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Review

CYCLODEXTRIN NANOSPONGES AS BIOENHANCERS OF PHYTOCHEMICALS

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ABSTRACT

Bioavailability is the biggest obstacle to the effectiveness of biologically active compounds. Based on a set of physicochemical requirements we can determine if the compound fulfills the drug-like character and if it has the potential to become an active pharmaceutical ingredient (API) with confirmed and thoroughly examined activities. This practice is widely used in drug design of entirely new APIs, but also in search of pharmacological active substances in large compound bases such as plant-derived substances. The chemical structure diversity of plant-based compounds assures that some of them have to be well bioavailable due to good lipid membrane permeability. However, their efficiency is often limited by poor water solubility. Thus, there is a special need for bioenhancers of naturally derived compounds. In this review we present the potential of cyclodextrin nanosponges (CDNSs) as bioavailability enhancers of selected phytochemicals, namely curcumin, resveratrol, oxyresveratrol and quercetin whose very poor water solubility is the biggest obstacle to high efficiency.

KEYWORDS: cyclodextrin nanosponge, phytochemicals, bioavailability, bioenhancers

1. Introduction - the topic of bioavailability and bioenhancers

Druglikeness is a term often used in drug design and drug discovery. It describes the potential of a given compound to have physicochemical properties similar to active pharmaceutical ingredients (APIs), which results in good bioavailability and a substantial impact on human organism. The convenience of determining if the compound meets the requirements for being orally active is that there is no need to synthesize and test the compound on a laboratory scale. Instead, there are methods of empirical approximation if the given compound exerts desirable physicochemical features to be classified as well bioavailable. The most popular and rather accurate of those methods is Lipinski's Rule of 5. It is based strictly on the chemical structure and its physicochemical consequences and determines the druglikeness. Including Veber's criteria which help to discriminate the potential active compounds in large databases, the overall criteria for good bioavailability are presented in Table 1 [1,2].

Table 1. Criteria for classification of well bioavailable compounds, according to Lipinski's Rule of 5.

Molecular mass (g/mol)[1]	< 500
Octanol/water partition coefficient (log*P*)[1]	(-0.4) – 5.6
H-bond donor[1]	< 5
H-bond acceptor[1]	< 10
Rotatable bonds[2]	< 10
Polar surface area (Å^2)[2]	< 140

[1] Lipinski's Rule of 5 criteria; [2] Veber's extended criteria

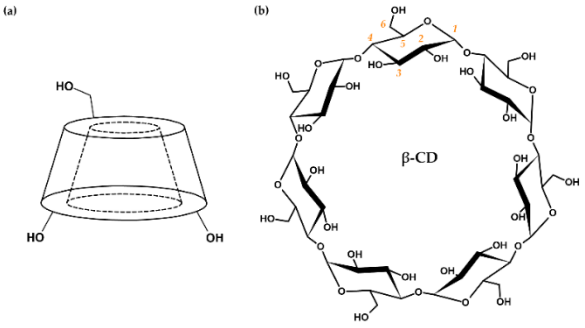
Moderate mobility of the chemical structure ensures the stability of the molecule in different conditions, while low molecular mass and adequate log*P* value assure good permeability through biological membranes. However, despite fulfilling the criteria of a well bioavailable compound and meeting the toxicity requirements, the majority of compounds are not suitable for medicinal use due to low water solubility. The division based on water solubility and lipid membrane permeability is included in the Biopharmaceutics Classification System (BCS, Table 2) [3]. Chemical alternation of the molecule

structure by the addition of hydrophilic substituents is a way to solve this problem, but it could influence the pharmaceutical activity of a compound. Thus, a safer and less time- and material-consuming pathway is the implementation of compounds into drug transporting systems.

Table 2. Classification of compounds according to the Biopharmaceutics Classification System.

Biopharmaceutics Classification System	
Class I	**Class II**
High water solubility	Low water solubility
Great membrane permeability	Great membrane permeability
Class III	**Class IV**
High water solubility	Low water solubility
Poor membrane permeability	Poor membrane permeability

Cyclodextrins (CDs) could play the role of solubility enhancers owing to their ability to encapsulate lipophilic compounds inside the cone-like cavity whose outer surface is strewn with primary and secondary hydroxyl groups (Fig. 1a) [4-6]. The CDs consist of multiple glucose units linked via α-(1→4)-glycosidic bonds. We can distinguish several types of CDs based on the number of glucose units and a variety of derivatives, being the basic CD with an additional substituent instead of one of the hydroxyl groups. Out of the entire group of compounds, the β-cyclodextrin (β-CD, Fig. 1b), consisting of seven units, is most commonly used because of its non-toxicity, low production costs, and the highest stability constants of



complexes with drugs [7,8].

Fig 1. (a) Schematic representation of the CD shape with outer hydroxyl groups and the inner cavity; (b) chemical structure of β-CD.

However, a stability constant of several hundred M^{-1} can result in a dissociation of the CD ring and a release of its constituents. Also, one CD molecule can be host mostly to one drug molecule [9,10]. Improvement of stability of complexes and loading capacity enhancement is available thanks to many hydroxyl groups capable of undergoing various reactions including polymerization. The use of structurally different cross-linkers (Fig. 2) in varying molar ratios (CD:cross-linker molar ratio, 1:*n*) enables one to obtain CD-based polymers called cyclodextrin nanosponges (CDNSs) [11,12]. In comparison with plain CDs, the CDNSs have a much higher loading capacity. The drug can be encapsulated inside the CD cavity and form more durable inclusion complexes, or be entrapped inside the nanochannels, the structures formed between CD units and cross-linkers in the form of less stable non-inclusion complexes (Fig. 3) [13-15]. This results in a much higher solubilizing improvement capacity as compared to plain CDs.

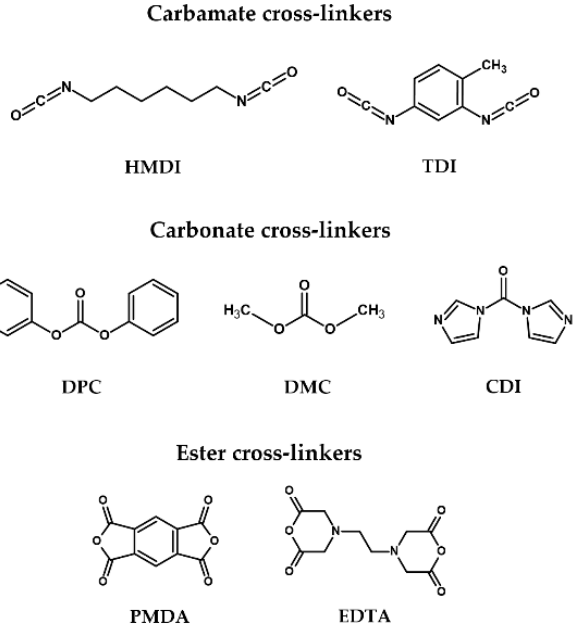


Fig 2. The chemical structure of selected cross-linkers (HMDI, hexamethylene diisocyanate; TDI, toluene diisocyanate; DPC, diphenyl carbonate; DMC, dimethyl carbonate; CDI, carbonyldiimidazole; PMDA, pyromellitic dianhydride; EDTA, ethylenediaminetetraacetic dianhydride).

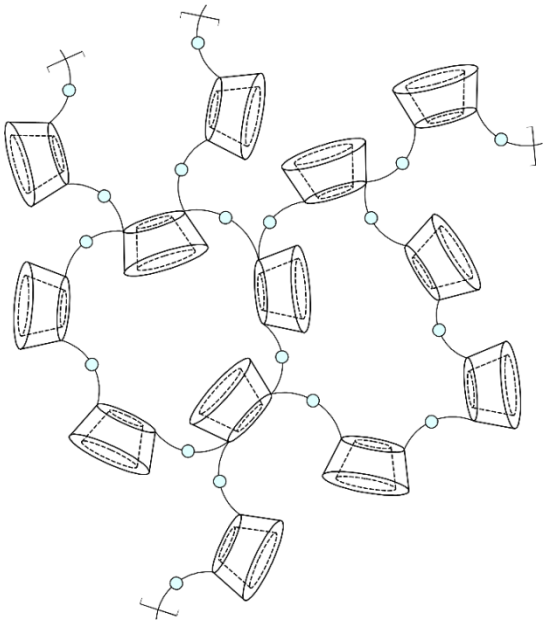


Fig 3. Schematic representation of the CDNS structure. Blue beads represent cross-linkers which form with CDs nanochannels capable of drug encapsulation. Adapted from [16].

The role of CDNSs as bioenhancers was thoroughly examined using many types of registered drugs including anti-inflammatory drugs [17,18], antibiotics [19], antivirals [20], anticancer drugs [21,22], and finally antihypertension [23] and psychiatric drugs [24,25]. However, the beneficial effects of CDNSs can also be used for plant-derived compounds. Polyphenols are one of the

biggest groups of phytochemicals that consists of a variety of phenol-based substances, ranging from macromolecules, usually found in the group of tannins, to smaller compounds belonging to the flavonoid group [26]. The physicochemical properties of the latter usually classify them as potential well bioavailable compounds, but their poor water solubility often limits their use substantially. In what follows we present some examples.

2. Phytochemicals in need (of bioavailability enhancement)

Curcumin (Cur, Fig. 4a) is the leading compound of a group of curcuminoids, linear diarylheptanoids belonging to the group of flavonoids. It is derived from the rhizome of turmeric (*Curcuma longa*) which was shown to possess antioxidant, anti-inflammatory and anticarcinogenic activities [27]. It was proven in various animal and human models that Cur is well tolerated and safe in a wide spectrum of administered doses [28,29]. Nonetheless, the bioavailability of Cur is strongly reduced due to its water insolubility (< 1 μg/ml) [30-32]. This results in poor absorption from the gastrointestinal tract, which contributes to rapid elimination from the organism [33]. Several studies showed the repercussions of the mentioned characteristics such as an inadequate serum concentration to the administered dose, invalid tissue distribution and a short half-life [34].

Resveratrol (Res) and its analog – oxyresveratrol (Oxy) (Fig. 4b) – belong to the class of stilbenoids that can be found in high concentrations in peanuts, mulberries and grape juice. As phytoalexines, they have antibacterial properties, but also anti-inflammatory, antioxidant, cardio-, neuro-, and chemoprotective activities [35,36]. However, due to high photosensitivity and low water solubility (Res: < 0.1 mg/ml; Oxy: < 1 mg/ml), their poor bioavailability prevents the beneficial effect of the majority of administered doses of Res and Oxy [37,38].

Quercetin (Que, Fig. 4c) is one of the basic flavonols, anthoxanthins belonging to the group of flavonoids. It was shown to possess anticancer activity against some cancer cell types and enhance the effect of other drugs by reversing multidrug resistance [39,40]. Owing to its chemical structure which is rich in hydroxyl groups, Que has also strong antioxidant properties [41]. However, similarly to Cur, the Que aglycon exhibits very poor bioavailability due to very low water solubility (< 60 μg/ml), which results in bioavailability at a level of 1-5% [42,43].

It is worth noting that all the mentioned compounds fulfill the requirements of good oral bioavailability (Table 3) [37,42,44,45], but the only missing component is a boost

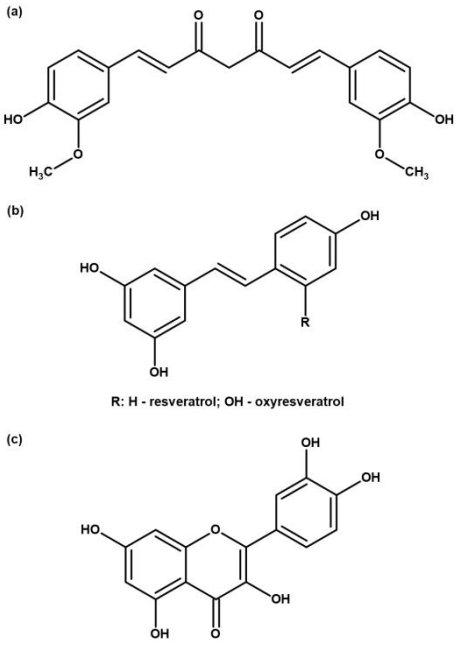


Fig 4. The chemical structure of (a) curcumin, (b) resveratrol/oxyresveratrol and (c) quercetin.

of water solubility. This however can be obtained via implementation into cyclodextrin nanosponges. We will investigate the legitimacy of using CDNS in the case of Cur, Res, Oxy, and Que and their influence on the release profile as well as whether or not the implementation into CDNS would disrupt the activity of selected compounds.

3. Materials and methods

For the purpose of this review, a literature search was carried out using the Web of Science database with the keywords "cyclodextrin nanosponges", "curcumin", "resveratrol", "oxyresveratrol" and "quercetin". The studies written in the English language during the years 2011-2024 were considered.

4. Bioenhancement activity of CDNS

4.1. Water solubility improvement

Each of the examined CDNSs showed an increase in water solubility of a given compound, which is a very promising result for the overall use of CDNSs as water solubility enhancers (Table 4). It is worth mentioning that some CDNS types showed better solubilizing efficiency than others, e.g. Cur-loaded β-CD:DMC [47] and β-CD:EPI [48] or Res-loaded β-CD:CDI [49]. This phenomenon suggests that the choice of the appropriate cross-linker

Table 3. A comparison of physicochemical parameters of well available compounds with selected phytochemicals.

Parameter	Well bioavailable compound	Curcumin	Resveratrol	Oxyresveratrol	Quercetin
Molecular mass (g/mol)	< 500	368.40	228.24	244.24	302.23
Octanol/water partition coefficient (log*P*)	(-0.4) – 5.6	3.2*	3.1*	2.8*	1.5*
H-bond donor	< 5	2	3	4	5
H-bond acceptor	< 10	6	3	4	7
Rotatable bonds	< 10	8	2	2	1
Polar surface area (Å^2)	< 140	93.1	60.7	80.9	127

* log*P* calculated as XLogP3-AA, based on a more precise algorithm including the contribution of each atom in the molecule [46].

Table 4. The results of water solubility and release profile studies of selected phytochemical-CDNS complexes.

Drug	CDNS	Water solubility		Release profile		Ref.
		1:n	Solubility increase	Plain drug	Drug-CDNS complex	
Cur	ß-CD:DPC	1:2	5.8-fold	-	Release rate and cumulative drug released percent enhancement for both CDNS (1:2) types in 0.1N HCl solution, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and water, greater for ß-CD:PMDA (1:2) as compared with ß-CD:DPC (1:2)	[32]
		1:4	4.6-fold			
		1:6	4.5-fold			
		1:8	3.5-fold			
	ß-CD:PMDA	1:2	18.2-fold			
		1:4	10.5-fold			
		1:6	7.5-fold			
		1:8	5.6-fold			
	ß-CD:DMC	-	52-fold	-	Initial burst release (~8% in 1 hour) Sustained release (~25% in 24 hours)	[47]
	ß-CD:EPI	1:2	59-fold	-	Initial burst release (~25% in 6 hours) Sustained release (~27% in 48 hours)	[48]
		1:4	47-fold		Initial burst release (~23% in 6 hours) Sustained release (~33% in 48 hours)	
		1:8	34-fold		Initial burst release (~18% in 6 hours) Sustained release (~37% in 48 hours)	
	ß-CD:DPC	1:4	2.95-fold	-	Enhancement of release rate as compared with plain drug (CDNS 1:6)	[50]
		1:6	2.55-fold			
		1:8	2.51-fold			
	ß-CD:DPC	1:8	~2.5-fold	-	-	[53]
	ß-CD:EDTA	1:8	~1.5-fold	-	-	
	ß-CD:PMDA	1:4	-	-	Initial burst release (~60% in 8 hours) Sustained release (~100% in 40 hours)	[54]
	ß-CD:PMDA	1:2	-	No release observed in the first 4 hours	~10-fold release enhancement in 8 hours	[55]
Res	ß-CD:PMDA	1:4	-	Release observed in the first 4 hours	~2.5-fold release enhancement in 8 hours	
	ß-CD:CDI	1:2	33-fold	~10% in 2 hours	~55% in 2 hours	[49]
		1:4	48-fold		~95% in 2 hours	
	ß-CD:DPC	1:2	~3.2-fold	-	Release rate and cumulative drug released percent enhancement for both CDNS (1:4) types in 0.1N HCl solution and pH 6.8 phosphate buffer, greater for ß-CD:PMDA (1:4) as compared with ß-CD:DPC (1:4)	[51]
		1:4	~3.4-fold			
		1:6	~3.1-fold			
	ß-CD:PMDA	1:2	~3-fold			
		1:4	~3.4-fold			
		1:6	~3-fold			
	ß-CD:CDI	1:4	~3-fold	10.3% in 24 hours	47.74% in 24 hours	[38]
Oxy	ß-CD:CDI	1:4	~2-fold	~100% in 5 hours	60% in 24 hours	
	ß-CD:CDI	1:4	-	70% in 12 hours (pH 7.4)	45% in 12 hours (pH 7.4) 39% in 12 hours (pH 5.5)	[56]
Que	ß-CD:DPC	1:2	-	~1% in 2 hours ~3% in 24 hours	Rapid burst release (~100% in 1 hour)	[43]
		1:4	-		Initial burst release (~30% in 1 hour Sustained release (~95% in 24 hours)	

ß-CD:DPC	1:2	~6-fold	~3% in 6 hours ~4% in 24 hours	Rapid burst release (~100% in 1 hour)	[52]
	1:4	~14.5-fold		Sustained release	
	1:6	~15-fold		Sustained release	
	1:8	~10-fold		Initial burst release (in the first 2 hours) followed by sustained release	
	1:10	~5-fold		Initial burst release (in the first 2 hours) followed by sustained release	

Abbreviations: DMC, dimethyl carbonate; EPI, Epiclon B-4400; DPC, diphenyl carbonate; EDTA, ethylenediaminetetraacetic dianhydride; CDI, carbonyldiimidazole.

leads to substantial solubility enhancement, probably due to the chemical structure and chemical character of the linking agent and favorable incorporation of the drug in the form of inclusion complexes. Also, it can be seen that 1:*n* exerts some influence on solubility enhancement. For Cur-loaded CDNS, the solubilizing efficiency is the highest at the lowest 1:*n* because of steric hindrances caused by a long linear structure of the compound [32,48,50]. Complexes of smaller Res [49,51] and Que [52] with different CDNSs showed the highest solubilizing efficiency for medial 1:*n* for which the saturation of polymeric matrix was obtained. A further increase of 1:*n* contributed to the branching of the polymer, resulting in obstacles in the formation of inclusion complexes. Thus, to obtain the highest solubilizing efficiency the screening through different CDNS types and different 1:*n* used seems to be advisable.

4.2. Release profile modulation

The results of *in vitro* release profile studies showed that the use of CDNSs enhanced the release rate and increased the cumulative release percent of Cur, Res, and Que as compared with plain compounds, regardless of the CDNS type or the applied 1:*n* ratio. The incorporation of selected compounds resulted in a change into one of three release kinetic types: rapid burst release, sustained release, or biphasic release. Rapid burst release occurs in the case when the compound is incorporated into CDNS mainly in the form of non-inclusion complexes. This can be the result of a combination of solubility enhancement and insufficient cross-linking occurring for the CDNS matrices with a low 1:*n* ratio from which the compound can be released without resistance coming from the weakly polymerized matrix [43,52]. With the increase of 1:*n*, the matrix structure becomes more organized and the compounds can be encapsulated simultaneously and equally in the form of inclusion and non-inclusion complexes. This situation results in a sustained release which is a combination of the initial release from a weakly complexed compound in non-inclusion complexes, followed by the prolonged release from a stronger complexed compound in inclusion complexes [49,21]. A further increase of 1:*n* results in the branching of the polymers and limiting the access to the CD cavities, which results in a renewed increment of non-inclusion complexes formation. This results in a biphasic release model which is similar to the sustained release with a more pronounced initial release phase [43,47,52,54]. Naturally, the release model also depends on the applied CDNS type and the encapsulated compound itself. The use of ß-CD:DPC and ß-CD:PMDA for Cur and Res complexation showed the advantage of ß-CD:PMDA in the release rate and the cumulative release percent in a variety of conditions, which may be addressed to the more hydrophilic nature of PMDA resulting in better wettability of the CDNS surface, which in turn together with solubility enhancement results in better release improvement as compared with DPC-based CDNS [32,51,55]. The initial burst release observed for Cur-loaded ß-CD:EPI decreases in denser CDNSs due to steric hindrances occurring between the matrix and a long linear structure of Cur [48]. In the case of Oxy, its incorporation into CDNS results in slowing the release rate and transforming a fast release into a sustained one, which is favorable in the aspect of possible cytotoxic adverse effects [38,56]. Overall, the influence of CDNS on the release rate of plant-based compounds is beneficial with much flexibility in the release profile modification, which can be useful in planning the formulations for the chosen ailment.

4.3. Biological activity evaluation

The CDNSs are known for their non-toxic activity [54]. However, the antibiotics or anticancer drugs that can be transported by CDNSs exert a cytotoxic effect. Thus, it should be verified whether or not the encapsulation of a cytotoxic compound would limit its effectiveness. The same applies to plant-based compounds. The most commonly used cytotoxic screening test is the MTT assay which is based on color change in reaction and informs about the viability of cell lines tested with a given compound. The MTT assay can also be used to confirm the non-toxic or cytotoxic activity. In the case of Cur, the MTT assay showed no adverse cytotoxic effect on healthy cell lines of Cur-loaded ß-CD:EPI and ß-CD:PMDA on MCF 10A (human epithelial cell line) [48,54] and Cur-loaded ß-CD:DPC on L929 (mouse fibroblast cell line) [57]. On the other hand, the MTT assay against the predominantly used cancerous cell line - MFC-7 (human breast cancer cell line) showed no change [32,47] or enhancement of the cytotoxic effect [54,55] after Cur encapsulation into different types of CDNS. Similarly, the MTT assay on MCF-7, HCPC-1 (hamster buccal mucosa cancer cell line), DU-145, PC-3 (human prostate cancer cell lines), HT-29 and HCT-116 (human colon cancer cell lines) showed an increase of the cytotoxic effect of Res and Oxy as a result of the increase of water solubility and bioavailability by the implementation into CDNSs [38,49,51,55,56]. The effect of the compound, the same as its water solubility and release profile, can be altered by the type of the applied CDNS. For example, studies on 4T1 human breast cancer cell line showed a different effect of Cur-loaded ß-CD:EPI depending on the 1:*n* ratio. In the first 24 hours, the inhibitory effect was higher for CDNS with lower 1:*n*, whereas after 48 hours the pattern reversed [48]. Those results are strictly connected with the influence of the CDNS structure on the release profile

(as described above) and they show that the duration and potency of the compound can be regulated by the choice of nanosponge with specific characteristics, which can be changed as early as during the synthesis process.

Apart from the cytotoxic effect, plant-based compounds often exert an antioxidative effect owing to their chemical structure which is rich in hydroxyl groups (Figure 4). The results of the DPPH assay, the most commonly used test for antioxidant activity, showed that the loading of Res and Oxy into ß-CD:CDI resulted in a significant enhancement of free radical scavenging activity as compared with plain Res and Oxy [38]. As concerns Que, the DPPH, anti-superoxide formation and superoxide-anion scavenging activity assays showed a several hundred-fold enhancement of the antioxidant activity of CDNS complexes as compared with plain Que [52], which makes CDNSs great enhancers of radical scavenging activity.

5. Conclusions

As shown by the presented results, the use of CDNSs for the transport of plant-based compounds is justified and very promising. Being the enhancers of water solubility, the CDNSs contribute to bioavailability improvement, which leads to a greater pharmacological effect. Moreover, scrutiny of the available research makes it possible to determine different patterns of the influence of CDNS on physicochemical properties and pharmacokinetics of encapsulated plant-based compounds. The knowledge and understanding of the network of those dependencies are currently in progress for registered drugs [16]. Further investigations are necessary into plant-based compounds as concerns the implementation of CDNSs as bioavailability enhancing agents.

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