has been recently reported. Que and its derivatives are found predominantly in the Western diet, and people might benefit from their protective effect just by taking them *via* diets or as a food supplement. Bioavailability related drug delivery systems of Que have also been markedly exploited, and Que nanoparticles appear as a promising platform to enhance their bioavailability. Nanotechnology also improves drug bioavailability, targeted drug release, and penetrating *via* blood brain barrier.

Keywords: Quercetin; Anti-microbial; Anti-inflammatory; Cardiovascular; Nanoparticles

INTRODUCTION

Neurodegenerative Disorders (NDs) have become a major public health concern in the twenty first century and now there is no helpful treatment for these types of disorders. These disorders are caused by functional or structural abnormalities of the neurons or nervous system. These types of long-term developing damages may cause impairments in thoughts, movement of the body, and recall capacity. Various neurological disorders like Parkinson's Disease (PD), Alzheimer's Disease (AD), Huntington's Disease (HD); and Amyotrophic Lateral Sclerosis (ALS) are the frequent NDs seen in the aged people. Hereditary predisposition, age, everyday life, eating habits, chemicals, certain viruses, and some environmental toxins exposure are believed to be principal endanger factors of NDs. The frequency of NDs related to age is rapidly increasing nowadays. Various stimulating Nuclear factor erythroid-2 (Nrf2) in the antioxidant system, fork head transcription and neurotrophic factors, and also inhibitory activity of sirtuins as well as the Acetylcholinesterase (AChE) have an impact on neurodegenerative diseases.

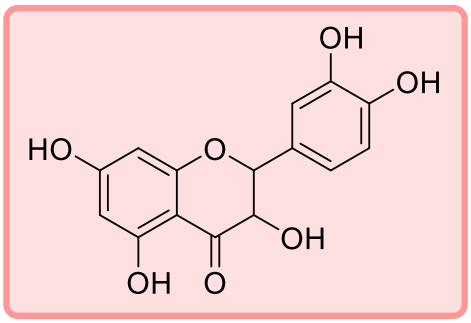
Quercetin QC has been reported to control NF-κB which could involve in improvement of inflammatory mechanism involved in NDs According to global death report in 2019, report for most 10 causes of death, all neurological dementia like Parkinson's Disease (PD), Alzheimer's Disease (AD), etc. were classified as the seventh highest cause of mortality in the World Health Organization (WHO) report on 10 causes of worldwide death in 2019. At present medication for NDs have significant complicacy, thus there is a need to look for new strategies with reduced side effects yet It has been observed through previous studies that natural products appear promising in this regard as regular intake of phytochemicals improves psychological and substantial performance, boosts the antioxidant system, and in turn increasing neuronal cell survival [1]. Antioxidant and anti-inflammatory properties of various phytochemicals have the prospective to treat neurodegenerative disorders. Bioactive polyphenols present in herbal drugs have a vital in the improvement of neurodegenerative disorders caused by oxidative stress. Although phytochemicals perforation through the BBB is the most stumbling block to their transportation to the brain. For this approach, pharmaceutical nanotechnology offers better drug releasing systems for the treatment of NDs by improving and controlling diagnosis at root cause level. Formulations of these natural bioactive polyphenols developed through nanotechnology offer excellent strategies to conquer these issues and improve their bioavailability. Quercetin is a predominant poyphenolic flavonoid typically found in edible plants. Flavonoids are the most dissimilar set of phytochemicals with excellent therapeutic potential. Flavonoids are classified into 6 classes according to their diversity in structure. Flavones, flavanones, flavanols, flavanols, isoflavanoids, and anthocyanidins are various categories of flavonoid. Quercetin (QUE) is a nutritional flavonoid that possesses significant antioxidant potential as compared to other flavonoids and helps to treat or inhibit the progress of neurodegenerative disorders. Quercetin was observed to have protective effects against NDs at the concentration range of 10 μM to 30 μM. Quercetin can penetrate BBB and prevent cytotoxicity induced by H_2O_2. Furthermore, quercetin has been shown that protective effect on NDs is through controlling the oxidative amount of the cells or connections with proteins in brain cell existence pathways. It has been observed that elevated levels of neurotransmitters especially acetylcholine led to the evolution of AD and can be considered as a symbol for the evolution of the disease. Quercetin treatment reduced AChE activity which is responsible for the Aggregation of β-amyloid peptide (Aβ) which is considered a key hallmark of AD. Although having advantageous effects, poor solubility, faster degradation and low brain permeability has limited its clinical use. The drawback of faster degradation in the bloodstream can overcome by use of higher doses with long period management which may have adverse effects. Efforts have been taken for the development of novel nanoformulations such as nanosuspensions, nanocapsules, and microsphere to overcome these restrictions. Nanotechnology also improves drug bioavailability, targeted drug release, and penetrating *via* blood-brain barrier [2].

LITERATURE REVIEW

Chemistry and sources

Quercetin QC is related to the polyphenolic flavanoids family present in various edible plant life like fruits, tea, onions, strawberries etc. Quercetin was first isolated in 1936 by Albert Szent Gyorgi. Quercetin has a chemical structure with formula $C_{15}H_{10}O_7$, an IUPAC name is 3,3',4',5,7-pentahydroxy-2-phenylchromen-4-one and a molecular weight of 302.24 g/mol, described in Figure 1.

Figure 1. The chemical structure of Quercetin.



The availability of hydroxyl group at 3rd, 5th and 7th position in ring A are responsible for making hydrogen bonds as well as its antioxidant property. The OH group on quercetin's third carbon has long been thought to be a high prospective site for acceptance of electrons and responsible for its antioxidant property. On ring B, the catechol portion and double bound between the 2nd and 3rd position with an oxo of the carbonyl group in the ring C contribute to the biological properties of quercetin. Various derivatives of quercetin having substituted 3rd, 5th and 7th position also possess antioxidant activity. The synthesized derivatives have more scavenging ability as compared to free quercetin. They proposed that radical scavenging activity is more in Chloro-naphthoquinoneq (CHNQ) than monochloro pivaloyl Q (CPQ) which is greater than Di-Tetra-Acetylquinoylq (DTAQ) and Acetyl Diacetylcaffeoyl Q (ADCQ). However, it has been observed that O-substitution of hydroxyl groups reduced the scavenging activity of the compounds and both these groups are considered powerful scavengers for free radicals in quercetin. Furthermore, the low solubility of quercetin is attributed to the hydrophobic nature of phenol rings present in quercetin, which is considered as one of the major limitations related to the structure of quercetin. Quercetin expresses the best solubility in a water-ethanol mixture among the variety of solutions [3]. The small value for bioavailability of quercetin is credited to its low solubility as well as absorption and fast metabolism. So, it is critical to improve its solubility. Quercetin being aglycone shows low solubility, attachment of glycosyl moieties like glucose, rhamnose, etc., at 3-OH leads to the formation of quercetin glycoside improves its solubility in water, so quercetin glycoside shows better solubility in water as compared to free quercetin however absorption capacity may be different depending on the type of sugar molecule attached [4].

Sources of quercetin

Quercetin term was used since 1857, originated from the Latin word quercetum, from quercus that is oak. It is a flavonoid found abundantly in higher plants and its glycosidic forms, such as quercetin-3-O-rutinoside, quercetin-3-O-glucoside, and quercetin-3-O-galactoside. The concentration of Quercetin is high in various foods like apples, onions, shallots, asparagus, tea, tomatoes, red leaf lettuce, capers, and berries. QC can be recovered in a free state from various leaf surfaces, fruits, seeds, and bark (Table 1). Plant families having high quercetin content are Compositae, Rhamnaceae, Passiflorae, and Solanaceae [5].

Table 1. Botanical sources of quercetin.

Part used	Biological source	Common name	Family
Fruits	Punica granatum	Pomegranate	Lythraceae
	Allium cepa	Red onion	Amaryllidaceae
	Mangifera indica	Mango	Anacardiacea
	Solanum lycopersicum	Tomato	Solanaceae
Leaves	Ruta graveolens	Rue	Rutacea
	Camellia sinensi	Green tea	Theaceae
	Moringa oleifera	Drumstick tree	Moringaceae
Seeds	Phaleria macrocarpa	Mahkotadewa	Thymelaceae
Bark	Rhamnus alaternus	Buckthorn Bark	Rhamnaceae

Neuropharmacology of quercetin

Neuropharmacology deals with the study of the effects of drugs on the nervous system. It focuses on the mode of actions and targets of the medicines at molecular and cellular levels for neuropsychiatric disorders as well as of drugs of abuse. Various studies reported that several drugs are used as the tools for better understanding of normal

functioning of the nervous system as well as to implicate those in the plethora of neurological disorders or diseases like ataxia, epilepsy, addiction, dystonia, neuropathic pain, intellectual disability, and Alzheimer's disease to transform this knowledge into discovery and development of novel therapeutics or regimens. Disorders of the nervous system are regarded as the most severe health condition of the modern world due to their inevitable growth and giving socio-economic burden to society. Hence, the aim is to apply all the information of the drugs and their mechanisms to evolve the safer, highly effective, curative, and precautionary measures for abnormalities of the nervous system in the hosts [6].

Drugs such as sedatives, antianxiety, antidepressants, anticonvulsants, antipsychotic agents, and anti-parkinsonian are among those used most widely. Although, these medicines acting on CNS and other commonly prescribed drugs acting on other organ systems may have many side effects and also can alter the clinical utility of various drugs [7].

Moreover, the usage of herbal drugs for the management of neuropsychiatric disorders has been discussed fora long. Due to the presence of bioactive components such as flavonoids, curcumin, lycopene, resveratrol, etc., in numerous compounds have been tested *in vitro* as well as *in vivo* which showed their neuroprotective effects. A unique bioflavonoid, quercetin which is chemically, 3,3′,4′,5,7-pentahydroxyflavone and abundantly found in numerous fruits and leafy foods e.g., elderberries, cranberries, cilantro, junipers, dill, canned capers, onions, apples, etc., that exhibits diverse pharmacological properties including anti-inflammatory, antioxidant, and protective properties against nervous system disorders, including seizure, convulsions, loss of memory, Huntington's disease, parkinson disease, etc (Table 2) [8].

Table 2. Levels of quercetin in various dietary food supplements.

Food source	Quercetin content (mg/100 gm)
Fruits	
West Indian cherry (Acerola)	4.74
Apricots	2.55
Apple with skin	4.42
Raw elderberries	26.77
Arctic bramble berries	9.1
Raw bayberries	4.36
Blue berries	7.67
Bill berries	3.04
Cherries (raw and sweet)	2.29
Black berries	3.58
Raw crowberries	5.45
Raw cranberries	14.84
Dates, degletnoor	0.93
Raw figs	5.47
Raw black diamond plums with peel	12.45
Raw sea buckthorn berry	7.58
Raw rowanberries	7.4
Dried goji berry/wolfberry	13.6
Raw gooseberries	1.23
Black grapes, black	2.08
Ripe juniper berries	46.61
Raw mulberries	2.47
Raw prickly pears	4.86
Vegetables and their products	
Raw sprouted, alfalfa seeds	1.7
Fresh bay leaves	3.19
Raw asparagus	13.98

Raw beans (green)	2.73
Bee pollen	20.95
Raw coriander (cilantro) leaves	52.9
Poppy leaves	26.3
Annual saw thistle leaves	16
Raw broccoli	3.26
Raw drumstick leaves	16.65
Raw fennel leaves	48.8
Raw okra	20.97
Raw mustard greens	8.8
Wild raw rocket	66.19
Raw lettuce, red leaf	7.61
Raw onions	20.3
Raw spinach	3.97
Raw sweet potato leaves	16.94
Herbs and species	
Canned capers	180.77
Fresh dill weed	55.15
Turmeric (steamed)	4.92
Fresh oregano	7.3
Cereal grains	
Buckwheat	15.38
Buckwheat flour	3.47

As per the literature, with the diversity of the symptoms connected with the above disorders of Neurological and psychiatric disorders, the mechanisms for neurodegeneration in the brain are intermingled. Glutamate and NMDA excitotoxicity, oxidative stress, cholinesterase overexpression, neuronal inflammation, mitochondrial dysfunction, protein aggregation, and alteration in metal ion homeostasis are the familiar factors leading to neuropsychiatric disorders. Based on these mechanisms, recognition of various novel drugs or compounds such as quercetin that crosses the Blood Brain Barrier (BBB) may offset the described pathological mechanisms to slow down or prevent the progression or onset of various neurodegenerative disorders respectively. These mechanisms are summarized here for the multitargeted therapeutic approach of quercetin [9].

Quercetin, a target molecule to oxidative stress

Various studies have verified that aging increases free radicals/reactive oxygen species resulting in enhanced oxidative stress that mediates neuronal damage and hence neurodegeneration and vessels related degradation in the brain. Quercetin is a compound that acts as a free radical scavenger and metal chelator directly and efficiently by inhibiting the neuronal damage caused by oxidative stress. It also attenuates oxidative stress indirectly by efficiently inhibiting nitric oxide synthase and xanthine oxidase. It has also been observed that quercetin also helps in counteract the neuronal insult by activating a factor, nuclear factor like 2-Antioxidant Responsive Element (Nrf2-ARE). Its activation facilitates an enzyme expression *i.e.,* g-Glutamyl-Cysteine Synthetase (GCS), which further synthesizes cellular endogenous antioxidant (free radical scavenger) *i.e.,* GSH (Glutathione).

Paraoxygenase-2 (PNO-2) is another enzyme present in the human brain that prevents oxidative stress induced mitochondrial damage in the brain cell. Available literature suggests that quercetin enhances the PNO_2 expression at both protein levels and mRNA levels in striatal astrocytes, brain cells, neurons, and macrophages by modulating the JNK/AP-1 pathway, or through its phytoestrogenic activity [10].

Quercetin suppresses the inflammatory mediators

Inflammation in the brain is a secondary response occurred due to early episodes of a brain injury like infections, accumulation of abnormally formed proteins (like Ab and phosphorylated tau proteins), and trauma which results in relentless destruction to the neurons when compared to the injury caused initially. Inflammation is responsible for the

progression of multiple neuropathological disorders. Activation of microglia and astrocytes persuade the expression of Inflammatory messengers such as acute phase proteins, cytokines (TNFα and IL-1b), and complement components, which sequentially stimulate NO and iNOS production with impaired phagocytic activity. All of the above events lead to complex interactions, neuronal damage, responsible for the progression of neurodegeneration in the brain. An anti-inflammatory molecule like quercetin helps in modulating NO production, pro-inflammatory cytokines, and glial signaling cascades that help in suppressing neuroinflammation and prevent neuronal death [11].

Quercetin abrogates glutamate mediated toxicity

Glutamate, the prime CNS excitatory Neuro Transmitter (NT), perpetuates the synaptic excitation or plasticity and establishes fresh networks between neurons that manifest our learning and memory. After the release from the pre-synaptic terminal of a neuron, glutamate initiates fast excitatory transmission by binding with NMDA and AMPA receptors (ionotropic receptors) and metabotropic receptors (G protein coupled receptors) in the post-synaptic nerve terminal. Excitotoxicity is propagated mainly by the excessive influx of Ca^{2+} through NMDA and AMPA receptors and voltage gated calcium ion channels, which activates enzymes like proteases & nucleases causing cell necrosis and tissue injury, such as hypoxic-ischemic brain damage, neurotrauma, etc. It was observed that quercetin prevents the neuronal cells against excitotoxicity by dropping the glutamate mediated influx of Ca^{2+} and intracellular free radical production and by modulating the potential of mitochondrial membranes and downregulating various apoptosis-related biochemical markers [12-17].

Quercetin modulates abnormal protein aggregation

Post Translational Modifications (PTMs) like glycosylation, ubiquitination, and phosphorylation may lead to aggregation or misfolding of proteins with degeneration of neurons, which are the most frequently observed indicators of numerous neurodegenerative diseases pathologically. Also, Phosphorylation of Alpha-synuclein (a-Syn) by various protein kinases leads to a-Syn protein aggregation which brings defects in neurotransmission and homeostasis of synaptic vesicle leading to Parkinsonian disease. In addition, hyper phosphorylation of tau protein forms neurofibrillary tangles that ultimately cause neuronal death. Available literature shows that quercetin has a protective role against these mechanisms like aggregation, hyper phosphorylation, and misfolding of the above proteins [18].

Pharmacokinetics of quercetin

Quercetin efficiently acts against multiple neurodegenerative disorders or diseases *via* suppressing inflammation, oxidative stress, and enhancing neurogenesis. Quercetin itself has low bioavailability as it does not cross the BBB (Blood Brain Barrier) efficiently. Hence, different methods such as enzymatic modification and nanoencapsulation have been used to improve quercetin's bioavailability.

The available pharmacokinetic data shows that quercetin derivatives like isoquercetin have their absorption (Cmax) are about 40 times higher than absorption of quercetin alone and can reach the maximum levels in 15 min in the bloodstream and works proficiently in the brain.

Also, various target carriers, nanotechnologies, and many other possibilities of modern research are the way ahead to prevail over the problem of lower bioavailability, solubility, brain penetration, and increased metabolism of bioactive components like quercetin. In addition, Transferrin-functionalized liposomes after induction of quercetin are found to assist quercetin diffusion into the brain [19].

Therapeutic potential of quercetin for neurodegenerative diseases

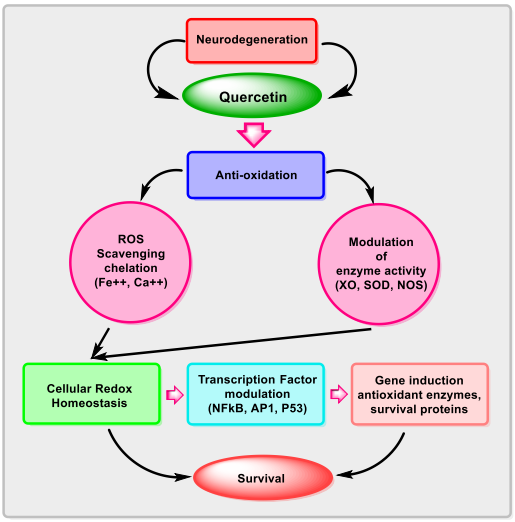
The brain is chiefly at risk to the possessions of Reactive Oxygen Species (ROS) owing to their higher oxygen demand and a profusion of extremely peroxidizable substrates. In prevalent neurodegenerative ailments including, Parkinson and Alzheimer disease, oxidative stress is a key constituent, implicated in numerous pathogenic pathways leading to neuronal death, which is produced by cell's redox state, imbalancing *via* excessive generation of ROS or malfunctioning in the antioxidant system.

Brain ischemia triggers several cellular activities such as activation of NMDA receptors, the liberation of neurotransmitters, particularly glutamate, and an increase in the entry of calcium into cells, and also control the production of reactive species of oxygen and nitrogen (ROS and RNS), which leads to DNA damage, disruption of the cell membrane and lipid peroxidation, that cause death of the neuronal cells. Several reports indicated that upon treatment with quercetin, survival of neurons increased, cultured *in vitro* in contrast to oxidative lethal stimuli.

Quercetin is an omnipresent flavonoid, that originates in a ample range of beverages, foods, and plants that have been established to play an essential function in the treatment of neurodegenerative disorders. It is considered as one of the utmost powerful antioxidants, which show its ability of scavenging ROS and binding of transition metal ions, therefore defense the body from oxidative stress. Quercetin exhibited several therapeutic and biological properties such as antioxidative effects, reduction of Blood Pressure (BP), obesity, anti-inflammatory, anti-allergic, anti-microbial, antitumor, antiplatelet, anti-cataract, and ameliorating hyperglycemia related diseases. A significant key opinion for the comprehensive usage of quercetin as a neuroprotective agent is its pro-oxidant nature and cytotoxic effects, including the scavenging of free radicals and their metal chelation activity.

Quercetin contribute an imperative role in iron homeostasis and is known to have several neuroprotective properties, including the capability to protect the neurons from neurotoxin-induced injury and neuro inflammation, to cross the BBB, as well as the capability to improve memory and learning, development of Aβ fibrils and prevent the neuronal cell deaths from Aβ-mediated toxicity. By modulating the cell death processes, it can boost the neuron's resistance in contrast to oxidative stress and excitotoxicity. A schematic representation of pharmacological actions exhibited by quercetin in neurodegeneration is depicted in Figure 2.

Figure 2. A schematic summary of pharmacological actions exhibited by quercetin in neurodegeneration.



Enhancement of therapeutic potential by nanotechnology applications

Quercetin is a potent neuroprotective drug that attenuates striatal neuronal cell death and alleviates motor dysfunction. The retention of antioxidant and anti-inflammatory activities has been documented in the preclinical approaches as a neuroprotective mediator in Alzheimer's disease and several other related neurological diseases. Being a potent antioxidant, it scavenges free radicals, inhibits xanthine oxidase, suppresses lipid peroxidation, and alters the antioxidant defense.

Procurement of this safer flavonoid agent and its derivatives as potential therapeutics in the pharmaceutical field is limited due to their low intrinsic activity, poor oral bioavailability, poor aqueous solubility, poor brain permeability, high metabolic rate, hydrophobic nature, first-pass metabolism, physiological pH instability, and rapid body clearance. These circumstances lead to the rapid deprivation of quercetin in blood flow, resulting in the usage of high concentrations and longer duration of treatment with quercetin, which causes severe adverse effects. As a result, awareness about the manufacturing of nanostructures based quercetin derivatives has been established, which aids the researchers in increasing the bioavailability of drugs, drug delivery at the target site, and crossing the drug-loaded structures through the Blood Brain Barrier.

Several drug delivery systems including phospholipid vesicles, polymeric nanoparticles, nanoemulsions, co-crystals, inclusion complex, inorganic nanoparticles, micelles, microspheres, and solid dispersions have been formulated to improve its bioavailability and solubility. A novel drug delivery system has three major goals such as providing sustained release of drugs, targeting towards the selective site of action, and augmented patient acquiescence. Recently, the usage of polymeric NPs has been based upon non-biodegradable polymers e.g., polystyrene, polyacrylamide, and poly (methyl) methacrylate. These polymers ought to fulfill the two chief requirements: Safety and performance. They must have supreme biocompatibility to produce therapeutic efficacy and biodegradation as compatible with the healing of the target system/tissue [20].

Because of their enormous surface area, capacity to be modified for targeted drug delivery, protection against enzymes, better bioavailability, and physiological circumstances, nanoparticles have been used to improve the efficiency of phytochemicals. The pharmacological activities of quercetin coupled NPs is typically depended upon the drug carriers utilized, including liposomes, silica nanoparticles, silver nanoparticles, PLA (Poly-(D,L-Lactic Acid), PLGA (Poly lactic-co-glycolic acid), PCL (Poly-3-Caprolactone), polymeric micelles, chitosan nanoparticles, etc. Quercetin-loaded chitosan NPs and Zein NPs with improved encapsulation proficiency have been provided higher and sustained levels of drug concentration in plasma and improved bioavailability. The description of enhancement in the therapeutic potential of quercetin in neurodegeneration by using nanotechnology approaches is described in Table 3.

Table 3. Enhancement of therapeutic potential of quercetin in neurodegeneration by using nanotechnology approaches.

S. No.	Nanoparticles used	Therapeutic potential efficacy
1	Chitosan-alginate NPs	Substantial protection towards H_2O_2 induced oxidative stress damage in neuroblastoma SH-SY5Y cells, and 6-OHDA persuade neurotoxicity, enhance the antioxidant properties
2	Compritol and Tween-80	Improve the brain permeation of drugs, enhance drug entrapment efficiency
3	Quercetin loaded Poly lactic-co-glycolic acid (PLGA) nanoparticles	Increase the oral bioavailability of encapsulated drugs, sustain the quercetin activity, reduce $A\beta_{42}$- induced toxicity, and inhibit $A\beta_{42}$ fibrillation
4	Zein NPs	Enhanced oral absorption, cognition, and reduce memory impairments
5	Solid-Lipid nanoparticles (SLNs)	Diminished memory impairment, antioxidative, anti-lipid peroxidative, and acetylcholinesteraseinhibitory properties
6	ApoE-lipoproteins	Normalize the growth of neurons after nerve injury, prevent neurons from Aβ-induced toxicity, and promote cellular uptake in BCECs (Brain Capillary Endothelial Cells)
7	Quercetin-loaded PLGA	Protect oxidative impairment in ischemia reperfusion
8	PLA based Quercetin NPs	Reduction in Aβ-induced oxidative stress, and cytotoxicity, inhibit aggregation of Aβ, and destabilization of Aβ fibrils
9	Quercetin liposomes	Lowering of cholinergic neurons by reducing the oxidative stress

Challenges in nano-formulation development

Drug development for brain diseases is a challenging task. Clinical trials of CNS drugs are difficult due to the complex behavior of the brain, impermeability of the BBB, and side effects of CNS drugs.

The main challenge is the lack of a detailed understanding of BBB transport biology. Aside from the intricacy of brain diseases, the absence of effective technology to transfer medications across the BBB is a major impediment to the development of CNS drugs. Macro and small molecules are being studied as potential medicated agents for a variety of brain disorders. The BBB can only be crossed by molecules having properties such as lipid solubility and less than 400 Da molecular weight, macromolecules are not able to enter to the brain. The BBB prevents the most drugs to enter to the brain. The BBB is a dynamic barrier that regulates medication transport in the brain from the bloodstream. BBB disruption is linked with illness consequences such as Vascular dementia coexists with Alzheimer's disease vascular and it causes BBB pemeability increased of BBB in the case of some AD patients, but not in pure AD individuals.

Nano carriers are useful carriers for the administration of particular compounds to the brain and can pass across the BBB more easily. There are numerous issues that remain to be handled such route dislocation, influence clotting of blood and hemolysis, and create platelet accumulation because of nanoparticle size. For effective administration of drugs to CNS through BBB requires selection of an appropriate nanocarrier technology. The selection of a suitable nanocarrier technology is required for effective medication delivery to the CNS through the BBB. Nano carrier's size, surface charge, surface area, and shape all affect their ability to pass through CNS barriers. Specific nanocarriers with suitable size, surface charge, and surface area and having properties such as non-toxic, biodegradable, site-specific should be employed in CNS medication administration.

Imbalanced NP distribution in the brain can result in obvious dangers. The metabolism of these NPs is masked by inorganic portions of nanoformulations such as silica, iron, and cerium oxide particles. The influence of this substance on mitochondrial activity, intrusion with autophagy, neuronal inflammation, and apoptosis can cause neurotoxicity in the brain.

The lack of *in vivo* validation of *in vitro* BBB investigations is another issue. Designing novel Nano formulations and defining there *in vitro* features such as size, charge, shape, *in vitro* release, and cellular uptake, which is vital to analyze, receive far too much attention. All of these *in vitro* characterizations are worthless if they aren't accompanied by *in vivo* evaluations. All of these *in vitro* characterizations are worthless if they aren't accompanied by *in vivo* evaluations. Any given medicine might be delivered to the brain using a single nanoformulation. The nano formulation must be individually created and optimized for the medicine to be enclosed. Finally, the time it takes to develop CNS medications is typically substantially longer than it takes to produce non-CNS drugs. The above mentioned challenges affect the nano formulation development for neurodegenerative diseases.

Advantages of nano formulations over the classical formulations

For the treatment of NDs, the key goal is to target medicine delivery to the brain. Treatment options for NDs are

hampered by the existence of BBB. BBB is made up of brain micro vascular endothelial cells, pericytes, astrocytes, tight junctions, neurons, and basal membranes which form a constant barrier that protects the brain and regulates the control of the passage of solutes. Molecules with features such as lipid soluble and uncharged at physiological pH and molecular weight of less than 500 Da and a partition coefficient of 0.5 to 6.0 can cross the blood brain barrier. The BBB permeability is affected by changes in age and the diseases in terms of their structure and its functions. BBB permeability is increased in the case of AD patients with the existence of vascular dementia, which may be due to the changes in Adherens Junctions (AJs).

DISCUSSION

According to BCS, quercetin is a class IV-based chemical (biopharmaceutical classification system). Even when taken in high quantities, it has poor water solubility and oral absorption. Because of nanoparticles' low toxicity, good blood stability, excellent biocompatibility, and capacity to transfer functional cargo, nanotechnologies may give a viable therapeutic in the field of neurodegenerative illnesses. Two basic methods could be used to bypass the BBB and so facilitate pharmaceutical administration to the (CNS). The first is to "cross" it, and the other is to "bypass" it.

Polymeric Nanoparticles (PNPs) are used because they have a high capacity of drug loading, increased half-life circulation and increased ability for protecting the drug from degradation, as well as a wide range of surface handling options for molecules to enter through the blood brain barrier. Medication delivery systems based on NPs effectively increase drug transport *via* the BBB and surprisingly medication absorption in the brain. Nanoparticles have two advantages: Biodegradability and decreased toxicity to adjacent organs. Through Invasive and non-invasive manner, nanomaterials can pass through the blood-brain barrier. In first approach *i.e.* invasive, The BBB is punctured with physical methods, and nanoparticles are transferred through para cellular pathways such as intracerebral injection strategy such as intranasal, through receptor, cell, shuttle peptide, and Cell Penetrating Peptide (CPP). In the other approach *i.e* non-invasive approaches establishment of the Blood Brain Barrier (BBB) is protected and do not impair it during drug administration. The drug's encapsulation into nanocarriers makes it easier for it to enter the brain in a non-invasive manner.

Other benefits of using BBB nanoparticles for drug delivery include: Targeting free radicals and oxidative pathways in neural cells; suppressing and overexpressing inflammatory cytokines and chemokines; and having autophagy modulating and neuronal regeneration effects. They can also prevent apoptosis or toxicity in the brain.

NDs treatment therapy with NPs may have important repercussions, including improved biocompatibility and biodegradability, improved pharmacokinetics and therapeutic efficacy, and reduced medication side effects. Nanoparticles (NPs) may be a better carrier for improving brain delivery and their exterior surface can be fine-tuned by using a particular ligand to promote BBB penetration. Furthermore, numerous functionalization should be used to target disease molecular processes as well as assure BBB transit.

CONCLUSION

Quercetin is a flavonoid having high-potential antioxidant and neuroprotective properties. Quercetin can be used to treat a variety of neurological disorders by lowering stress, inflammation, etc., but poor bioavailability and less penetration to brain limit its efficacy in combating neurodegenerative disorders. This limitation could be removed using nontoxic nanoparticles. Efforts have been taken for the development of novel nanoformulations such as liposomes, nanocapsules, nanogels, microsphere etc., to overcome these restrictions. Nanostructures of quercetin significantly improve its absorption in tissue and cellular levels in animal models include in its benefits over quercetin.

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