International Journal of Advances in Pharmacy Medicine and Bioallied Sciences 2022;10(2):76-81.

International Journal of Advances in Pharmacy Medicine and Bioallied Sciences

An International, Indexed, Peer-reviewed Open Access Journal

www.biomedjournal.com

ISSN 2348-2109

International Journal of Advances in Pharmacy Medicine and Bioallied Sciences

www.biomedjournal.com

Indexed Peer-reviewed

Review Article

Polyphenol based novel drug delivery carriers for the treatment of ageing related neurodegenerative disorder: a modern approach

Anant Prakash Pandey*, Santosh Kumar Shukla.

Institute of Pharmaceutical Sciences & Research, Lucknow, UP, India.

ARTICLE INFO

Article History

Received : 14-Aug-2022
Revised : 19-Aug-2022
Accepted : 27-Aug-2022

Key words

Aging,
Neurodegenerative disease,
Polyphenols,
Bioavailability,
Solubility,
Nanoparticle-based delivery systems.

ABSTRACT

The main risk factor for the emergence and spread of neurodegenerative disorders (ND) is age. The growth in ND prevalence, particularly in emerging nations, is thought to be mostly caused by the expansion of longevity. The challenge for doctors and researchers is to find treatment approaches able to slow down neurodegeneration and/or improve the patient's quality of life because there is currently no cure for any of them. Increased cellular oxidative stress has been identified as one of the potential risk factors in ND, along with genetics and environmental stresses. The antioxidant effects of a heterogeneous class of natural substances known as nutraceuticals, including vitamins, carotenoids, and polyphenols, have drawn the attention of the scientific community in recent years. Among polyphenols, resveratrol and curcumin. Although polyphenols have substantial antioxidant properties, their poor bioavailability and quick metabolism are the main factors that limit their ability to provide neuroprotection. Polymeric nanoparticle-based polyphenol delivery systems, which stop bioactive compounds from degrading and increase their absorption and bioavailability, offer a viable option. The bioavailability of polyphenols is now enhanced by food-grade lipid-based nanoparticles, polysaccharide nanoparticles, nanoemulsions, biopolymeric nanoparticles, nanocomplexes (proteins, carbohydrates), and copolymers (protein-carbohydrate conjugates). The enormous potential of nanoparticle-based systems for the administration of nutraceuticals may make them an effective therapeutic approach for the management of ND.

*AUTHOR FOR CORRESPONDENCE: anantprakashpandey01@gmail.com

INTRODUCTION

One of the main risk factors for neurodegenerative disorders (ND) is ageing. A pathological disease called neurodegeneration is defined by the malfunction or slowly progressing death of particular neuronal cells in the brain and spinal cord [1, 2]. The cellular and molecular mechanisms that underlie ND, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), include protein misfolding and aggregation, mitochondrial dysfunction, defective cellular transport, and inflammation [3]. They are extremely debilitating, developing, and incurable illnesses, making them a serious issue in terms of suffering people and monetary cost [4, 5]. According to numerous reports, the prevalence of age-related neurodegenerative illnesses is predicted to rise, especially in emerging nations, where the population's share of seniors is projected to rise to 20% by 2050 [6, 7]. The current issue facing medical professionals and scholars is to identify novel therapeutic approaches to halt neurodegeneration and hence enhance the patient's quality of life.

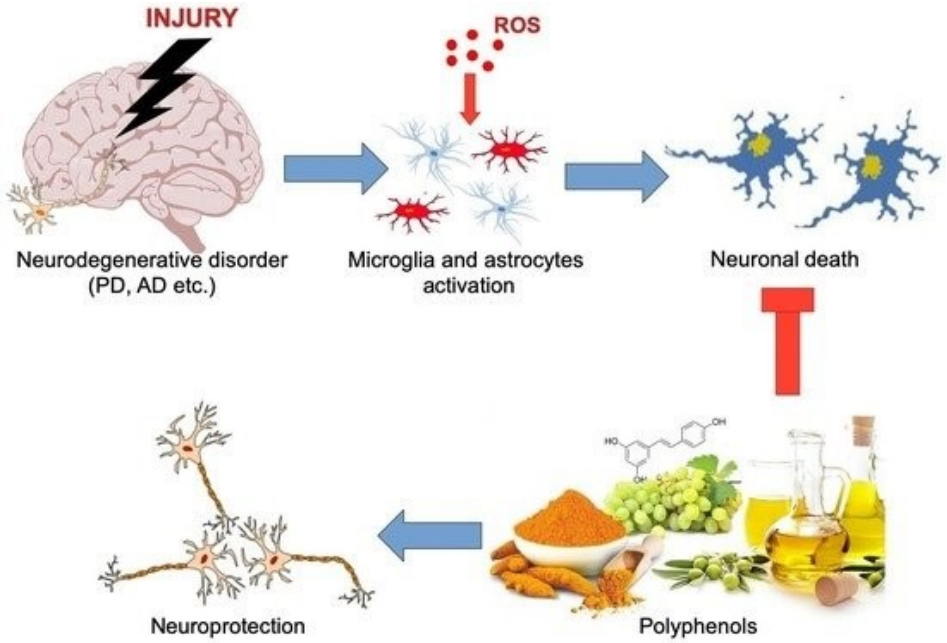

Figure 1: Reported scientific mechanisms for how natural polyphenols benefit the brain.

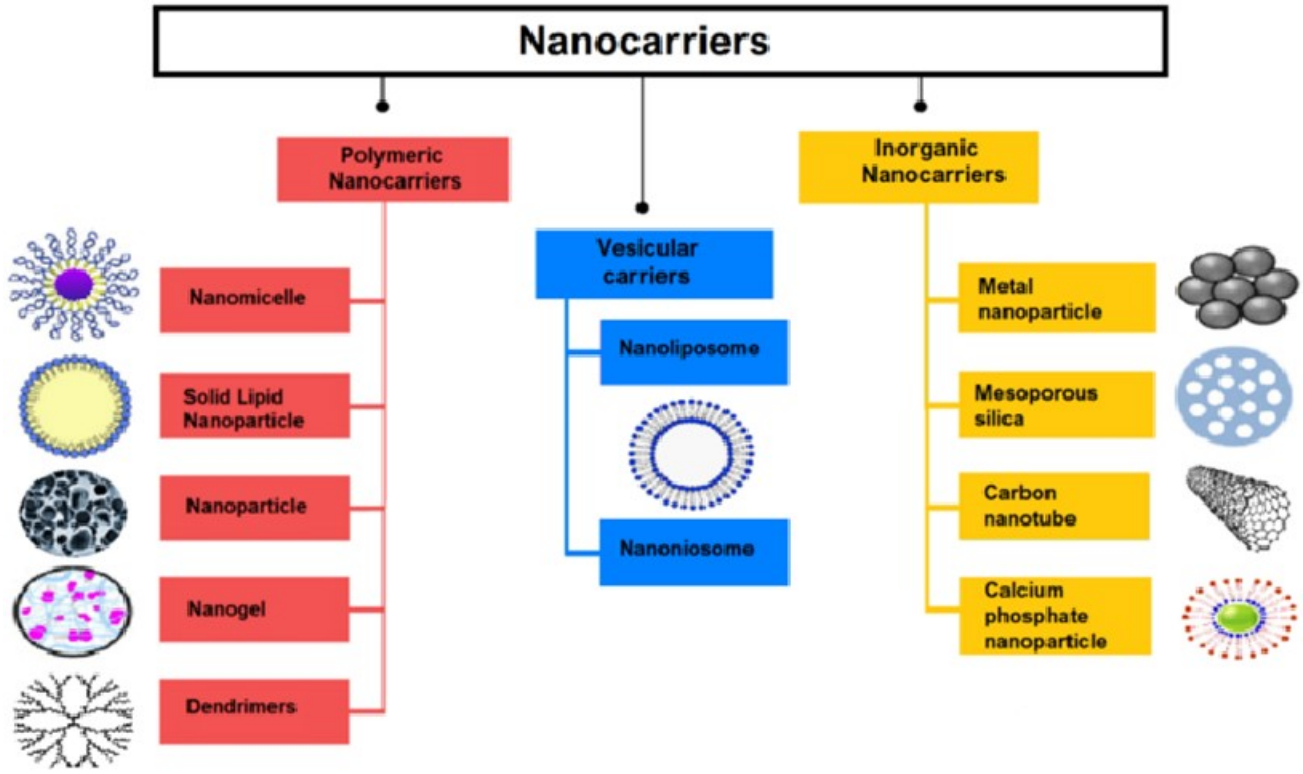

Figure 2. Diagram illustrating how delivery systems based on nanoparticles might improve the bioavailability of polyphenols by lengthening their stay in the digestive tract, boosting their concentration in the blood, and enhancing their ability to penetrate the blood-brain barrier.

And although the exact cause of ND is still unknown, risk factors like genetics and environmental stresses may be important. Additionally, it has been shown that one of the putative common etiologies of ND is an increase in cellular oxidative stress [2, 8]. Increased oxidative stress results in cell damage, weakened DNA repair mechanisms, and mitochondrial dysfunction, all of which are known to accelerate ageing and contribute to the onset and progression of ND [9, 10]. Recently, a sizable number of naturally occurring substances that are found in food and are capable of preventing the development of ND have been found. Vitamins, carotenoids, and polyphenols, which are extensively contained in fruit, vegetables, cereals, olives, dry beans, beverages (such as tea, wine, beer, and chocolate), as well as other natural products, have been the subject of several studies that have examined their antioxidant activity [11, 12]. Among nutraceutical compounds,

polyphenols are considered to be one of the most bioactive agents. Although polyphenols have strong antioxidant and other biological properties, their poor oral bioavailability and ineffective delivery route significantly limit their potential for neuroprotection and their use in functional foods and medications [13].

Both the biomedical and functional food industries have recently developed delivery technologies based on polymeric nanoparticles that encapsulate bioactive chemicals in order to protect them from the unfavourable environment of the gastrointestinal tract and transport them to target areas [14–16]. These methods provide an appropriate means of enhancing the administration of bioactive substances with poor oral bioavailability.

The antioxidant and neuroprotective characteristics of polyphenols, the primary parameters affecting their bioavailability, and the extensively researched nanoparticle-based antioxidant delivery systems are all included in the current mini-review.

Oxidative Stress and neurodegeneration

Both exogenous (ultraviolet rays, ionising radiation, medicines, environmental pollutants, and chemicals) and endogenous sources can produce cellular reactive oxygen species (ROS) (mitochondrial and non-mitochondrial ROS-generating enzymes). In a healthy environment, the defensive mechanisms of antioxidant enzymes (such as superoxide dismutase, catalase, and glutathione peroxidase) and small-molecule antioxidants balance the production of ROS (e.g. vitamin E and vitamin C). On the other hand, it has been observed that some pathological disorders, such as ND, have an imbalance between the antioxidant defense system and ROS generation that causes an excessive buildup of ROS [8,10]. Long-term oxidative stress has been identified as a key element in ND formation and progression as well as in speeding the ageing process. Additionally, variations in antioxidant enzyme activity, mitochondrial disturbance, and gene mutations are all frequently described in ND [2, 9]. A high concentration of polyunsaturated fatty acid in neuronal membranes makes them particularly vulnerable to oxidative stress, insufficient antioxidant defense methodologies, and, in particular, low levels of catalase, glutathione peroxidase, and vitamin E make the central nervous system one of the strongest metabolically active organs, making it extremely highly susceptible to ROS-mediated injury [17, 18]. According to these findings, the challenge for the scientific community is to find agents able to protect the brain against oxidative damage and thereby potentially treat neurodegeneration.

Polyphenols and neurodegeneration

Secondary plant metabolites known as polyphenols are frequently used in pathogen or ultraviolet radiation defense [19]. They can be divided into stilbenes, flavonoids, phenolic acids, diferuloylmethane, and tannins if they have at least one aromatic ring with one or more hydroxyl groups attached [20, 21]. Since they can reduce oxidative damage indirectly by influencing the expression of free radical-generating enzymes or the expression of intracellular antioxidant defense enzymes, polyphenols have a strong antioxidant activity [2]. Given their therapeutic potential for ND, curcumin (diferuloylmethane), resveratrol (stilbene), and the green tea polyphenol epigallocatechin-3-gallate (ECGC) (flavonoid) have received the greatest research attention [20, 21]. Many epidemiological studies have documented that moderate intake of wine, the most well-known source of resveratrol, can reduce the incidence of age-related ND. Additionally, regular use of foods high in flavonoids has been linked to a lower risk of dementia and a delay in the onset of AD symptoms [22]. A growing body of research points to the role curcumin and resveratrol play in boosting the activity of particular antioxidant enzymes such glutathione peroxidase, catalase, and superoxide dismutase [2, 11, 23]. The neuroprotective responsibility of polyphenols can be attributed to other methods of action in addition to their antioxidant activity, such as the decrease in amyloid-beta (A) fibril/aggregate establishment (a hallmark of AD) [2, 24], the ability to chelate metal ions accumulating in particular brain regions of AD, PD, HD, and ALS patients [2, 25], Preventing the expression of pro-inflammatory genes, such as cyclo-oxygenase, nitric oxide production, and numerous cytokines, has been shown to have anti-inflammatory effects [2, 26]. Although polyphenols have potent antioxidant and perhaps other biological properties, their poor oral bioavailability, and ineffective delivery route severely restrict their use in the medical industry. By "the proportion of an eaten molecule that reaches the systemic circulation and the precise locations where it can exert its biological activity" [13, 27], we mean the bioavailability of a substance. The first-pass metabolism, intestinal permeability, and/or polyphenols' low solubility all have a role in the bioavailability of these compounds. Polyphenols are exposed to the stomach acid state due to their interactions with salivary proteins that are high in proline, which affects their stability; they undergo quick metabolism and are conjugated to glucuronic acid, methyl, and sulphate groups in the liver and intestines. The structure and biological activity of polyphenols undergo striking modifications as a result of these metabolic processes [2, 28]. The ability of polyphenols and their metabolites to penetrate the

Blood-Brain Barrier (BBB), a selective diffusion barrier that restricts the movement of the majority of substances from the bloodstream to the brain tissue, is another significant concern [29, 30]. Less polar molecules show a greater absorption in the brain than more polar molecules, and the pace at which polyphenols permeate through the BBB is strongly associated with their lipophilicity. According to these results, the polyphenol fraction that reaches the bloodstream and consequently targets regions like the brain is different from that found in the food that has been consumed. Therefore, the scientific community faces a problem in developing a polyphenol delivery method that can pass the BBB and carry out its biological function.

Nanoparticle-based polyphenol delivery systems

Due to their ineffective systemic transport and low oral bioavailability, polyphenols can only be used to a limited extent in functional foods and medicines at the moment [14]. Therefore, it is urgently necessary to develop novel ways that can control polyphenol bioavailability. Recently, polymeric nanoparticle-based delivery systems that encapsulate bioactive compounds have been developed for both biomedical and functional food sectors in order to preserve and transport them to target functions [14-16]. By shielding bio-functional molecules from the unfavorable gastrointestinal tract environment and extending their duration there, the nanoparticle systems can increase the absorption and bioavailability of those molecules., boosting their solubility rate and bloodstream concentration, as well as their penetration in the small intestine, and facilitating their transportation to the target organ (Figure 2) [14, 31]. Food-grade macromolecules are the ideal polyphenol delivery vehicles for oral intake, according to a growing body of research, because of their safety. Food-derived macromolecules are biodegradable, biocompatible, and useful [14, 32]. Currently, food-grade nanoparticle systems that increase the bioavailability of polyphenols (such as curcumin, resveratrol, and ECGC, which are characterized by poor bioavailability) are being thoroughly investigated [14, 33, 34]. These systems include lipid-based nanoparticles, polysaccharide nanoparticles, nanoemulsions, biopolymeric nanoparticles, nanocomplexes (proteins, carbohydrates), and solubility and cell-membrane permeability of the polyphenols determine which nanoparticle-based delivery technique is most appropriate. Polyphenols are frequently divided into three groups: Curcumin has both low solubility and low cell-membrane permeability; resveratrol exhibits both low solubility and high cell-membrane permeability, and ECGC exhibits both high solubility and poor cell-membrane permeability [14, 35]. The ability of the solid lipid nanoparticle-based technology to increase the solubility and bioavailability of lipid-soluble polyphenols was demonstrated in a number of studies [14, 36, 37]. Solid lipid nanoparticles have been shown by Chen et al. to be able to regulate the release of curcumin and increase its bioavailability. Given their ability to adhere to mucosal surfaces, a critical quality for extending the polyphenol residence time in the colon, dietary polysaccharides are heavily researched for application in the creation of nanoparticles [14]. According to the literature, the protein-polysaccharide complex nanoparticles are a biocompatible method to boost polyphenol bioavailability. The delivery system created by the regulated self-assembly of a polysaccharide and a bioactive peptide derived from the digestion of milk casein was demonstrated by Hu et al. to increase the rate at which ECGC permeates cell membranes but also its antioxidant activity [14].

An expanding corpus of research over the past year has shown how food-grade nanoparticle-based delivery technologies effectively increase the solubility and bioavailability of polyphenols. Despite the encouraging outcomes, further work needs to be done to refine the design of nanoparticles, increase their stability in the gastrointestinal environment, and more clearly define how encapsulation affects the metabolism of polyphenols [14]. The solution to these problems could result in important innovations in science and technology.

The occurrence of potential side effects from the injection of nanoparticles presents another obstacle that needs to be overcome. A growing body of research suggested that factors like size, surface chemistry, chemical composition, surface activity, and solubility may influence how dangerous nanoparticles are, which has led to an increase in studies examining the adverse effects of their exposure. However, the creation of nanoparticles is increasingly using materials that are safe for consumption and biodegradable substances, which helps to reduce the likelihood of adverse health impacts. Additionally, in vitro experiments are frequently performed to determine the toxicity of nanoparticles using cell lines selected based on the exposure route and the target organ, and they produce invaluable results used to set up preclinical and clinical investigations. Poly (Lactic-co-Glycolic Acid) (PLGA) curcumin nanoparticles may be both safe and effective, according to an intriguing in vitro study.

CONCLUSIONS

Despite mounting evidence that polyphenols have therapeutic benefits in the management of ND, their limited bioavailability remains a major cause for worry. Polyphenol delivery techniques based on polymeric nanoparticles are currently thought to be a potential approach. Although it has been demonstrated that nanoparticles can increase the concentration of bioactive compounds in the blood, more work has to be done to take these results "from bench to bedside." For the treatment of ND, the optimization of nanoparticle-based systems may prove to be a successful technique for enhancing the transport of bioactive substances with low bioavailability, such as curcumin and resveratrol.

Abbreviations

ND: Neurodegenerative Disease; AD: Alzheimer's Disease; PD: Parkinson's Disease; HD: Huntington's Disease; ALS: Amyotrophic Lateral Sclerosis; ROS: Reactive Oxygen Species; ECGC: (-)-epigallocatechin-3-gallate; Aβ: amyloid-beta; BBB: Blood-Brain Barrier.

REFERENCES

1. Niccoli T, Partridge L. Ageing as a risk factor for disease. Curr Biol. 2012;22:R741-52.
2. Spagnuolo C, Napolitano M, Tedesco I, Moccia S, Milito A, Russo GL. Neuroprotective role of natural polyphenols. Curr Top Med Chem. 2016;16:1943-50.
3. Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nat Med. 2004;10:S10-17.
4. Andlin-Sobocki P, Jonsson B, Wittchen HU, Olesen J. Cost of disorders of the brain in Europe. Eur J Neurol. 2005;12:1-27.
5. Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011;21:718-779.
6. Howard G, Goff DC. Population shifts and the future of stroke: forecasts of the future burden of stroke. Ann N Y Acad Sci. 2012;1268:14-20.
7. Marr RA, Thomas RM, Peterson DA. Insights into neurogenesis and aging: potential therapy for degenerative disease? Future Neurol. 2010;5:527-41.
8. Kim GH, Kim JE, Rhie SJ, Yoon S. The Role of Oxidative Stress in Neurodegenerative Diseases. Exp Neurobiol. 2015;24:325-40.
9. Lin MT and Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 2006;443:787-95.
10. Gandhi S, Abramov AY. Mechanism of oxidative stress in neurodegeneration. Oxid Med Cell Longev. 2012;2012:428010. doi:https://doi.org/10.1155/2012/428010.
11. Russo M, Spagnuolo C, Tedesco I, Russo GL. Phytochemicals in cancer prevention and therapy: truth or dare? Toxins (Basel). 2010;2:517-51.
12. D'Archivio M, Filesi C, Di Benedetto R, Gargiulo R, Giovannini C, Masella R. Polyphenols, dietary sources and bioavailability. Ann Ist Super Sanita. 2007;43:348-61.
13. D'Archivio M, Filesi C, Vari R, Scazzocchio B, Masella R. Bioavailability of the polyphenols: status and controversies. Int J Mol Sci. 2010;11:1321-42.
14. Hu B, Liu X, Zhang C, Zeng X. Food macromolecule based nanodelivery systems for enhancing the bioavailability of polyphenols. J Food Drug Anal. 2017;25:3-15.
15. Li Z, Jiang H, Xu CM, Gu LW. A review: using nanoparticles to enhance absorption and bioavailability of phenolic phytochemicals. Food Hydrocoll. 2015;43:153-64.
16. Ganesan P, Ko HM, Kim IS, Choi DK. Recent trends in the development of nanophytobioactive compounds and delivery systems for their possible role in reducing oxidative stress in Parkinson's disease models. Int J Nanomedicine. 2015;10:6757-72.
17. Wang X, Michaelis EK. Selective neuronal vulnerability to oxidative stress in the brain. Front Aging Neurosci. 2010;2:12. doi: 10.3389/fnagi.2010.00012.
18. Friedman J. Why is the nervous system vulnerable to oxidative stress?. In: Gadoth, N., Göbel, H. (eds) Oxidative stress and free radical damage in neurology. Oxidative stress in applied basic research and clinical practice. Humana Press. 2011. doi: https://doi.org/10.1007/978-1-60327-514-9_2.
19. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009; 2: 270-278.
20. Pandareesh MD, Mythri RB, Srinivas Bharath MM. Bioavailability of dietary polyphenols: Factors contributing to their clinical application in CNS diseases. Neurochem Int. 2015; 89:198-08.
21. Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary (poly)

phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid Redox Signal. 2013;18:1818-92.

22. Vauzour D, Rodriguez-Mateos A, Corona G, Oruna-Concha MJ, Spencer JP. Polyphenols and human health: prevention of disease and mechanisms of action. Nutrients. 2010;2:1106-31.
23. Han X, Shen T, Lou H. Dietary Polyphenols and Their Biological Significance. Int J Mol Sci. 2007;8:950-88.
24. Jiménez-Aliaga K, Bermejo-Bescós P, Benedí J, Martín-Aragón S. Quercetin and rutin exhibit antiamyloidogenic and fibril-disaggregating effects *in vitro* and potent antioxidant activity in APPswe cells. Life Sci. 2011;89:939-45.
25. Mandel S, Amit T, Bar-Am O, Youdim MB. Iron dysregulation in Alzheimer's disease: multimodal brain permeable iron chelating drugs, possessing neuroprotective-neurorescue and amyloid precursor protein-processing regulatory activities as therapeutic agents. Prog Neurobiol. 2007;82:348-60.
26. Jayasena T, Poljak A, Smythe G, Braidy N, Münch G, Sachdev P. The role of polyphenols in the modulation of sirtuins and other pathways involved in Alzheimer's disease. Ageing Res Rev. 2013; 12:867-83.
27. Porrini M, Riso P. Factors influencing the bioavailability of antioxidants in foods: a critical appraisal. Nutr Metab Cardiovasc Dis. 2008;18:647-50.
28. Lewandowska U, Szewczyk K, Hrabec E, Janecka A, Gorlach S. Overview of metabolism and bioavailability enhancement of polyphenols. J Agric Food Chem. 2013;61:12183-99.
29. Ballabh P, Braun A, Nedergaard M. The blood-brain barrier: an overview: structure, regulation, and clinical implications. Neurobiol Dis. 2004;16:1-13.
30. Kavvadias D, Sand P, Youdim KA, Qaiser MZ, Rice-Evans C, et al. The flavone hispidulin, a benzodiazepine receptor ligand with positive allosteric properties, traverses the blood-brain barrier and exhibits anticonvulsive effects. Brit J Pharmacol. 2004;142:811-20.
31. Des Rieux A, Fievez V, Garinot M, Schneider YJ, Préat V. Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach. J Control Release. 2006;116:1-27.
32. Mezzenga R, Schurtenberger P, Burbidge A, Michel M. Understanding foods as soft materials. Nat Mater. 2005;4:729-40.
33. Huang Q, Yu H, Ru Q. Bioavailability and delivery of nutraceuticals using nanotechnology. J Food Sci. 2010;75:R50-7. doi: 10.1111/j.1750-3841.2009.01457.x.
34. Sekhon BS. Food nanotechnology – an overview. Nanotechnol Sci Appl. 2010;3:1-15.
35. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res. 1995;12:413-20.
36. Guri A, Gu I, Corredig M. Utilization of solid lipid nanoparticles for enhanced delivery of curcumin in cocultures of HT29-MTX and Caco-2 cells. Food Funct. 2013;4:1410-9.
37. Sun JB, Bi C, Chan HM, Sun SP, Zhang QW, Zhen Y. Curcumin-loaded solid lipid nanoparticles have prolonged *in vitro* antitumour activity, cellular uptake and improved *in vivo* bioavailability. Colloids Surf B Biointerfaces. 2013;111:367-75.