Advances in Biochemistry & Applications in Medicine

Chapter 6

Natural Polyphenol-Dendrimers Nano-Formulations for Therapeutic Applications in Medicine

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Abstract

Curcuminoids, alkaloids and flavonoids (or bioflavonoids) constitute the broadest and well-studied classes of natural polyphenols and they belong to plant-derived secondary metabolites. Recently, polyphenols have attracted significant interest in the scientific community due to their antioxidant potential to confront and scavenge the free radicals generated during the various pathological processes including neurodegenerative disorders, cancer, and cardiovascular diseases. Dendrimers are three-dimensional hyperbranched polymeric macromolecular structures consisting of symmetrically repetitive branched moieties around a central core, thus adopting a globular structure. Dendrimers, due to their multi-valency and modifiable surface functionality, can be conjugated with several ligands, thus developing targeted effective dendritic multifunctional drug delivery systems. Nanomedicine**,** a subcategory of nanotechnology, is a multidisciplinary combination of science and technology based on studies at the molecular and atomic level, and contributes to the development of innovative pharmaceutical nano-formulations in the field of medicine. Dendrimers constitute an advanced targeted drug delivery system, which due to its diversified properties, is a challenging advancement in nanomedicine and ensures the desired therapeutic efficacy. Herein, we present a

concise overview of natural polyphenol-dendrimers nano-formulations along with their novel therapeutic applications in the field of medicine.

Keywords: Dendrimers; Flavonoids; Nanocarriers; Therapeutic applications; Drug delivery; Natural polyphenols

1. Introduction

Plants are the main sources of biologically active substances that participate in their defensive mechanisms against herbivores, insects, and microorganisms. Curcuminoids are a class of linear diarylheptanoids, such as curcumin and its derivatives, bearing variable chemical groups that enhance their aqueous solubility, bioavailability and suitability as drug formulations. They are natural polyphenols with excellent antioxidant, antitumor, anti-inflammatory, radioprotective, anti-acidogenic and neuroprotective properties [1,2]. Encapsulation of curcuminoids into nanoparticulate formulations has been proved to provide stability against hydrolytic degradations, improved bioavailability and pharmacokinetics [3]. Alkaloids are a class of natural polyphenolic compounds with numerous structural diversities and exceptional pharmacological activities such as antimalarial, anticancer, vasolidatory, analgesic, and antibacterial activities [4]. However, their poor aqueous solubility and bioavailability limit their therapeutic potency [5]. Flavonoids constitute a large category of polyphenolic compounds that derive from herbal and plant-based beverages and foods [6]. Flavonoids exhibit various antioxidant, cell-signal modulating, anti-inflammatory, and cardioprotective properties. Furthermore, they can inhibit neurodegeneration and the growth of several viruses and microorganisms [7,8,9]. Despite their health benefits, their therapeutic efficacy depends on the improvement of the pharmacokinetic profile after their oral administration. Flavonoids possess limited water solubility, bioavailability, and permeability, and are considered unstable and sensitive to exogenous factors such as light, pH, and temperature [10,11,12]. As a result, encapsulation in nanocarriers for drug delivery applications can be a viable way to improve bio-efficacy and bioavailability of flavonoids by increasing the solubilization potential, altering the absorption pathways, and preventing the metabolic degradation.

Drug delivery constitutes a feasible way to improve patient compliance and therapeutic index via the controlled and targeted administration of a drug [13]. An efficient drug delivery nano-formulation is sufficiently protecting the drug from degradation processes and enables secure crossing through the biological barriers ensuring its safe and targeted transfer to the specific site of action [14]. Since the 1990s, apart from linear polymers, the polymer science has included a novel class of structurally diversified compounds, the branched polymers, such as cross-linked polymers, dendri-grafts, macromolecules, and most recently, dendrimers [15].

Dendrimers are hyper branched polymeric three-dimensional macromolecular structures **(Figure. 1)** with significantly beneficial, over ordinary linear polymers, utilities such as controlled and globular structure and various functionalities [16]. Dendrimers attracted researchers' scientific attention due to their unique structural characteristics and potential

utilization in drug delivery applications. Since the 1980s, various dendritic formulations have been synthesized with specific architectures according to the divergent or convergent synthetic strategy [17,18], starting from a multifunctional core and subsequently adding repeated branching cycles classified as generations of the dendrimer [19]. Several multifunctional dendritic nano-formulations have been utilized as optimal drug delivery molecules in vaccination and immunology, photodynamic therapy, and cancer treatment for the successful administration of proteins, genes, DNA, solubilizing and diagnostic agents [20], and as nano-particulate multifunctional frameworks for targeted treatments, diagnostics, and imaging applications [21]. Poly(propylene imine) (PPI) and Poly(amidoamine) (PAMAM) dendrimers are the most explored types of dendritic drug delivery vehicles as anticancer agents and nanocarriers for RNAi therapeutics [22,23].

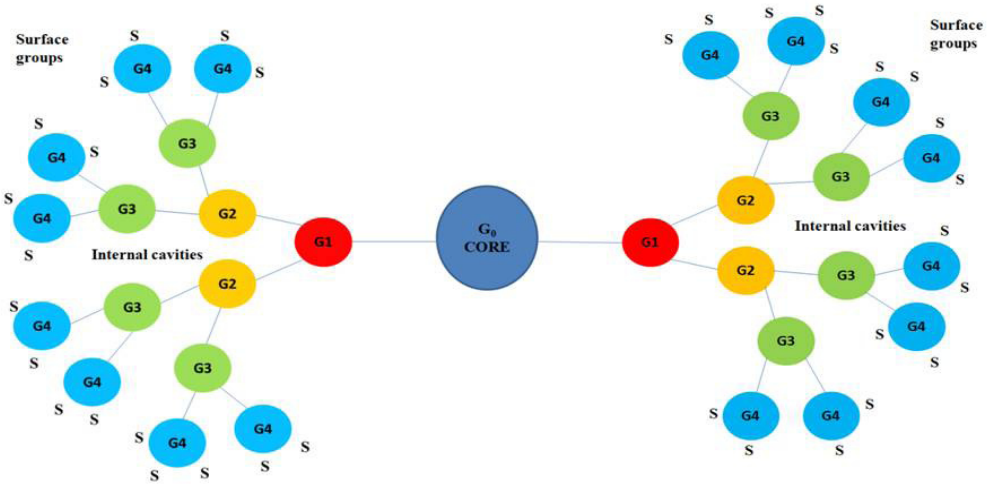
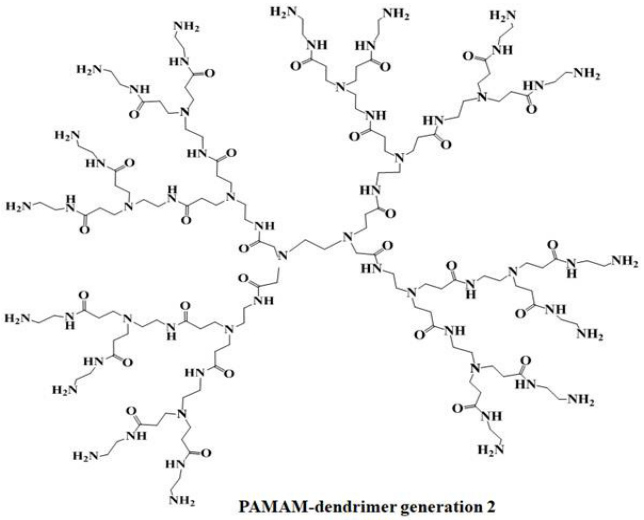


Figure 1: Indicative illustration of a dendritic structure with internal cavities and surface groups.

2. PAMAM dendrimers

PAMAM dendrimers **(Scheme 1)** are well-defined, nano-sized, hyper-branched macromolecules with an ethylene diamine central core and various reactive functional surface groups. PAMAM dendrimers are well-known for their effective enhancement of aqueous solubility and bioavailability of several hydrophobic compounds through encapsulation into their hydrophobic interior [24,25,26]. Furthermore, PAMAM dendrimers possess both active and passive targeting utilities due to their nano-size dimensions and the ability of the reactive peripheral amine groups to conjugate with bio-recognition molecules. However, one major drawback of PAMAM dendrimers is the reported cytotoxic profile of high-generation units. Dendrimers are used in order to enhance the aqueous solubility of water-insoluble drugs [27,28,29]. Interestingly, many researchers have demonstrated that the conjugation process of a drug to PAMAM dendrimers significantly reduces the dendrimer toxicity [30,31]. Folic acid (FA) constitutes the most commonly utilized targeting ligand, especially for its high affinity towards the folate receptors found on the outer membranes of several tumor cells such as colon, ovarian, breast, cervical, and lung cancers [32,33,34]. This specific binding of FA to the folate receptors can sufficiently increase the cellular uptake via clathrin-dependent endocytosis. It

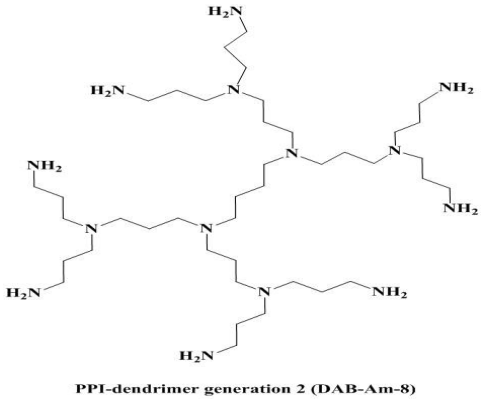
has been proved that FA-conjugated PAMAM dendrimers (FA-PAMAM) present enhanced cellular uptake by targeted cancer cells, improved drug accumulation, and minimum toxicity to normal healthy cells [35,36].



Scheme1: Indicative illustration of a PAMAM-dendrimer generation 2.

3. PPI dendrimers

In general, the main structural components of a dendritic molecule are classified into three distinct parts: a core, an interior, and an exterior. PPI dendrimers **(Scheme 2)** possess a core which is composed of diaminobutane moieties, an exterior that contains the outermost propylene imine chain, and an interior which is characterized as the intermediate component part between the exterior and the core [14]. PPI dendrimers constitute the most substantially explored category of dendrimers, adequate for drug delivery applications. The generations of PPI dendrimers are directly proportional to the surface cationic groups [37,38]. The augmentation of dendritic generations and their surface groups increasingly affects the toxicity of PPI dendrimers, as it has been well documented for PPI-G4 dendrimers which are less toxic compared to PPI-G5 dendrimers [39]. Several parameters such as hemolytic toxicity, drug loading and release behavior can affect the number and generation of PPI dendrimers [40,41], whereas the suitability of each generation depends on the purpose of the corresponding drug delivery procedure [40,42].

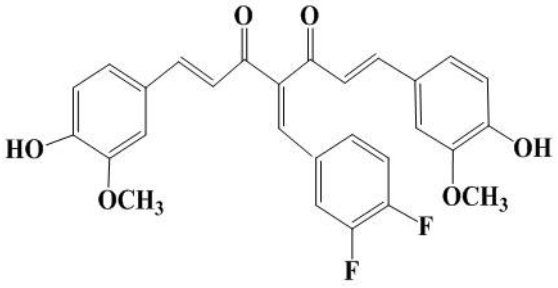


Scheme 2: Indicative illustration of a PPI-dendrimer generation 2 (DAB-Am-8).

4. Natural Polyphenol-Dendrimers Nano-Formulations

4.1. 3,4-Difluorobenzylidene Diferuloylmethane (DFC)

3, 4-difluorobenzylidene diferuloylmethane (DFC), (1E,6E)-4-(3,4-Difluorobenzy-lidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **(Scheme 3)** is a synthetic derivative of diferuloylmethane (curcumin), and an efficient anticancer polyphenol which has exhibited a 16-fold enhanced half-life combined with increased anticancer efficiency compared to its natural precursor, during tests on pancreatic tumors [43,44,45]. These observations are attributed to the improved bioavailability and stability of DFC compared to diferuloylmethane. Guided by these findings, researchers developed DFC-loaded dendritic nano-formulations conjugated to FA for the specific delivery of the drug to cervical cancer cells capable of over-expressing the folate receptors, thus increasing the anticancer activity of the compound. The engineered dendritic delivery nano-system possesses high DFC entrapment efficiency and loading capacity with outstanding bioavailability and aqueous solubility. The positive charge due to the conjugated FA ensures shielding and biological safety, improved anticancer potency *in vitro* and enhanced internalization compared to non-specifically targeted nano-formulations in SKOV3 and HeLa cells. Additionally, the dendritic nano-carriers augmented the apoptotic onset of the tumor cells, down-regulated NFκB and up-regulated the expression of PTEN, thus contributing in the debilitation of tumor recurrence rate and drug resistance after the initial drug treatment [46].



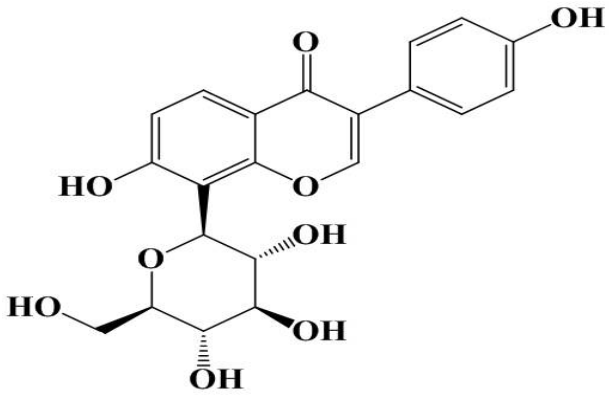
3,4-difluorobenzylidene diferuloylmethane (DFC)

Scheme 3: Formula of 3,4-difluorobenzylidene diferuloylmethane (DFC).

4.2. Puerarin

Puerarin,7-Hydroxy-3-(4-hydroxyphenyl)-8-[(3R,4R,5S,6R)-3,4,5-trihydroxy-6-hydroxyl methyl)oxan-2-yl]chromen-4-one **(Scheme 4)** constitutes a well-known isoflavone with excellent potential against cardiovascular disorders and anxiogenicity [47,48]. Studies on the effect of PAMAM dendrimers (G3, G4, G5, G3.5, G4.5) on the trans-epithelial transport and immortalized human corneal epithelium (HCE) cellular uptake of puerarin proved that PAMAM dendrimers (G3,G4,G5) with a cationic charge could significantly enhance the transport and uptake of the corresponding isoflavone. Confocal laser scanning microscopy

(CLSM) and flow-cytometry (FCM) examinations revealed a significantly strong internalization of PAMAM-G4 in the HCE cellular milieu, presumably due to the charge interactions and the easily manipulated design, size, surface functionality and charge of PAMAM dendrimers in their utilization as ocular drug nano-carriers [49,50]. It is suggested that both the type and generation of PAMAM dendrimers can affect the corneal permeation of puerarin mainly due to the provoked enhancement in its solubility induced by the encapsulation procedure and the ability of PAMAM dendrimers to successfully integrate with the lipid bilayer in the plasma membrane of corneal epithelial cells and loosen the corneal epithelial cell junctions [51,52]. Additional experimental and comparative results on the effects of dendrimer-puerarin complexes and eye drops containing free puerarin showed: a) the ability of these dendritic nanostructures to present long residence times inside the eyes, b) the slow in vitro puerarin release rates in biological buffers (PBS), and c) the absence of significantly different drug corneal permeation levels between the dendrimer-puerarin complexes and the free isoflavone [53]. Moreover, *in vivo* studies on the behavior of amine terminated (full generation) or carboxylate terminated (half generation) PAMAM dendrimers as solubility and bioavailability enhancers of puerarin indicated the ability of full generation PAMAM dendrimers to act as better solubilizing agents mainly due to the electrostatic intermolecular interactions between the phenolic hydroxyl groups of the isoflavone and the surface amine groups of the dendritic molecules. Furthermore, no hemolysis was observed after the administration of puerarin-dendrimer complexes to erythrocytes [54].



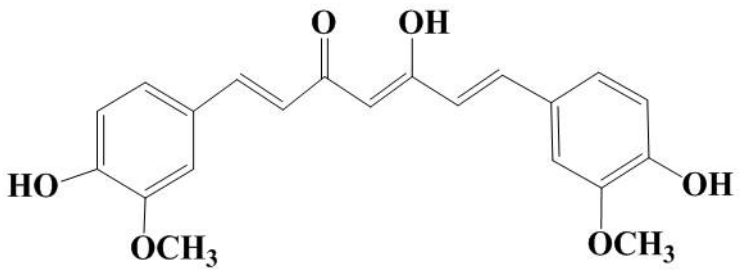
Puerarin

Scheme 4: Formula of Puerarin.

4.3. Curcumin

Curcumin,(1*E*,6*E*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione **(Scheme 5)** constitutes one of the three curcuminoid components present in turmeric, with bis-desmethoxycurcumin and desmethoxycurcumin being the other two. It is a natural phenol mainly used as a yellow food additive and colorant and a tautomeric compound present as keto and a more stable enolic form [55,56]. Curcumin has been the subject of much research

due to its various medicinal properties. Research studies have demonstrated its potent anti-inflammatory activity and anticancer role. Moreover, curcumin reduces the proliferation and transformation of tumors by regulating transcription and growth factors, protein kinases, inflammatory cytokines or other enzymes. In animal experimental studies, curcumin has been shown to possess a protective role against blood, mouth, pancreas, lung, skin, and intestinal tract cancer cells [57,58]. Research results on the antiproliferative activity of PAMAM encapsulated and free curcumin on T47D breast cancer cells via TRAP assay and a 24 h study of telomerase activity, indicated that the curcumin-loaded dendritic nano-carriers presented increased inhibitory effect, negligible cytotoxicity and enhanced antiproliferative potency [59]. Further *in vivo* studies on the treatment of various cancer cell lines with curcumin conjugated oligo(ethylene glycol) chains (curc-OEG) displayed high inhibition levels due to intense apoptotic activity. Furthermore, the intravenous injection of curc-OEG at high doses in SKOV-3 and MDA-MB-468 tumors provoked the decrease of tumor numbers and weights, with no observed subchronic and acute toxicities in the peripheral mouse visceral organs of the mice. Curc-OEG nano-formulations can also constitute effective carriers of camptothecin and doxorubicin anticancer drugs for the successful enhancement of cytotoxicity in drug-resistant cancer cells [60,61].



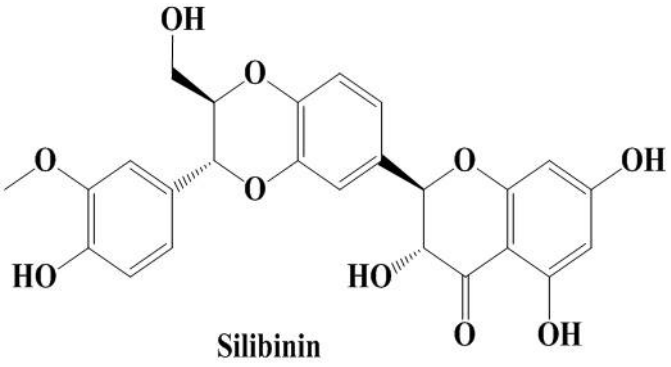
Curcumin

Scheme 5: Formula of Curcumin.

4.4. Silibinin

Silibinin,(2R,3R)-3,5,7-trihydroxy-2-[(2R,3R)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxyl-methyl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl]chroman-4-one**(Scheme6)** constitutes a flavonolignan with low bioavailability and water solubility, and nontoxic behavior even at concentrations of up to 13 g/day [62]. The anticancer potential of silibinin is currently under investigation [63]. However, it possesses anti-inflammatory, chemo-protective, anti-photocarcinogenic, anti-hepatitis, anti-cirrhosis and DNA repair properties [64,65,66]. Comparative studies between the amine-terminated PAMAM–G2 and G3 dendrimers and ester-terminated PAMAM–G1.5 and G2.5 dendrimers on their solubility enhancing properties as nano-carriers of silibinin indicated the improved solubilizing activity of the amine-terminated dendritic molecules mainly due to electrostatic interactions provoked by the formation of a complex between the corresponding dendritic nano-molecules and the phenolic hydroxyl moieties of the flavonolignan [67]. This complexation further leads to improved in vitro drug

release rates and in vivo bioavailability profiles of the encapsulated compound. Synthetic efforts on the development of surface-modified magnetic Fe_3O_4 nanotubes (Fe_3O_4NT) grafted with PAMAM-G3 dendrimers as nano-carriers of hydrophobic silibinin revealed the potential effect of PAMAM incorporation in the enhancement of silibinin loading capacity and sustainability of drug release rate, yet maintaining the magnetic properties of the nano-formulation compared to the unmodified Fe_3O_4 nanotubes and other similar nano-systems. As a result, the Fe_3O_4NT-PAMAM system could be utilized as a promising nano-carrier for drug-delivery applications [68].

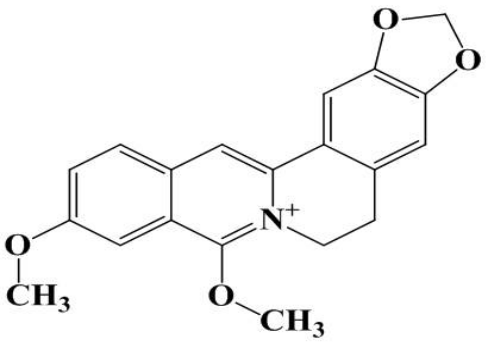


Silibinin

Scheme 6: Formula of Silibinin.

4.5. Berberine

Berberine,5,6-Dihydro-9,10-dimethoxybenzo[*g*]-1,3-benzodioxolo[5,6-a]quinolizinium **(Scheme 7)** constitutes a naturally produced nitrogenous cyclic benzylisoquinoline alkaloid with proved anticancer, apoptotic and antiproliferative activity [69]. However, the low bioavailability and poor pharmacokinetics have limited its utilization as an anticancer compound [70]. Recent studies on the synthesis of berberine-conjugated or encapsulated PAMAM-G4 dendrimers indicated the development of significantly nano-sized formulations (100-200 nm) with similar *z*-potential to that of an empty or unmodified PAMAM-G4 dendrimer. Furthermore, the conjugation percentage of berberine exceeded the encapsulation percentage of the corresponding compound, whereas both types of nano-formulations presented a sustained release rate of berberine in biological buffers and aqueous media. *Ex-vivo* and *in vivo* hemolytic studies on toxicity showed that both dendritic nanostructures are considered significantly biocompatible and relatively nontoxic. Moreover, the MTT results proved that the berberine-conjugated dendritic molecules showed excellent anticancer activity against MDA-MB-468 and MCF-7 breast cancer cells. Additionally, the *in vivo* pharmacokinetic parameters such as AUC (area under the curve) and half-life ($t_{1/2}$) of the novel dendritic formulations and the conjugated or encapsulated berberine were significantly improved. The overall conclusions imply that the conjugation of natural compounds to PAMAM dendrimers leads to improved delivery of these molecules and the development of more efficiently therapeutic dendritic nano-formulations [71].

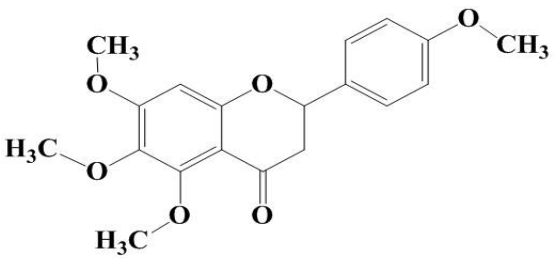


Berberine

Scheme 7: Formula of Berberine.

4.6. Tetramethylscutellarein

Tetramethylscutellarein, [5,6,7-trimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one] **(Scheme 8)** is a flavonoid with well-established anti-inflammatory potential [72], moderate cytotoxic activity against MCF-7 breast cancer cells and anti-tuberculosis properties [73]. Experimental studies on the synthesis of tetramethylscutellarein-loaded PAMAM-G4 dendrimers with amines as terminal moieties confirmed the solubility enhancement provoked by a complex formation between the surface functional amine moieties of the dendrimer and the flavonoid mainly due to electrostatic interactions and hydrogen bonding. Furthermore, the results at hand indicated the influence of pH on the solubility of the dendritic formulations and the *in vitro* release rates of the encapsulated flavonoid [72].



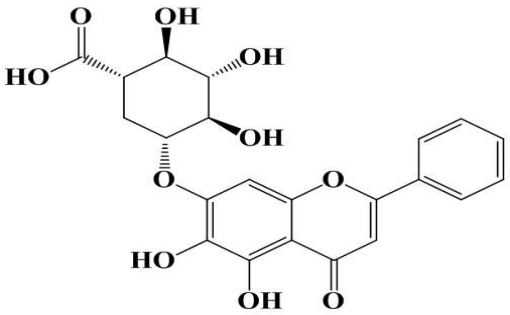
Tetramethylscutellarein

Scheme 8: Formula of Tetramethylscutellarein.

4.7. Baicalin

Baicalin, (2*S*,3*S*,4*S*,5*R*,6*S*)-6-(5,6-dihydroxy-4-oxo-2-phenyl-chromen-7-yl) oxy-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid **(Scheme 9)**, the glucunoride derivative of baicalein, constitutes a flavonoid with excellent potential for the prevention and treatment of allergy, hypertension, cardiovascular disorders, inflammation, and bacterial infections [74,75]. Moreover, baicalin presents cytostatic and cytotoxic potency *in vitro*, antitumor growth effect *in vivo* [76], and sufficient anticancer activity on lung, bladder, prostate, breast, liver, ovarian, and colorectal cancer cells [77]. However, the limited bioavailability and water solubility

in combination with the non-specific targeting of tumors limits the clinical application of the corresponding flavonoid [78]. Recent studies on the development of baicalin-loaded FA-conjugated PAMAM dendrimers indicated the beneficial effect of dendrimers and the corresponding generation of the PAMAM formulations on the aqueous dispersion, biological and physicochemical profile of baicalin [79]. More specifically, FA-modified PAMAM-G3 and PAMAM-G6 dendrimers demonstrated excellent entrapment efficiency and sustained release rates of baicalin in acidic PBS (pH 5.4). Furthermore, the corresponding nano-formulations provided targeted delivery of the encapsulated flavonoid and enhanced toxicity and flavonoid uptake in the folate receptor (FR) of HeLa cells as proved by MTT assays. All the experimental results were significantly related to the generation of the utilized PAMAM dendrimers. Further cell apoptosis and cell cycle analyses indicated the tumor-specific efficacy of the novel dendritic nano-formulations for the targeted delivery of baicalin to tumor cells [80].

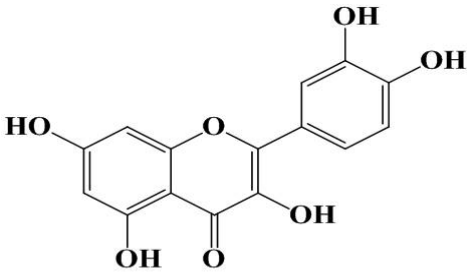


Baicalin

Scheme 9: Formula of Baicalin.

4.8. Quercetin

Quercetin, 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one **(Scheme 10)** constitutes a well-known flavonol with excellent antioxidant [81], cardio-protective [82], anti-ulcer [83], gene regulatory [84], anti-inflammatory [85], anticancer, and neuroprotective properties [86]. However, the poor solubility and bioavailability of quercetin limit its wide therapeutic applicability. Recent research works have established PAMAM dendrimers as effective quercetin delivery systems. More specifically, spherical nano-sized formulations (34.4-100.3 nm) of PAMAM dendrimers G0–G3 were proved to enhance the aqueous solubility of quercetin. Moreover, the novel dendritic quercetin-loaded nanostructures showed sustained *in vitro* release rates and prolonged stability at 4±2 ^{o}C. Furthermore, the results at hand indicated that orally administrated quercetin-loaded dendritic nano-formulations showed improved anti-inflammatory activity in rats compared to free quercetin suggesting that the incorporation of the corresponding flavonoid in PAMAM dendrimers can result in the development of an effective tool for the oral quercetin targeted delivery [87].

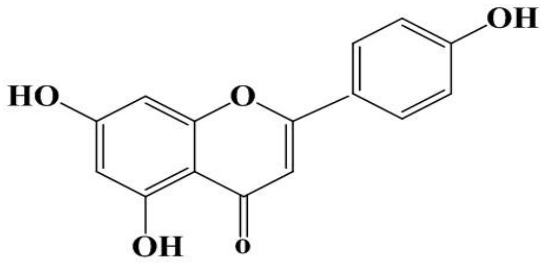


Quercetin

Scheme 10: Formula of Quercetin.

4.9. Apigenin

Apigenin, 5,7-Dihydroxy-2-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one **(Scheme 11)** belongs to the flavone family. It induces autophagy in leukemia cells supporting a chemo-preventive role [88], whereas it possesses a specific function in the prevention of renal damage [89]. Additionally, it exerts sedative and anxiolytic effects [90]. However, *in vitro* studies have shown that apigenin presents toxicity in red blood cells [91]. In recent studies, flavonoid apigenin was utilized as the fluorophore core of benzylic dendrimers. In general, fluorescent dendrimers are used as analytical tools and organic light emitting devices (OLEDs). Apigenin possesses three phenol moieties and weak blue light emission. These properties render apigenin an ideal precursor for the synthesis of Freshet-type dendrimeric structures [92]. Simulations of molecular dynamics were used for the estimation of branching and side effects. The overall data suggested that the 3rd and 4th dendrimer generations possess larger asphericities. Additionally, the fluorescence spectra implied the existence of aggregation phenomena for non-spheric dendritic structures [93].



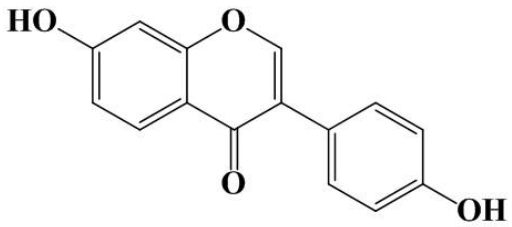
Apigenin

Scheme 11: Formula of Apigenin.

4.10. Daidzein

Daidzein, 7-Hydroxy-3-(4-hydroxyphenyl)chromen-4-one **(Scheme 12)** is a natural compound which belongs in the class of isoflavones. Recent research results have proved the viability of daidzein treatment as an effective remedy for osteoporosis, blood cholesterol, menopausal relief, heart disease, and hormone-related cancers [94,95]. However, the low bioavailability

and aqueous solubility of isoflavones, and their rapid metabolizing rates prevent their efficient oral or intravenous administration. As a result scientists have focused their efforts on the development of effective nano-carriers of isoflavones aiming at the improvement of their solubility and further clinical applicability [96,97,98]. More specifically, studies on daidzein liquid formulations encapsulated in PAMAM and PPI dendritic nano-carriers showed the remarkable improvement of the aqueous solubility of the corresponding isoflavone. PPI dendritic molecules showed a more efficient daidzein loading capacity compared to that of PAMAM dendrimers, mainly due to the presence of the large number of hydrophobic internal cavities inside the PPI dendritic structure. Moreover, the release rates of daidzein were slower from the daidzein-loaded PPI dendrimers compared to that from the daidzein-loaded PAMAM dendritic molecules. However, PPI nano-formulations were far more toxic and less stable compared to PAMAM dendrimerson A549 and MCF-7 cells. Furthermore, the daidzein-loaded PAMAM-G3 nano-formulations presented a contiguous protective activity against H_2O_2-induced cytotoxicity on A549 and MCF-7 cells similar to that of free daidzein. As a result, daidzein-loaded PAMAM dendrimers have been proved an effective and safe choice in the design of daidzein delivery systems with improved bioavailability, prolonged daidzein delivery and release rates, and sustained bioactivity [99].



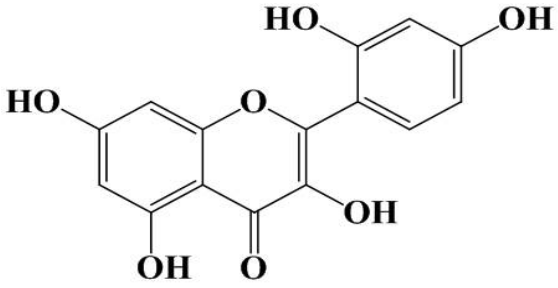
Daidzein

Scheme 12: Formula of Daidzein.

4.11. Morin

Morin, 2-(2,4-Dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one **(Scheme 13)** constitutes a well-known polyhydroxy flavonol with various pharmaceutical and biological activities [100,101]. Morin possesses structural, physicochemical and therapeutic properties such as hydrophobicity, planarity, electrostatic, antioxidant and anti-amyloid aggregation activities [102], that depend on the changes of the surrounding environment. As a result, scientists have focused their efforts on the complete investigation of the interactions of morin with various biological molecules, such as PAMAM dendrimers, in order to fully understand the drug-dendrimer interactions and develop an effective dendritic drug delivery nano-formulation. Recent modeling docking and spectroscopic reports on the interactions of morin-loaded modified PAMAM dendrimers with a 25% surface attachment of N-(2-hydroxydodecyl) groups (PAMAM-C12 25%) confirmed the morin-(PAMAM-C12 25%) complex formation in the aqueous phase through hydrophobic, electrostatic, hydrogen bonds, and van der Waals forces. Morin presented three different types of binding sites with PAMAM-C12 25%, reinforcing the

view that morin encapsulation into PAMAM dendrimers can lead to the functionalization of efficient nano-formulations adequate for polyphenol delivery applications [103].



Morin

Scheme 13: Formula of Morin.

5. Summary

This chapter is a concise collection of data of natural polyphenol-dendrimer nano-formulations with potential therapeutic activities. Dendrimers can be produced with highly controllable properties such as shape, size, functionality, and architecture. Their diversified surface groups determine their targeting function and toxicity behavior. Moreover, dendrimers, as nano-carrier vehicles of globular structure, can improve the bioavailability and therapeutic efficacy of the encapsulated natural compounds, thus formulating an adequate natural polyphenol delivery system for the development of effective medicinal treatment against various diseases.

6. References

1. Jayaprakasha GK, Rao LJ, Sakariah KK. Antioxidant activities of curcumin, demethoxycurcumin and bisdemethoxycurcumin. Food Chemistry. 2006; 98: 720–724.

2. Amalraj A, Pius A, Gopi S, Gopi S, Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives – A review. J. Tradit. Complement. Med. [Internet]. 2017; 7: 205-233.

3. Tiyaboonchai W, Tungpradit W, Plianbangchang P. Formulation and characterization of curcuminoids loaded solid lipid nanoparticles. Int. J. Pharm. [Internet]. 2007; 337: 299–306.

4. Williams P. Review of modern alkaloids. Structure, isolation, synthesis and biology. J. Nat. Prod. 2012; 75: 1261–1261.

5. Amirkia V, Heinrich M. Alkaloids as drug leads – A predictive structural and biodiversity-based analysis. Phytochem. Lett. 2014; 10: xlviii-liii.

6. Bilia AR, Isacchi B, Righeschi C, Guccione C, Bergonzi MC. Flavonoids loaded in nanocarriers: An opportunity to increase oral bioavailability and bioefficacy. Food Nutr. Sci. 2014; 5: 1212-1227.

7. Ross JA, Kasum CM. Dietary flavonoids: Bioavailability, metabolic effects, and safety. Annu. Rev. Nutr. 2002; 22: 19-34.

8. Yao LH, Jiang YM, Shi J, Tomás-Barberán FA, Datta N, Singanusong R, Chen SS. Flavonoids in food and their health benefits. Plant Foods Hum. Nutr. 2004; 59: 113-122.

9. Heim KE, Tagliaferro AR, Bobilya DJ. Flavonoid antioxidants: Chemistry, metabolism and structure-activity relationships. J. Nutr. Biochem. (2002); 13: 572-584.

10. Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am. J. Clin. Nutr. 2005; 81: 230-242.

11. Stahl W, van den Berg H, Arthur J, Bast A, Dainty J, Faulks RM, Gärtner C, Haenen G, Hollman P, Holst B, Kelly FJ, Polidori MC, Rice-Evans C, Southon S, van Vliet T, Viña-Ribes J, Williamson G, Astley SB. Bioavailability and metabolism. Mol. Aspects Med. [Internet]. 2002; 23: 39-100.

12. Tsolaki MN, Koutsouraki E, Katsipis GK, Myserlis PG, Chatzithoma MA, Pantazaki AA. Alternative anti-infective/ anti-inflammatory therapeutic options for fighting Alzheimer's disease. 2017; 6: 1-153.

13. Narayan PS, Pooja S, Khushboo A, Diwakar T, Ankit S, Singhai A. A novel drug delivery system. Int. J. Pharm. Life Sci. [Internet]. 2010; 1: 382–388.

14. Mishra I. Dendrimer: a novel drug delivery system. JDDT. 2011; 1: 70–74.

15. Kaur D, Jain K, Mehra NK, Kesharwani P, Jain NK. A review on comparative study of PPI and PAMAM dendrimers. J. Nanopart. Res. 2016; 18: 146.

16. Pandey RP, Gurung RB, Sohng JK. Dietary sources, bioavailability and biological activities of naringenin and its derivatives. In book: Apigenin and naringenin: natural sources, pharmacology and role in cancer prevention. Publisher: Nova Science Publishers. Editors: Stacks NM. (2015).

17. Hawker CJ, Frechet JMJ. Preparation of polymers with controlled molecular architecture. A new convergent approach to dendritic macromolecules. J. Am. Chem. Soc. [Internet]. 1990; 112: 7638-7647.

18. Tomalia DA, Naylor AM, Goddard WA. Starburst dendrimers: molecular-level control of size, shape, surface chemistry, topology, and flexibility from atomsto macroscopic matter. Angew. Chem. Int. Ed. Engl. [Internet]. 1990; 29: 138-175.

19. Liu M, Fréchet JMJ. Designing dendrimers for drug delivery. Pharm. Sci.Technol. Today. 1999; 2: 393-401.

20. Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. Prog. Polym. Sci. [Internet]. 2014; 39: 268-307.

21. Gillies ER, Fréchet JMJ. Dendrimers and dendritic polymers in drug delivery. Drug Discov. Today. [Internet]. 2005; 10: 35-43.

22. Mignani S, Rodrigues J, Tomas H, Zablocka M, Shi X, Caminade AM, Majoral JP, Dendrimers in combination with natural products and analogues as anti-cancer agents. Chem. Soc. Rev. [Internet]. 2018; 47: 514-532.

23. Kesharwani P, Banerjee S, Gupta U, Mohd Amin MCI, Padhye S, Sarkar FH, Iyer AK. PAMAM dendrimers as promising nanocarriers for RNAi therapeutics. Mater. Today. [Internet]. 2015; 18; 565–572.

24. Kukowska-Latallo JF, Candido KA, Cao Z, Nigavekar SS, Majoros IJ, Thomas TP, Balogh LP, Khan MK, Baker JR Jr. Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer. Cancer Res. [Internet]. 2005; 6512; 5317–5324.

25. Malik N, Evagorou EG, Duncan R. Dendrimer-platinate: a novel approach tocancer chemotherapy. Anticancer Drugs. 1999; 10: 767–776.

26. D. Luong, P. Kesharwani, R. Deshmukh, M.C.I. Mohd Amin, U. Gupta, K. Greish, Iyer AK. PEGylated PAMAM dendrimers: enhancing efficacy and mitigating toxicity for effective anticancer drug and gene delivery. Acta Biomater. 2016; 43: 14-29.

27. Milhem OM, Myles C, McKeown NB, Attwood D, D'Emanuele A. Polyamidoamine Starburst dendrimers as

solubility enhancers. Int. J. Pharm. [Internet]. 2000; 197: 239–241.

28. Devarakonda B, Hill RA, de Villiers MM. The effect of PAMAM dendrimer generation size and surface functional group on the aqueous solubility of nifedipine. Int. J. Pharm. 2004; 284: 133–140.

29. Devarakonda, B, Hill RA, Liebenberg W, Brits M, de Villiers MM. Comparison of the aqueous solubilization of practically insoluble niclosamide by polyamidoamine (PAMAM) dendrimers and cyclodextrins. Int. J. Pharm. 2005; 304: 193–209.

30. Goldberg DS, Vijayalakshmi N, Swaan PW, Ghandehari H. G3.5 PAMAM dendrimers enhance transepithelial transport of SN38 while minimizing gastrointestinal toxicity. J. Control. Release . 2011; 150: 318–325.

31. Mazzaferro S, Bouchemal K, Ponchel G. Oral delivery of anticancer drugs III: formulation using drug delivery systems. Drug Discov. Today. 2013; 18: 99-104.

32. Lu Y, Low PS. Folate-mediated delivery of macromolecular anticancer therapeutic agents. Adv. Drug Deliv. Rev. 2002; 54: 675–693.

33. Holm J, Hansen SI, Høier-Madsen M, Helkjaer PE, Nichols CW. Folate receptors in malignant and benign tissues of human female genital tract. Biosci. Rep. 1997; 17: 415–427.

34. Holm J, Hansen SI, Høier-Madsen M, Helkjaer PE, Bzorek M. Folate receptor in malignant effusions of ovarian carcinoma. APMIS [Internet]. 1995; 103: 663–670.

35. Pan J, Feng SS. Targeted delivery of paclitaxel using folate-decorated poly (lactide)-vitamin E TPGS nanoparticles. Biomaterials. 2008; 29: 2663–2672,

36. Mi Y, Liu Y, Feng SS. Formulation of Docetaxel by folic acid-conjugated d-α-tocopheryl polyethylene glycol succinate 2000 (Vitamin E TPGS2k) micellesfor targeted and synergistic chemotherapy. Biomaterials. 2011; 32: 4058–4066.

37. Gupta U, Agashe HB, Jain NK. Polypropylene imine dendrimer mediated solubility enhancement: effect of pH and functional groups of hydrophobes. J. Pharm. Pharm. Sci. [Internet]. 2007; 10: 358–367.

38. Hembade MJ, Kangane MR, Mansuk AG, Lukkad HR. Dendrimers: as promising nanocarriers for drug delivery. Int. J. Pharm. Arch. 2013; 2: 61–70.

39. Kesharwani P, Tekade RK, Jain NK. Generation dependent cancer targeting poly(propyleneimine) dendrimer. Biomaterials. 2014; 35: 5539–5548.

40. Bagre AP, Jain K, Jain NK. Alginate coated chitosan coreshell nanoparticles for oral delivery of enoxaparin: in vitro and in vivo assessment. Int. J. Pharm. 2013; 456: 31–40.

41. Jain K, Gupta U, Jain NK. Dendronized nanoconjugates of lysine and folate for treatment of cancer. Eur. J. Pharm. Biopharm. 2014; 87: 500–509.

42. Jain K, Verma AK, Mishra P, Jain NK Characterization and evaluation of Amphotericin B loaded MDP conjugated poly(propylene imine) dendrimers. Nanomedicine. [Internet]. 2015; 11: 705-713.

43. Kesharwani P, Banerjee S, Padhye S, Sarkar FH, Iyer AK. Parenterally administrable nano-micelles of 3, 4-difluorobenzylidene curcumin for treating pancreatic cancers. Colloids Surf. B Biointerfaces. 2015; 132: 138-145.

44. Padhye S, Banerjee S, Chavan D, Pandye S, Swamy KV, Ali S, Li J, Dou QP, Sarkar FH. Fluorocurcumins as cyclooxygenase-2 inhibitor: molecular docking, pharmacokinetics and tissue distribution in mice. Pharm. Res. 2009; 26: 2438–2445.

45. Padhye S, Yang H, Jamadar A, Cui QC, Chavan D, Dominiak K, McKinney J, Banerjee S, Dou QP, Sarkar FH. New difluoro Knoevenagel condensates of curcumin, their Schiff bases and copper complexes as proteasome inhibitors and

apoptosis inducers in cancer cells. Pharm. Res. 2009; 26: 1874–1880.

46. Luong D, Kesharwani P, Killinger BA, Moszczynska A, Sarkar FH,Padhye S, Rishi AK, Iyer AK. Solubility enhancement and targeted delivery of a potent anticancer flavonoid analogue to cancer cells using ligand decorated dendrimer nano-architectures. J. Colloid Interface Sci. [Internet]. 2016; 484: 33–43.

47. Yeung DKY, Leung SWS, Xu YC, Vanhoutte PM, Man RYK. Puerarin, an isoflavonoid derived from Radix puerariae, potentiates endothelium-independent relaxation via the cyclic AMP pathway in porcine coronary artery. Eur. J. Pharmacol. 2006; 552: 105–111.

48. Overstreet DH, Kralic JE, Morrow AL, Ma ZZ, Zhang YW, Lee DY. NPI-031G (puerarin) reduces anxiogenic effects of alcohol withdrawal or benzodiazepine inverse or 5-HT2C agonists. Pharmacol. Biochem. Behav. 2003; 75: 619–625.

49. Tao Q, Xiudi Z, Junhua W, Wanhui L, Youxin L, Kaoxiang S. Potential of poly (amidoamine) dendrimers as ocular carriers of puerarin based on human corneal epithelial cell line.2012 CRS Annual Meeting Abstracts.

50. Yavuz B, Pehlivan SB, Ünlü N. Dendrimeric systems and their applications in ocular drug delivery. Sci. World J. 2013; 2013: 732340.

51. Yao WJ, Sun KX, Liu Y, Liang N, Mu HJ, Yao C, Liang RC, Wang AP. Effect of poly(amidoamine) dendrimers on corneal penetration of puerarin. Biol. Pharm. Bull. 2010; 33: 1371-1377.

52. Yao C, Wang W, Zhou X, Qu T, Mu H, Liang R, Wang A, Sun K. Effects of poly (amidoamine) dendrimers on ocular absorption of puerarin using microdialysis. J. Ocul. Pharmacol. Ther. 2011; 27: 565-569.

53. Yao WJ, Sun KX, Mu HJ, Na L, Liu Y, Yao C, Rongcai L, Aiping W. Preparation and characterization of puerarin dendrimer complexes as an ocular drug delivery system. Drug Dev. Ind. Pharm. 2010; 36: 1027–1035.

54. Gu L, Wu ZH, Qi X, He H, Ma X, Chou X, Wen X, Zhang M, Jiao F. Polyamidomine dendrimers: an excellent drug carrier forimproving the solubility and bioavailability of puerarin. Pharm. Dev. Technol. [Internet]. 2013; 18: 1051–1057.

55. Akram M, Uddin S, Ahmed A, Usmanghani K, Hannan A, Mohiuddin E, Asif M. Curcuma longa and curcumin: A review article. Rom. J. Biol.-Plant Biol. [Internet]. 2010; 55: 65-70.

56. Manolova Y, Deneva V, Antonov L, Drakalska E, Momekova D, Lambov N. The effect of the water on the curcumin tautomerism: A quantitative approach. Spectrochim. Acta A. 2014: 132; 815–820.

57. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems ans promises. Mol. Pharm. 2007; 4: 807-818.

58. Burgos-Morón E, Calderón-Montaño JM, Salvador J, Robles A, López-Lázaro M. The dark side of curcumin. Int. J. Cancer. 2010; 126: 1771–1775.

59. Mollazade M, Nejati-Koshki K, Akbarzadeh A, Zarghami N, Nasiri M, Jahanban-Esfahlan R, Alibakhshi A. PAMAM dendrimers augment inhibitory effects of curcumin on cancer cell proliferation: possible inhibition of telomerase. Asian Pac. J. Cancer Prev. 2013; 14: 6925–6928.

60. H. Tang, C. J. Murphy, B. Zhang, Shen Y, Sui M, Van Kirk EA, Feng X, Murdoch WJ. Amphiphilic curcumin conjugate-forming nanoparticles as anticancer prodrug anddrug carriers: in vitro and in vivo effects.Nanomedicine. 2010; 5: 855–865.

61. Shindikar A, Singh A, Nobre M, Kirolikar S. Curcumin and resveratrol as promising natural remedies with nanomedicine approach for the effective treatment of triple negative breast cancer. J. Oncol. 2016; 2016.

62 . Flaig TW, Gustafson DL, Su L-J, Zirrolli JA, Crighton F, Harrison GS, Pierson AS, Agarwal R, Glodé LM. A phase

I and pharmacokinetic study of silybin-phytosome in prostate cancer patients. Invest. New Drugs. 2007; 25: 139–146.

63. Bosch-Barrera J, Sais E, Cañete N, Marruecos J, Cuyàs E, Izquierdo A, Porta R, Haro M, Brunet J, Pedraza S, Menendez JA. Response of brain metastasis from lung cancer patients to an oral nutraceutical product containing silibinin. Oncotarget. 2016; 7: 32006–32014.

64. Singh RP, Agarwal R. Cosmeceuticals and silibinin. Clin. Dermatol. 2009; 27(5); 479–484.

65. Kvasnicka F, Biba B, Sevcik R, Voldrich M, Kratka J. Analysis of the active components of silymarin. J. Chromatogr. A. 2003; 990: 239–245.

66 . Tedesco D, Tava A, Galletti S, Tameni M, Varisco G, Costa A, Steidler S. Effects of silymarin, a natural hepatoprotector, inperiparturient dairy cows. J. Dairy Sci. 2004; 87: 2239–2247.

67. Huang X, Wu Z, Gao W, Chen Q, Yu B. Polyamidoamine dendrimers as potential drug carriers for enhanced aqueous solubility and oral bioavailability of silybin. Drug Dev. Ind. Pharm. 2011; 37: 419–427.

68. Chávez G, Campos CH, Jiménez VA, Torres CC, Díaz C, Salas G, Guzmán L, Alderete JB. Polyamido amine (PAMAM)-grafted magnetic nanotubes as emerging platforms for the delivery and sustained release of silibinin. J. Mater. Sci. (2017); 52: 9269–9281.

69. Kim JB, Yu JH, Ko E, Lee KW, Song AK, Park SY, ShinI, HanW, Noh DY. The alkaloid berberine inhibits the growth of anoikis-resistant MCF-7 and MDA-MB-231breast cancer cell lines by inducing cell cycle arrest. Phytomedicine. 2010; 17: 436-440.

70. Chen W, Miao YQ, Fan DJ, Yang SS, Lin X, Meng LK. Bioavailability study of berberine and the enhancing effects of TPGS on intestinal absorption in rats. AAPS Pharm. Sci. Tech. 2011; 12: 705-711.

71. Gupta L, Sharma AK, Gothwal A, Khan MS,Khinchi MP, Qayum A, Singh SK, Gupta U. Dendrimer encapsulated and conjugated delivery of berberine: A novel approach mitigating toxicity and improving in vivo pharmacokinetics. Int. J. Pharm. 2017; 528: 88-99.

72. Pandith H, Zhang X, Thongpraditchote S, Wongkrajang Y, Gritsanapan W, Baek SJ. Effect of Siamweed extract and its bioactive component scutellarein tetramethyl ether on anti-inflammatory activity through NF-κB pathway. J. Ethnopharmacol. 2013; 147: 434–441.

73. Shadrack DM, Mubofu EB, Nyandoro SS. Synthesis of polyamidoamine dendrimer for encapsulating tetramethyl scutellarein for potential bioactivity enhancement. Int. J. Mol. Sci. 2015; 16: 26363–26377

74. Ikemoto S, Sugimura K, Yoshida N, Yasumoto R, Wada S, Yamamoto K, Kishimoto T. Antitumor effects of Scutellariae radix and its components baicalein, baicalin, and wogonin on bladder cancer cell lines. Urology. 2000; 55: 951–955.

75. Chen H, Gao Y, Wu J, Chen Y, Chen B, Hu J, Zhou J. Exploring therapeutic potentials of baicalin and its aglycone baicalein for hematological malignancies. Cancer Lett. 2014; 354: 5–11.

76. Li-Weber M. New therapeutic aspects of flavones: the anticancer properties of Scutellaria and its main active constituents Wogonin, Baicalein and Baicalin. Cancer Treat. Rev. 2009; 35: 57–68.

77. Chen Y, Minh Le V, Liu J, Angelov B, Drechsler M, Garamus VM, Willumeit-Romer R, Zou A, Baicalin loaded in folate-PEG modified liposomes for enhanced stability and tumor targeting. Colloids Surf. B: Biointerfaces. 2016; 140: 74–82.

78. Chen Y, Minh LV, Liu J, Angelov B, Drechsler M, Garamus VM, Willumeit-Römer R, Zou A. Baicalin loaded in folate-PEG modified liposomes for enhanced stability and tumor targeting. Colloids Surf. B Biointerfaces. 2016; 140: 74-82.

79. Pavan GM, Albertazzi L, Danani A. Ability to Adapt: Different Generations of PAMAM Dendrimers Show Different Behaviors in Binding siRNA. J. Phys. Chem. B. 2010; 114: 2667–2675.

80. Lv T, Yub T, Fang Y, Zhang S, Jiang M, Zhang H, Zhang Y, Li Z, Chena H, GaoY. Role of generation on folic acid-modified poly(amidoamine) dendrimers for targeted delivery of baicalin to cancer cells. Mater. Sci. Eng. C. 2017; 75: 182–190.

81. Silva MM, Santos MR, Caroço G, Rocha R, Justino G, Mira L. Structure-antioxidant activity relationships of flavonoids: a re-examination. Free Radic. Res. 2002; 36: 1219–27.

82. Hubbard GP, Wolffram S, Lovegrove JA, Gibbins JM. Ingestion of quercetin inhibits platelet aggregation and essential components of the collagen-stimulated platelet activation pathway in humans. J. Thromb. Haemost. 2004); 2: 2138–2145.

83. Beil W, Birkholz C, Sewing KF. Effects of flavonoids on parietal cell acid secretion, gastric mucosal prostaglandin production and Helicobacter pylori growth. Arzneimittelforschung. 1995; 45: 697–700.

84. Carluccio MA, Ancora MA, Massaro M, Carluccio M, Scoditti E, Distante A, Storelli C, De Caterina R. Homocysteineinduces VCAM-1 gene expression through NF-kappaB and NAD(P) Hoxidase activation: protective role of Mediterranean diet polyphenolic antioxidants. Am. J. Physiol. Heart Circ. Physiol. 2007; 293: H2344–2354.

85. Lee KM, Hwang MK, Lee DE, Lee KW, Lee HJ. Protective effect of quercetin against arsenite-induced COX-2 expression by targeting PI3K in rat liver epithelial cells. J. Agric. Food Chem. 2010; 58: 5815–5820.

86. Dajas F. Life or death: neuroprotective and anticancer effects ofquercetin. J. Ethnopharmacol. 2012; 143: 383–396.

87. Madaan K, Lather V, Pandita D. Evaluation of polyamidoamine dendrimers as potential carriers for quercetin, a versatile flavonoid. Drug Deliv. 2016; 23: 254-262.

88. Ruela-de-Sousa RR, Fuhler GM, Blom N, Ferreira CV, Aoyama H, Peppelenbosch MP. Cytotoxicity of apigenin on leukemia cell lines: implications for prevention and therapy. Cell Death Dis. [Internet]. 2010; 1: 1–11.

89. Chakravarthi S, Wen CF, Nagaraja HS. Apoptosis and expression of bcl-2 in cyclosporin induced renal damage and its reversal by beneficial effects of 4,5,7-Trihydroxyflavone. J. Anal. Bio-Sci. [Internet]. 2009; 32: 320–327.

90. Viola H, Wasowski C, Levi De Stein M, Wolfman C, Silveira R, Dajas F, Medina JH, Paladini AC. Apigenin, a component of Matricaria recutita flowers, is a central benzodiazepine receptors-ligand with anxiolytic effects. Planta Med. 1995; 61: 213–216.

91. Zbidah M, Lupescu A, Jilani K,Fajol A, Michael D, Qadri SM, Lang F. Apigenin-induced suicidal erythrocyte death. J. Agric. Food Chem. 2012; 60: 533–538.

92. Hawker CJ, Frechet JMJ. Preparation of polymers with controlled molecular architecture. A new convergent approach to dendritic macromolecules. J. Am. Chem. Soc. 1990; 112: 7638-7647.

93. Vinš P, Vermachová M, Drašar P, del Barrio M, Jarne C, Cebolla VL, de CózarA, Zangi R, Cossío FP. Size and branching effects on the fluorescence of benzylic dendrimers possessing one apigenin fluorophore at the core. Tetrahedron. 2013; 69: 10361-10368.

94. Sun M-Y, Ye Y, Xiao L, Rahman K, Xia W, Zhang H. Daidzein: A review of pharmacological effects. Afr. J. Tradit. Complement. Altern. Med. 2016; 13: 117.

95. Ahmed T, Javed S, Tariq A, Budzyńska B, D'Onofrio G, Daglia M, Nabavi SF, Nabavi SM. Daidzein and its effects on brain. Curr. Med. Chem. 2017; 24: 365-375.

96. Xavier CR, Silva APC, Schwingel LC, Borghetti GS, Koester BL, Mayorga P, Teixeira HF, Bassani VL. Improvement of genistein content in solid genistein/beta-cylcodextrin complexes. Quim. Nova. 2010; 33: 587–590.

97. Stancanelli R, Mazzaglia A, Tomamasini S, Calabro ML, Villari V. The enhancement of isoflavones water solubility by complexation with modified cyclodextrins: a spectroscopic investigation with implications in the pharmaceutical analysis. J. Pharm. Biomed. Anal. 2007; 44: 980–984.

98. Lee SH, Kim YH, Yu HJ, Cho NS, Kim TH, Kim DC, Chung CB, Hwang YI, Kim KH. Enhanced bioavailability of soy isoflavones by complexation with beta-cyclodextrin in rats. Biosci. Biotechnol. Biochem. 2007; 71: 2927–2933.

99. Zhao C, Wang Y, Su Y, Zhang H, Ding L, Yan X, Zhao D, Shao N, Ye X, Cheng Y. Inclusion complexes of isoflavones with two commercially available dendrimers: Solubility, stability, structures, release behaviors, cytotoxicity, and anti-oxidantactivities. Int. J. Pharm. 2011; 421: 301-309.

100. Makris DP, Rossiter JT. Hydroxyl free radical-mediated oxidative degradation of quercetin and morin: a preliminary investigation. J. Food Comp. Anal. 2002; 15: 103–113.

101. Choi BC, Choi JS, Han HK. Altered pharmacokinetics of paclitaxel by the concomitant use of morin in rats. Int. J. Pharm. [Internet]. (2006); 323(1-2); 81–85.

102. Noor H, Cao P, Raleigh DP. Morin hydrate inhibits amyloid formation by islet amyloid polypeptide and disaggregates amyloid fibers. Protein Sci. 2012; 21: 373–382.

103. Zhang H, Cao J, Wang Y. Spectroscopic and molecular modeling studies of the interaction between morin andpolyamidoamine dendrimer. Luminescence. 2014; 29: 573–578.