

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 in 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 has high-potential antioxidant and neuroprotective properties. Quercetin can be used to penetrate 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.

REFERENCES

1. Abraham MH, et al. On the solubility of quercetin. J Mol Liq. 2014;197:157-159.
2. Akyuz E, et al. Enlightening the neuroprotective effect of quercetin in epilepsy: From mechanism to therapeutic opportunities. Epilepsy Behav. 2021;115:107701.
3. Ali T, et al. Anthocyanin loaded PEG-*PLGA* nanoparticles for the treatment of Alzheimer's disease. Mol Neurobiol. 2017;54:6490-6506.
4. Alok S, et al. Herbal antioxidant in clinical practice: A review. Asian Pac J Trop Biomed. 2014;4:78-84.
5. Altaf R, et al. Phytochemistry and medicinal properties of *Phaleria macrocarpa* (Scheff.) Boerl. extracts. Pharmacogn Rev. 2013;7:73.
6. Aluani D, et al. *In vitro* protective effects of encapsulated quercetin in neuronal models of oxidative stress injury. Biotechnol Biotechnol Equip. 2017;31:1055-1063.
7. Amanzadeh E, et al. Application of quercetin in neurological disorders: From nutrition to nanomedicine. Rev Neurosci. 2019;30:555-572.

8. Ansari MA, et al. Protective effect of quercetin in primary neurons against A β (1-42): Relevance to Alzheimer's disease. *J Nutr Biochem*. 2009;20:269-275.
9. Arredondo F, et al. After cellular internalization, quercetin causes Nrf2 nuclear translocation, increases glutathione levels, and prevents neuronal death against an oxidative insult. *Free Radic Biol Med*. 2010;49:738-747.
10. Bischoff SC, et al. Quercetin: Potentials in the prevention and therapy of disease. *Curr Opin Clin Nutr Metab Care*. 2008;11:733-740.
11. Boesch-Saadatmandi C, et al. Effect of quercetin on paraoxonase 2 levels in RAW264. 7 macrophages and in human monocytes role of quercetin metabolism. *Int J Mol Sci*. 2009;10:4168-4177.
12. Boussahel S, et al. Flavonoid profile, antioxidant and cytotoxic activity of different extracts from Algerian *Rhamnus alaternus* L. bark. *Pharmacogn Mag*. 2015;11:102.
13. Bovy A, et al. Metabolic engineering of flavonoids in tomato (*Solanum lycopersicum*): The potential for metabolomics. *Metabolomics*. 2007;3:399-412.
14. Burlec AF, et al. Essential oils in wellness centers: Overview on European Union legislation, potential therapeutic effects and toxicity. *Farm*. 2020;68:992-998.
15. Caruso G, et al. Could nanoparticle systems have a role in the treatment of cerebral gliomas? *Nanomedicine: Nanotechnology*. 2011;7:744-752.
16. Chakraborty S, et al. Tailoring of physicochemical properties of nanocarriers for effective anti-cancer applications. *J Biomed Mater Res A*. 2017;105:2906-2928.
17. Chakraborty S, et al. The use of nano-quercetin to arrest mitochondrial damage and MMP-9 upregulation during prevention of gastric inflammation induced by ethanol in rat. *Biomaterials*. 2019;33:2991-3001.
18. Chen J, et al. Quercetin attenuates tau hyperphosphorylation and improves cognitive disorder *via* suppression of ER stress in a manner dependent on AMPK pathway. *J Funct Foods*. 2016;22:463-476.
19. Choi GN, et al. Effect of quercetin on learning and memory performance in ICR mice under neurotoxic trimethyltin exposure. *Food Chem*. 2012;132:1019-1024.
20. Choudhary M, et al. Medicinal plants with potential anti-arthritic activity. *J Intercult Ethnopharmacol*. 2015;4:147.