Review

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Review

Porous Silica Nanomaterials as Carriers of Biologically Active Natural Polyphenols: Effect of Structure and Surface Modification

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Abstract: For centuries, humans have relied on natural products to prevent and treat numerous health issues. However, biologically active compounds from natural sources, such as polyphenols, face significant challenges, including low solubility, rapid metabolism, and instability, which hinder their effectiveness. Advances in science and nanotechnology have provided solutions to overcoming these problems through the use of porous silica materials. These materials possess unique properties, such as a high specific surface area, adjustable particle and pore sizes, and a surface that can be easily and selectively modified. In this review, we summarize and discuss findings on how the pore and particle size, structure, and surface modification of silica materials influence the preparation of efficient delivery systems for biologically active polyphenols from natural sources. The available data demonstrate how parameters such as adsorption capacity, release and antioxidant properties, bioavailability, solubility, stability, etc. of the studied delivery systems could be affected by the structural and chemical characteristics of the porous silica carriers.

Keywords: porous silica; drug delivery; surface modification; natural bioactive compounds; polyphenols

1. Introduction

Nanotechnology is considered one of the most rapidly developing sciences of the 21st century due to its economic potential in the production of new or optimized products and its expected contributions to minimizing ecological stress and resource consumption [1]. The impact of nanotechnology on the various fields of human life is far-reaching. Proper use of the technology will bring miraculous achievements in the field of medicine, industry, electronics, and other essentials.

Porous nanomaterials offer numerous advantages due to their unique structures and the methods for their obtaining have been intensively studied with regard to these materials' application in different fields. According to the IUPAC definition, porous materials are divided into three classes: microporous (pore size < 2 nm), mesoporous (2–50 nm) and macroporous (>50nm) materials [2]. In addition, also the term ''nanoporous'' is increasingly being used. Among the family of microporous materials, the best-known members are zeolites, which have a narrow and uniform micropore size distribution due to their crystallographically defined pore system. However, zeolites suffer from some limitations due to the mass transfer limitations in the microporous solids when large molecules are involved in the process of interest. Attempts to improve the diffusion in the pores have so far focused on increasing the zeolite pore sizes, on decreasing zeolite crystal size or on providing an additional mesopore system within the microporous crystals [3–5].

The first synthesis of an ordered mesoporous silica material was described in the patent literature in 1970 [6]. This material differs from the zeolites by its' chemical composition as in this case the material is not an aluminosilicate containing anionic Si-O-Al linkages, but a silicate containing anions consisting only of silicon and oxygen. However, the remarkable features of this

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product were not recognized because of its insufficient characterization [7,8]. In 1992, a similar material was obtained by scientists in the Mobil Oil Corporation who discovered the remarkable properties of this novel type of silica and opened up a whole field of research [9]. MCM-41, which stands for Mobil Composition of Matter No. 41, shows a highly ordered hexagonal array of unidimensional pores with a very narrow pore size distribution [7]. The walls, however, very much resemble amorphous silica. The general concept of mesoporous silica synthesis is presented in Figure 1.

Mesoporous silicate materials are synthesized based on the liquid-crystal template mechanism, in which long-chain surfactants are used as structure-determining agents [10].

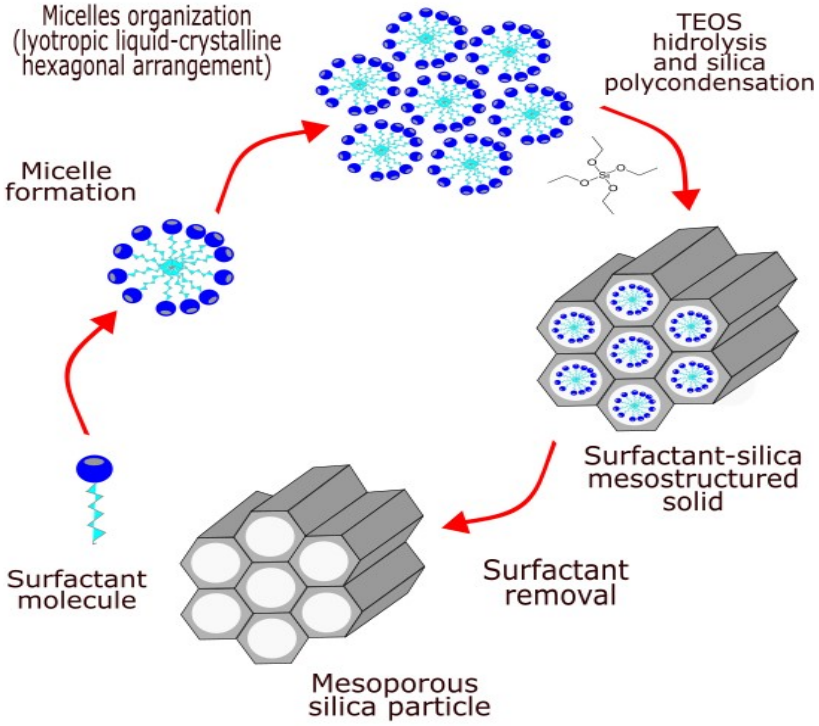

Figure 1. General concept for synthesis of mesoporous silica from micelle template.

Mesoporous silica nanoparticles with their high specific surface area, large pore volume, uniform porosity, stable aqueous dispersion, excellent biocompatibility, *in vivo* biodegradability, and their capability to be functionalized with different organic groups or/and metal (oxide) particles, are attractive candidates for a wide range of biomedical purposes, such as controlled drug and gene delivery, bone tissue regeneration, cell tracking and immobilization of proteins or enzymes, etc. (Figure 2). In addition, silica nanoparticles were generally recognized as safe and listed as an anticaking agent by the United States' Food and Drugs Agency and as food additive (E551) in European Union [8,11–13].

Mesoporous silica materials have been proposed for the first time as carriers for drug delivery in 2001 by Vallet-Regi et al. [10]. They were applied as drug carriers in the field of controlled drug release, to meet the need for prolonged and better-control of drug administration.

Mesoporous materials fulfill the conditions for homogenous distribution of the bioactive molecules through the matrix in contrast with the conventionally used polymeric materials [14–17]. Several key factors should be considered when designing delivery systems based on porous silica: i) the size selectivity – the pore size of the mesoporous materials determines the size of the molecule that can be hosted into the mesopores; ii) interactions - the chemical and the electrostatic interactions between bioactive molecules and the mesopore wall can be easily modified in order to increase the affinity of the host molecule to the carrier and to modify their release profiles; iii) administration – depending of the way of application the size, shape and surface chemistry of the silica particles can

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be modified to enhance the efficiency of the treatment. Due to their unique pore structure when silica materials are applied as carriers in delivery systems they can solve the problem of low water solubility and respectively the bioavailability of some bioactive molecules by finely dispersing them in the pores of the carrier, preventing formation of bigger hardly soluble crystals of the pure drug. Another major problem that can be solved by using porous silica particles as delivery vehicles is reducing the undesirable side effects of some therapeutics by encapsulate them and thus assuring target delivery and controlled release.

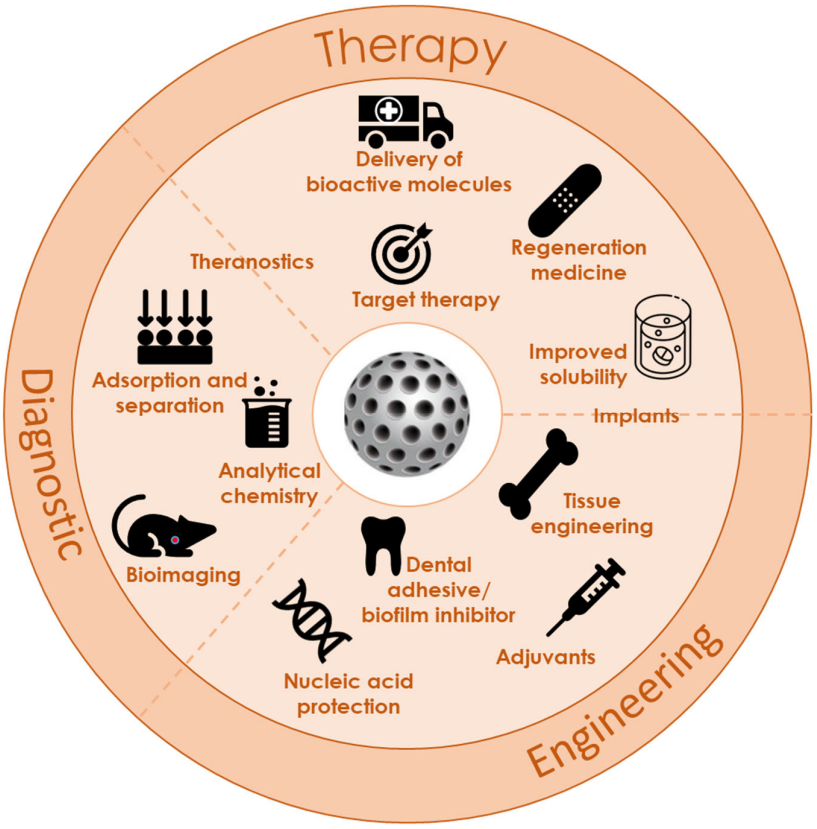

Figure 2. Application of mesoporous materials in various biomedical fields.

For many years porous silica and zeolites have been used to design highly efficient systems for delivery of synthetic therapeutics commonly used in the medical practice. However, the latest tendencies in the therapy and healthy lifestyle are mainly focused on bioactive compounds from natural origin. The botanical and plant-derived drugs market has increasingly grown worldwide as the estimated growth for the next 5 years is 8.18% [18]**.** Encouraged by governmental initiatives and private funds, many academic and industrial groups focus their research on the development of formulations based on naturally-derived health-promoting compounds. One of the biggest groups of natural bioactive compounds considered as extremely promising for prevention and treatment of numerous health issues is the group of polyphenols. Many studies prove their free radical scavenging capacity, antioxidant, anti-inflammatory, analgesic, anti-anxiety, anti-tumor, anti-allergic, antibacterial, antifungal, antiviral, and antidiabetic activity [19–21]. Agents from this group are found in fruits (apples, citruses, berries, etc.) and vegetables (red onion, broccoli, etc.), cereals, olives, extra virgin olive oil, red wine, coffee, green and black tea, chocolate, and flowers [22,23]. Despite the proven high biological activity and health benefits, the development of an efficient pharmaceutical formulation for the application of a compound from natural origin meets challenges related to the low water solubility of the most of these compounds, which is an obstacle in achieving optimal bio accessibility. Other major obstacles to reaching their pharmacological potential are burst release, rapid metabolism, and fast excretion of the dietary polyphenols after administration, which

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leads to low bioavailability [24]. A promising approach to overcoming these drawbacks and to reaching high therapeutic efficiency of polyphenols is the design of a suitable porous silica/zeolite-based delivery system for their application.

2. Porous Silica Materials with Different Structures as Carriers in Delivery Systems of Polyphenols

Porous silica can be obtained with a variety of shapes (spherical, tube, cubic, etc.), sizes (50 nm – 5 μm), surface morphology, pore structure and volume. All of these characteristics can significantly influence the properties of the material. Many studies are focused on clarifying the relationship structure-properties. For example, spherical MCM-41 with hexagonal arrangement of 2D cylindrical mesopores, KIL-2 with wormhole pore structure and zeolite BEA with three-dimensional nanosized pore system, have been used as carriers of natural polyphenol resveratrol (RES, Figure 3). This compound is extremely photosensitive and with low chemical stability, where the trans-form is with higher biological activity, which limits its beneficial therapeutic effects. Thus, loading of resveratrol in nanoporous silica systems is a premise for the stabilization of the most active form and protection from photoinduced degradation. The resveratrol was loaded in these three carriers by solid-state procedure that ensures simultaneous amorphization and loading of the poorly water-soluble drug. The results for resveratrol loading are 32% for MCM-41, 40% for BEA and 37% for KIL-2. The obtained numbers for percentage loaded resveratrol indicate that the structure of the material plays a role in the loading capacity. Resveratrol release carried out in phosphate buffer at pH = 7.4 and repeated 3 times with a period of one week between them shows the presence of only trans-resveratrol. This result is an indication that the loading on the nanoporous carriers prevents the transformation of the supported bioactive trans-form to the less active cis-form. Thus, deposition of resveratrol on powdered silica-based carriers with mesoporous texture resulted in its stabilization and enhanced solubility.

The release profiles of the resveratrol from the loaded supports are similar and total release in about three hours was achieved for all resveratrol-loaded samples. On the contrary, the free resveratrol dissolves much slower. For the KIL-2 support slower initial release profiles are observed and that can be explained by the presence of much larger mesopores formed among the nanoparticles of the KIL-2 carrier, where the formation of bigger hardly soluble crystals is possible. In the case of MCM-41 and the zeolite BEA the presence of multiple pore systems (internal and external mesoporosity in MCM-41, and a simultaneous presence of micro- and mesopores in nanosized zeolite) presumes selective access of resveratrol to and out of the pore system of the supports. This can result in diversity in the release kinetics. The presence of narrower pore channels in the zeolite carrier is the reason for the lower rate of resveratrol delivery from it, compared to MCM-41[25].

Another study compares the mesoporous silica type MCM-41(2D pore structure; spherical particles with sizes in the range of 150–400 nm) and MCM-48 (3D pore structure consists of the interlaced pore system divided by a continuous pore wall; quasi-spherical particles with sizes in the range of 150–400 nm) as carriers for caffeic acid (CA), p-coumaric acid (p-CA) and trans-ferulic acid (FA). The results from thermogravimetrical and surface area measurements evidenced higher loading of all three polyphenols on the MCM-41 carrier in comparison with the MCM-48. This observation can be explained with the difference in the pore structure of the used materials, where, despite the higher pore volume of MCM-48, higher loading for MCM-41 can be a consequence of the easier access into the cylindrical pores. For the same reason the release profiles of polyphenols from MCM-41 and MCM-48 supports differs. For the samples loaded with caffeic acid significant difference can be observed for both silica supports – the release from MCM-48 is slower and the degree of CA recovery for the studied period is only ~50%, as for MCM-41/CA it was ~70%. Similar tendency is noticed for t-FA loaded samples. Unlike the CA and t-FA the release profiles of p-CA for both MCM-41 and MCM-48 are very similar. This indicates that the chemical structure of the loaded molecules and their interactions with the support are also important factors that can influence the release properties of the obtained systems.

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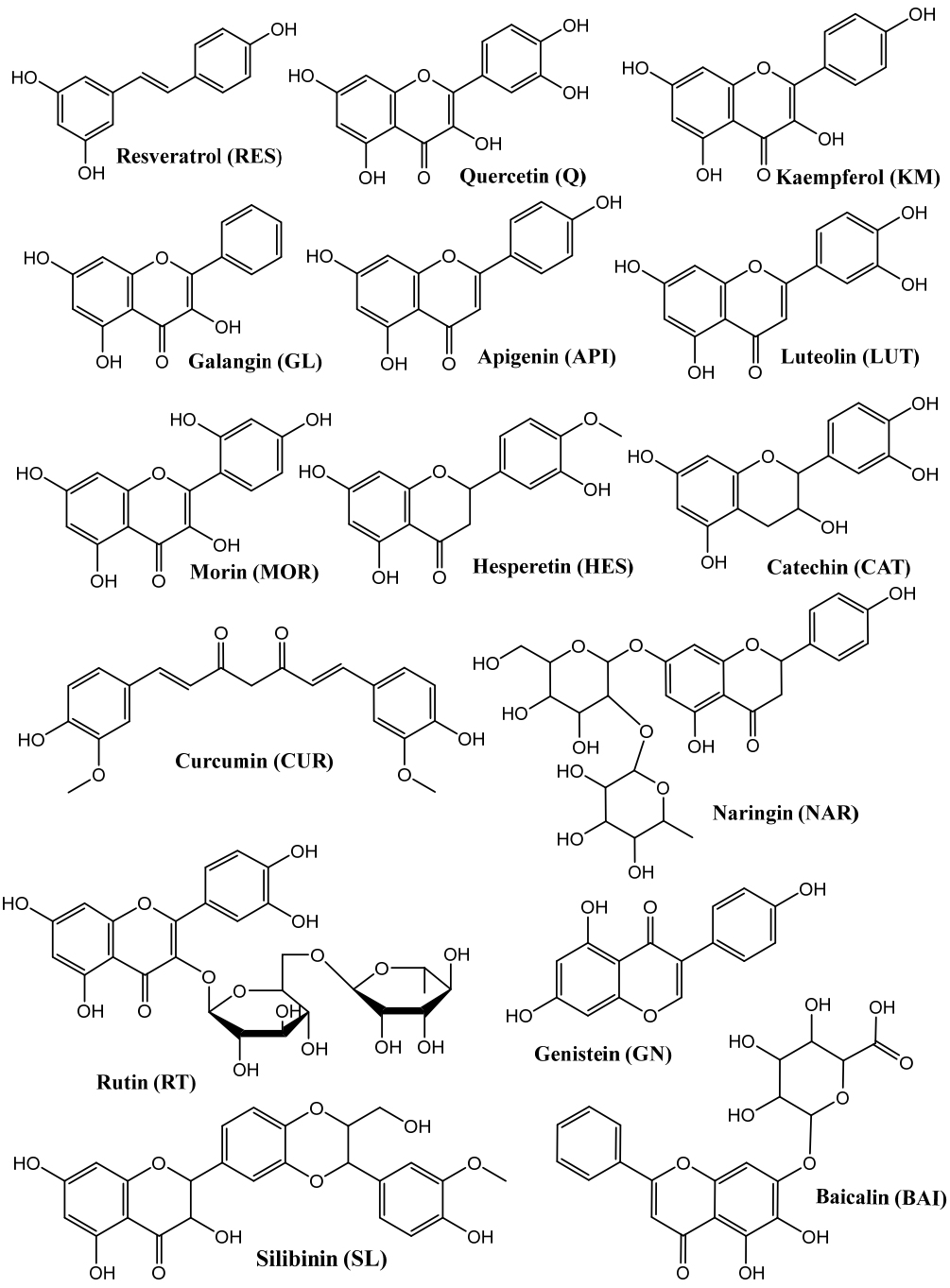

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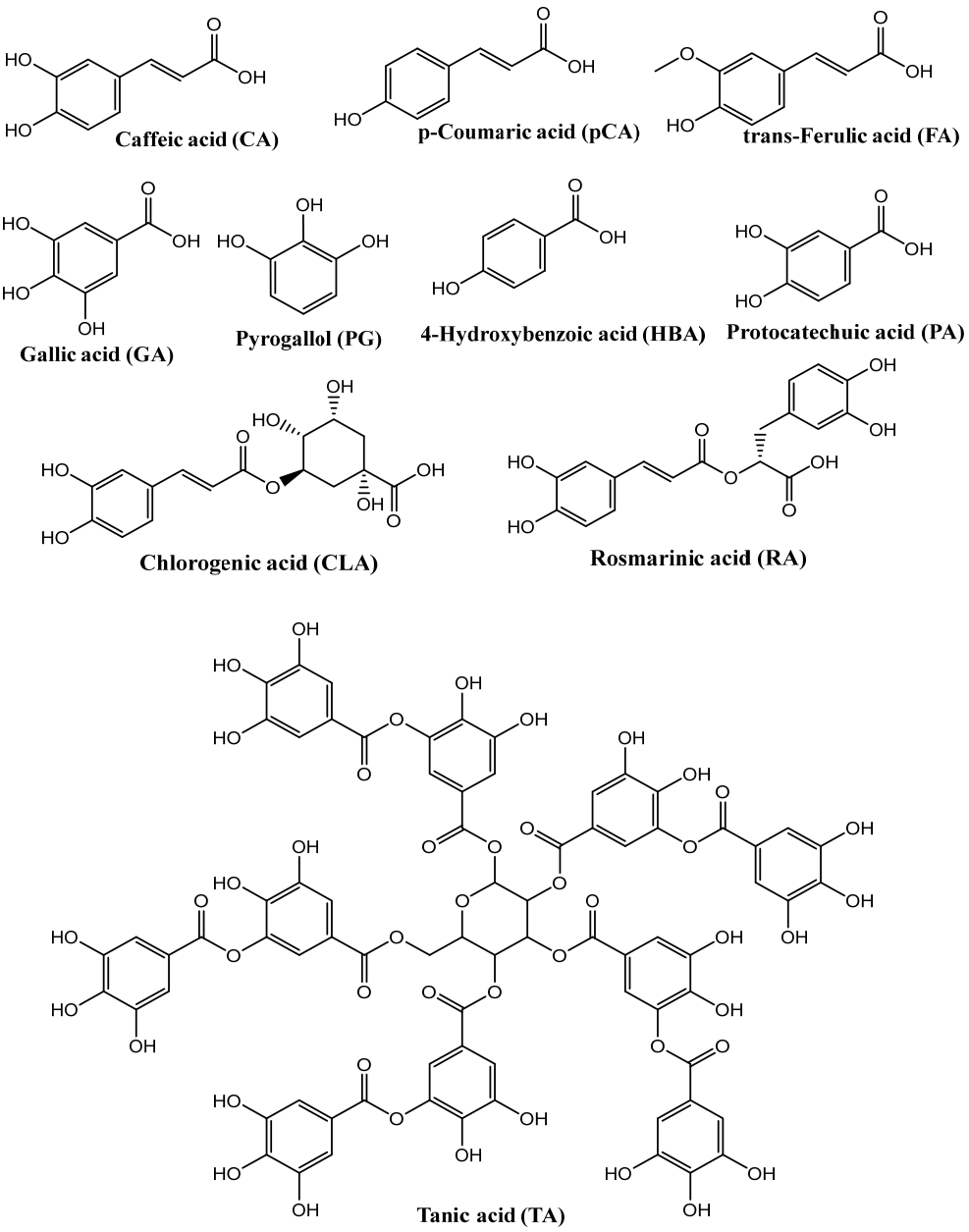

Figure 3. Chemical structure of some polyphenols.

A detailed study compares the two mesostructured silicas with wormhole-like pore arrangement (quasi-spherical HMS (1.4–5.2 μm) and spherical MSU-2 (0.5–1.9 μm) particles) with hexagonal mesostructured silica (rod-like SBA-15 particles (1 × 0.5 μm)) as carriers of quercetin (Q) and naringin (NAR). Their adsorption capacity and encapsulation efficiency as well as their ability to modify the release kinetics and antioxidant activity of the loaded polyphenols were evaluated. For quercetin, HMS showed higher encapsulation and loading capacity than SBA-15 and MSU-2, whereas for naringin the loading capacity for the three supports was similar. The study showed that the HMS material required more time (2 h) than SBA-15 (30 min) to achieve maximum adsorption capacity of quercetin, but it can be considered as more suitable due to its higher encapsulation efficiency. For the naringin, all carriers achieved maximum encapsulation efficiency in 30 min. HMS showed not only the greatest quercetin encapsulation but also the highest amount released at tested pH values (2.0 and 7.0). These observations could be explained with the molecular size of these polyphenols and the

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different textural properties of the materials, and in particular with the pore size which increases from 25.2 Å, through 31.2 Å to 55.5 Å for HMS, MSU-2, and SBA-15, respectively [26].

The significance of the pore structure over the efficiency of the delivery system is well described in a comparative study that used one-, two-, and three-dimensional silica nanocarriers (Figure 4, GA was used as a model drug). For the studied carriers the absorption of GA decreased in the following order: SBA-16 (3D) ~ KIT-6 (3D) > MCM-41 (2D) > ultra large pore FDU-12 (ULPFDU-12; 3D) > Q10 (1D) ~ mesostructured cellular silica foam (MSU-F). The analysis showed that the 3D-type silicas accommodate GA in amorphous (non-crystalline) form while for Q10 silica, ULPFDU-12 and MSU-F the GA was found only in crystalline form. This way, using the same impregnation procedure and conditions, it is possible to control the crystallinity of the loaded compound only by changing the structure of the porous silica. On the other hand, the most favorable impregnation of GA occurs at pH 3, where the tick walls of the 3D material showed significant stability. On the contrary, ULPFDU-12 and MSU-F supports suffer structural damage and textural changes during the impregnation procedure in acidic conditions [27].

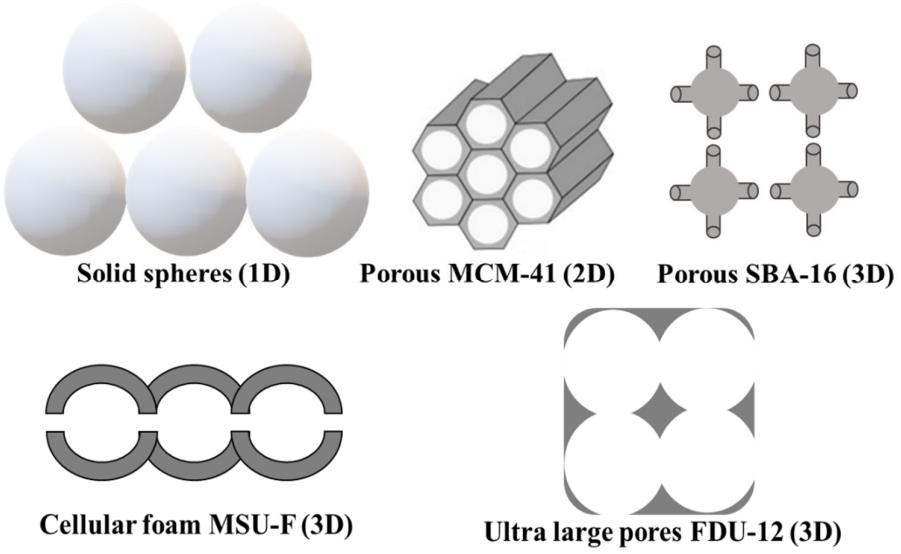

Figure 4. Schematic representation of 1D, 2D, and 3D pore structure of different silica materials.

Regarding the pore size:loaded molecule size ratio, controversial opinions can be found in the literature, and no particular pattern is observed. For example, for the GA (0.8 nm) it was found that an increase of the MCM-41 pore size from 2.4 to 3.4 nm enhanced two times the loaded amount [28], but it was also observed that the adsorption of GA onto SBA-15 (pore size 6 nm) was lower than the adsorption on MCM-41 (pore size 2.5 nm) [29]. On the basis of these results, it can be assumed that there is an optimal ratio pore size:molecule, but no information in the literature was found.

These results clearly showed that the pore structure, textural properties, and morphology of the mesoporous support play a crucial role in the adsorption capacity and release profiles and can influence the properties of the obtained delivery system. Thus, when the delivery system is designed, the choice of porous silica support type is essential and has to be made in accordance with the requirements for application of a particular biologically active substance.

3. Functionalized Porous Silica Materials as Carriers in Delivery Systems of Polyphenols

3.1. Functionalization with Organic Groups

The surface of silica materials is mainly presented of OH-groups, which are not highly selective in reactions of adsorption. A suitable approach to increasing the selectivity of the adsorbent or affinity of the target molecules to the adsorbent is functionalization of the surface with appropriate moieties. In this case, the presence of OH-groups on the silica surface is an advantage as these groups allow easy introduction of different organic groups in one-step procedures. The most commonly used

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modified agents are organosilanes - monomeric Si-containing chemicals with at least one direct silicon-carbon bond in the molecule [30]. The structure of a typical organosilane monomer consists of an organic functional group and organic moieties attached to a silicon atom (Figure 5 a). During the silica surface modification reaction, the Si-OH groups react with the parent silica's OH-groups by hydrolysis and condensation as illustrated in Figure 5 b and c. This way, the organic functional groups remain available on the surface of the silica support and can be involved in further interactions with molecules of interest.

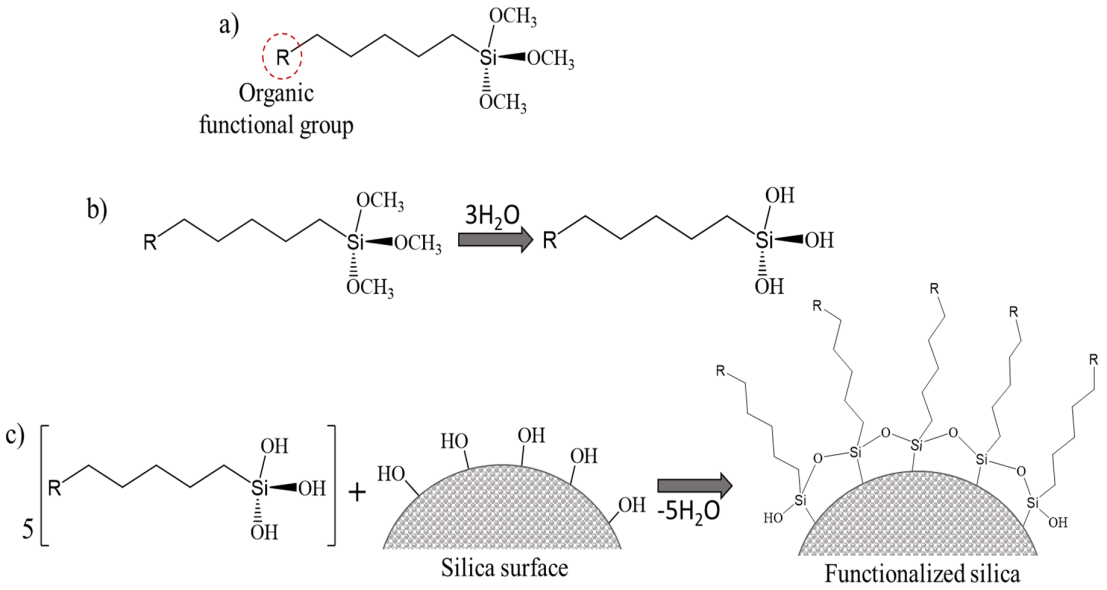

Figure 5. Structure of organosilane (a), hydrolysis of organosilane (b), and schematic presentation of silica surface functionalization with organosilane (c).

The organic group in the modifying organosilane should be selected according to the reactivity of molecules for absorption/immobilization. In the cases when the reversibility of the adsorption process is desired, weaker interactions (electrostatic, H-bonds) between adsorbents and adsorbates are preferred. On Figure 6 are illustrated the two types of weak bonds that occur most commonly between the silica carrier and the cargo molecules.

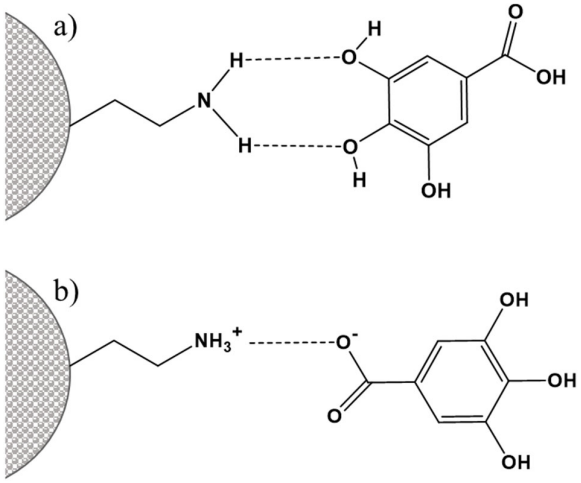

Figure 6. Graphical representation of hydrogen bonding (a) and electrostatic interactions (b) between adsorbent's surface groups and the adsorbate.

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In drug delivery systems modification of the surface of the support could increase the affinity of the bioactive molecule to the silica support and result in more efficient loading. Furthermore, an interaction of the bioactive molecules with the appropriate group from the surface of the carrier can influence the release properties of the already adsorbed molecules, making it possible to achieve controlled release and/or targeted or triggered (photothermal, pH, enzymatic) delivery.

The surface charge of the silica carrier can be easily controlled by modifications with different organic groups. It was shown that the silica surface charge doesn't affect the loading of resveratrol (RES), but can play a role in the release profile of the drug at pH 7.4 and pH 5.5. Therefore, the delivery system obtained on the base of negatively charges silica (PO_3-silica) demonstrated significantly higher anti-proliferative activity on a panel of prostate cancer PC3 cell line compared to the free RES and the system based on positively charged silica (NH_2-silica). In the same study, it was demonstrated that functionalized silica carriers loaded with a combination of polyphenol and chemotherapeutic agent (RES and Docatexal) possess improved sensitization of Docatexal in hypoxia-induced drug resistance in prostate cancer [31].

Using silica particles modified with organic groups as carriers gives the opportunity for obtaining efficient antioxidant systems with a longer lifetime by preventing the deterioration of the antioxidant agent. An example of this is a system based on aminopropyl-modified silica (NH_2-silica) with covalently immobilized gallic acid (GA). The covalent bond was realized by the formation of amide bonds between the amine groups of the silica surface and the carboxyl group of GA activated by the EDC (N-(3-

dimethylaminopropyl)-N′-ethyl carbodiimide hydrochloride) coupler. The electron paramagnetic resonance (EPR) test confirmed that the applied immobilization procedure doesn't compromise the antioxidant activity of the grafted GA molecules and they are capable of forming radicals and are capable of participating in radical scavenging reactions. The prepared nonantioxidant material showed excellent results for scavenging DPPH radicals via fast H-atom transfer reactions. With respect to their application, reusability tests were performed and they confirmed that the obtained materials are reusable and their RSC (radical-scavenging capacity) was not weakened after reactions with the DPPH radicals [32].

In another study, MCM-41, SBA-15, SBA-NH_2, and SBA-SH materials are used as potential carriers of GA. It was found that the adsorption efficiencies increased in order: SBA-15, SBA-SH < MCM-41 < SBA-NH_2. The highest absorption for amino-modified SBA-15 might be a result of ionic interactions between the positively charged silica surface amino (-NH_3^+) groups and the negatively charged carboxyl (R-COO^-) group of GA. In the case of the remaining three supports only weaker hydrogen bonds interactions between the hydroxyl or carboxyl groups of the GA and the silanol groups of the silica surface are possible. In the same study the adsorption and interactions between the amino-modified surface of SBA-NH_2 and the carboxyl group of chlorogenic acid (CGA), protocatechuic acid (PA), and 4-hydroxybenzoic acid (4-HBA) have also been confirmed. The highest adsorption efficiency among the acids onto SBA-NH_2 silica was noticed for CGA, which can be explained with the highest number of functional groups in the molecule of this polyphenol in comparison with the other three. Logically, the increasing of the number of hydroxyl groups in the polyphenol structure increased the absorption efficiency as in this case it follows the order 4-HBA < PCA < GA < CGA for molecules containing 1, 2, 3, or 5 hydroxyl groups, respectively [33]. A similar phenomenon of increased adsorption for amine-modified MCM-41 in comparison with a non-modified material was observed for tannic acid (TA) as well [34]. An interesting study compares the polyphenolic acids (GA, CLA, CA, pCA, and rosmarinic acid - RA) adsorption of mesoporous silica materials functionalized with different amino-silanes ((3-aminopropyl)trimethoxysilane, trimethoxy[3-(methylamino)propyl]silane, N-[3-(trimethoxysilyl)propyl]ethylenediamine and 3-[(trimethoxysilyl)propyl]diethylenetriamine, Figure 7). Regarding the five polyphenol compounds the adsorbed amount for all amino-modified silicates increases in the order GA< CA< pCA< CLA< RA. The results for comparison of the absorption values for the different silica modifications showed that the carrier modified with amino-silane containing 3 nitrogen atoms has the highest adsorption for all phenolic acids, second highest for the carrier containing 2 nitrogen atoms and the least effective

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are the mono nitrogen organosilanes. It can be concluded that the increasing number of amino-group leads to increased adsorption efficiency. Although there is a pattern, there are multiple interactions as steric hindrance, solvent effect, competitive action, hydrogen bonding and electrostatic interactions during the adsorption process that have to be taken into account [35].

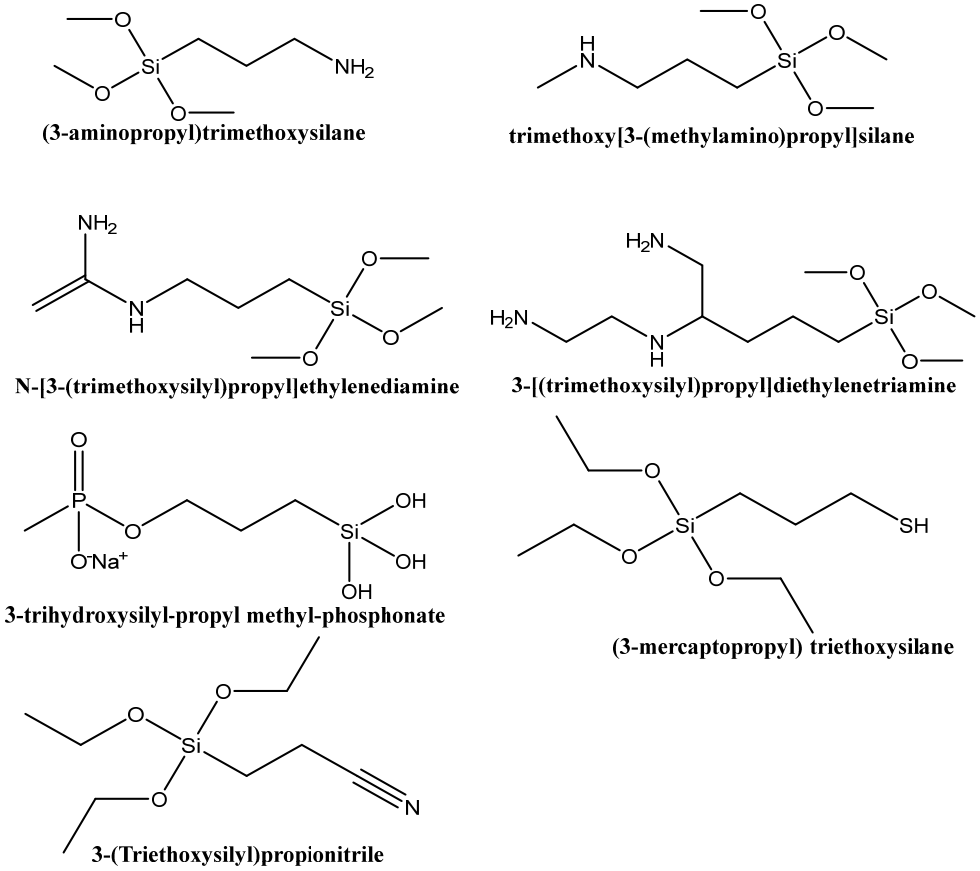

Figure 7. Functionalized organo-silanes.

The animo-modified mesoporous KIL-2 (textural mesoporosity) and order KIT-6 (interpenetrating cylindrical pore system) nanoparticles with sizes around 40 and 60 nm, respectively, were used as curcumin supports. The theoretical calculations suggest that curcumin (in both enol and keto forms) interacts weakly with the amino groups ($(CH_2)_3NH_2$) via phenolic single bond OH group or via keto group with ammonia groups ($(CH_2)_3NH_3^+$). The calculated vibrational frequencies are in good agreement with the obtained IR results [36].

The mesoporous silica materials modified with organic groups were also tested as supports in delivery systems for not only one type of polyphenol, but also for plants' extracts containing a mixture of polyphenols. In a study the polyphenolic extract (grape pomace) loading into MCM-41 silica functionalized with propionitrile (MCM-CN), propionic acid (MCM-COOH), mercaptopropyl (MCM-SH) and propyl sulfonic acid (MCM-SO_3H) moieties was studied. The influence on the extract's biocompatibility and RSA were evaluated for all pure silica and functionalized samples. The result showed that the stability and the RSA of the silica-embedded extract are preserved for a longer time period and the *in vitro* antioxidant effect is improved in comparison with the free polyphenolic extract. The release experiments at pH 5.7 in phosphate-buffered saline (PBS) were evidence of a relationship between the acidity of the silica surface moieties and the amount of released phytochemicals. As the main tendency is decrease of the functional groups' acidity leads to a decreasing of the amount released. The results from intracellular assay showed correlation between the amount of cytosolic ROS and released polyphenolic compounds in PBS – the higher the release the lower the ROS concentration [37].

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3.2. Functionalization with Metal Species

Polyphenols are well known as a good chelating agent, due to the presence of hydroxy and keto-groups in their structure [38]. The most favorable metal-chelating sites in some polyphenol molecules are: (i) the 3-hydroxy-4-ketone groups in the C-ring, (ii) the 5-hydroxy group in the A-ring and 4-carbonyl group in the C–ring, and (iii) 3′,4′-dihydroxy groups in the B-ring (Figure 5) [39].

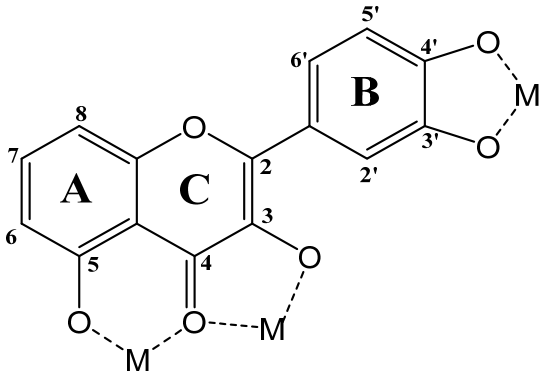

Figure 8. Most favorable chelating sites in flavonoid molecules.

Studies have shown that the formation of polyphenol-metal ion complexes can affect the properties of the parent biologically active molecules and lead, in most cases, to superior antioxidant, antimicrobial, anticancer, and antidiabetic activities, significantly increasing their therapeutic potential [40,41]. For example, the coordination of kaempferol in complexes Ca(II), Sr(II), and Ba(II), or coordination of quercetin, rutin, galangin, and catechin with Cu(II), Fe(II), Al(III) and Zn(II) ions increases their radical scavenging efficiency, as well as their antiproliferative activities on various human cancer cell lines [42–45]. In the *in vivo* experiment vanadium complex of kaempferol was found to possess better antihyperglycemic activity compared to the free flavonoid [46]. Published data demonstrate that the oxidovanadium(IV) complexes with baicalin, apigenin, silibinin, and luteolin have superior antimetastatic action on human lung cancer cell line in comparison with the free ligands [47]. Several studies suggested synergistic effects of polyphenolic ligands in complex with Ru(II)/(III), and, in the majority of the cases, obtained compounds are with improved antiproliferative and/or enzyme inhibitory activity than it was observed for the polyphenols themselves [48]. The metal complexation of flavonoids results in better pharmacological activities and the complexes are characterized with higher stability as *in vitro*, like at *in vivo* conditions [49].

The formation of these complexes changes also the physico-chemical properties of the molecules, such as their absorbance in the UV-Vis region, which makes UV-Vis spectroscopy a suitable method for the detection of complexation. Due to electronic π–π^* transitions, flavonoids are characterized with two absorption bands in the UV-Vis region - benzoyl and cinnamoyl at 240–280 nm and 320–385 nm, respectively (Figure 9), which are bathochromically shifted after chelating with metals [41,50].

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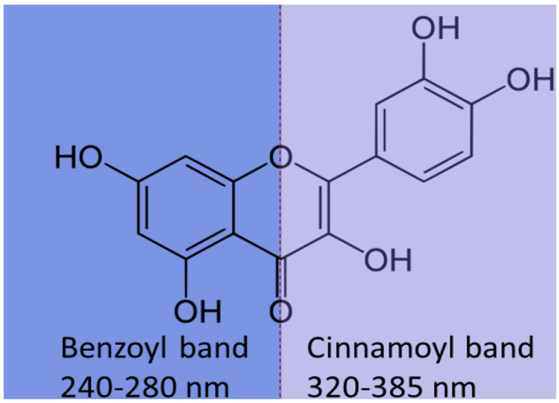

Figure 9. UV-Vis absorption regions for benzoyl and cinnamoyl structures (quercetin molecule is used as an example).

Nevertheless, some of the major drawbacks of these compounds, such as hydrophobicity and low solubility, can't be overcome just by simple complexation with metal ions. On the other hand, polyphenols' ability to interact with metal ions is a promising approach to achieving higher loading capacity by modifying suitable drug carriers with an appropriate metal. Over the last decade, published data suggest metal-modified mesoporous silica materials with different pore structure, particles size, and shape as favorable supports for biologically active polyphenols. Usually, for biomedical applications, as silica surface modifying species are used metal nanoparticles/ions that have beneficial health properties such as Ca, Ag, Zn, Mg, Fe [51–56], this way they can act not only as attaching moiety for the bioactive molecules, but also to contribute to the prevention/treatment of the target problem.

For example, quercetin was loaded on pure silica type MCM-41, SBA-15, and SBA-16, and on Zn-modified analogues prepared by a post-synthesis method (Figure 10). Spectroscopic data suggest interactions between quercetin and the surface of pure or Zn-modified mesoporous silicates, confirming the formation of a Zn-quercetin complex. Theoretical calculations confirmed quercetin's higher binding affinity for the Zn^{2+} cation than to the silanol groups, which are the only functional groups present on the surface of the parent silica. The higher affinity of the quercetin to Zn-containing supports leads to a slower *in vitro* release process at pH 5.5 PBS, in comparison with formulations based on non-modified silica carries. The comparative cytotoxic experiments for the formulations on the basis of SBA-15 mesoporous support show that quercetin encapsulated in Zn-modified silica proved to exert superior antineoplastic potential against HUT-29 cells compared to free drug. Obtained mesoporous silica delivery systems with Zn-quercetin complex showed promising results for further use in dermal formulations [57,58].

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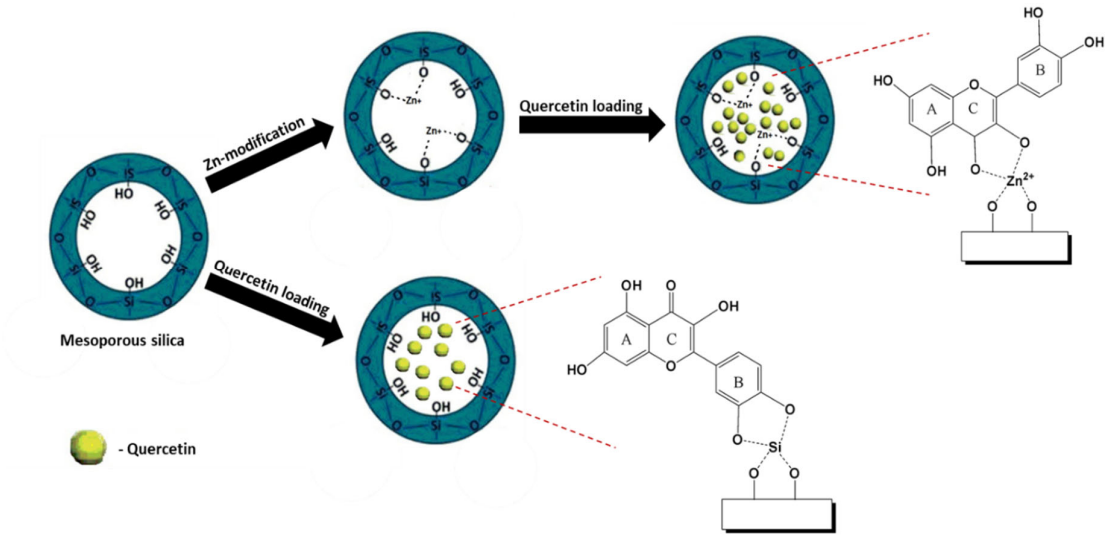

Figure 10. Schematic representation of the quercetin interactions with the surface OH groups from the non-modified and the Zn cation from the modified silica carriers.

Another system, based on Ag-modified MCM-41 porous silica, for topical administration of quercetin has been proposed as here the health-beneficial properties of this polyphenol were combined with those of the silver. For the incorporation of the Ag-species in the silica matrix two different approaches were applied: 1) modification by direct synthesis; or 2) post-synthesis methods. The *in vitro* release process at pH suitable for dermal formulations (5.5) showed lower and incomplete quercetin release for silver-modified samples in comparison with the parent MCM-41. A possible explanation of the observed results is the formation of a strong complex between quercetin and Ag. The high quercetin loading (over 40%) and slower release indicates that the obtained delivery systems are promising for dermal application. The cytotoxicity experiments show that Ag-modified and quercetin-loaded silica carriers prepared by the post-synthesis method exert superior antineoplastic potential against HUT-29 cells compared to free drug [59].

In another study systems for the delivery of morin and hesperetin were designed on the basis of Ag- and Mg-containing SBA-16 nanoparticles. The post-synthesis procedure for modification leads to the incorporation of Mg in the silica framework as ionic species, while for the silver the formation of nanoparticles present in the channels of the carrier and on the outer surface of silica particles was observed. *In vitro* experiments reveal that the formation of metal-flavonoid complexes influences the release of the loaded molecules. It was found that the morin release depends on available surface groups because of the different affinity of its molecules to the surface moieties (-OH, Ag, Mg), while for hesperetin the effect of the carrier surface modification doesn't affect its' release properties, most probably due to the less pronounced interaction of the drug and the carriers. The evaluation of the cytotoxicity and the antioxidant capacity of the obtained delivery systems showed improved properties in comparison with the pure morin and hesperetin [60]. Another work on the topic of Mg-containing silica (MCM-41) studies the influence of the modification procedure (*in situ*, template ion exchange, incipient wetness impregnation) on the physicochemical and pharmacokinetic properties of the obtained delivery system based on these carriers. It was demonstrated that the efficiency of the Mg incorporation and materials' textural properties strongly depends on the applied approach. The as prepared materials were studied as carriers for kaempferol in a delivery system for oral administration. The loading of the flavonoid into the Mg-silica supports leads to improvement of kaempferol's solubility. The evaluation of free RSA against DPPH radicals shows that loading of the flavonoid into the parent and post-synthesis Mg-modified silica supports doesn't compromise their activity. On the contrary, for the delivery system on the basis of MCM-41 modified with Mg by direct synthesis the RSA is decreased nearly in half, which could be the effect of the formation of a strong Mg-kaempferol complex with the Mg species incorporated into the silica walls during the formation

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of the material. In conclusion, different approaches for silica modification with Mg can be used to obtain materials with desired properties [61].

On the basis of Ag-containing silica particles a system for faster healing of wounds by achieving rapid hemostasis and preventing bacterial infection has been developed. A complex system with Janus structure containing mesoporous silica nanoparticles decorated by tannic acid, silver nanoparticles, and calcium ions was obtained in a stepwise manner by reactions of surface modification with NH_2-groups, Ag coordination, followed by reduction reaction between tannic acid and Ag^+, and finally Ca^{2+} coordination (Ca-TA-MSN@Ag, Figure 11). The as-obtained material accelerates the coagulation reaction and causes faster fibrin network formation. These formulations showed excellent biocompatibility and antibacterial activity (~99%) against *E. coli* and *S. aureus* [62].

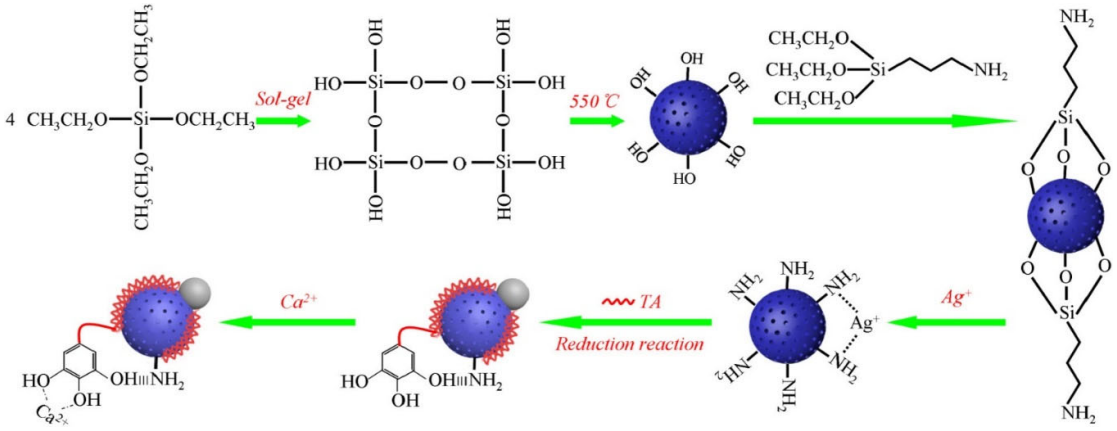

Figure 11. Step-by-step diagram of the synthesis of Ca-TA-MSN@Ag.

In a recently published work, phosphotungstic acid (TPA) was used for functionalization of MCM-48 nanoparticles' surface and the obtained material was explored as a carrier in delivery systems for curcumin (CUR) and quercetin (Q). Phosphotungstic acid was chosen because of its potential for obtaining conjugated nanomatrices for highly effective and selective medical applications. The release profiles of Q and CUR loaded in modified MCM-48 were evaluated in PBS at different pH (5, 6.2, 7.4). C and Q loaded TPA/MCM-48 nanoparticles demonstrated the prolonged and sustainable drug release for 60 h, and exhibited significant antibacterial activity against *E Coli.* Figure 12 is a schematic representation of the synthesis strategy and antimicrobial action of Q-TPA/MCM-48 and C-TPA/MCM-48. The loaded amount of both polyphenols into the modified porous silica is very close (86 mg for CUR and 84 mg for Q in 100 mg nanocomposite). These results show that neither of both bioactive molecules has stronger affinity to the modifying surface groups. On the other hand, faster release and slightly higher burst release of CUR in comparison with that of the Q, where also the pH of the release medium plays a role in the speed and the amount of release, was observed. As the optimal condition pH 7.4 was chosen. For both substances sustainable and prolonged release (up to 60h) from the phosphotungstic modified silica was achieved. The significant antimicrobial activity of the modified silica and modified silica loaded with CUR or Q against *E. coli* was proven, where the loaded formulations exhibit activity twice higher that the modified support alone [63].

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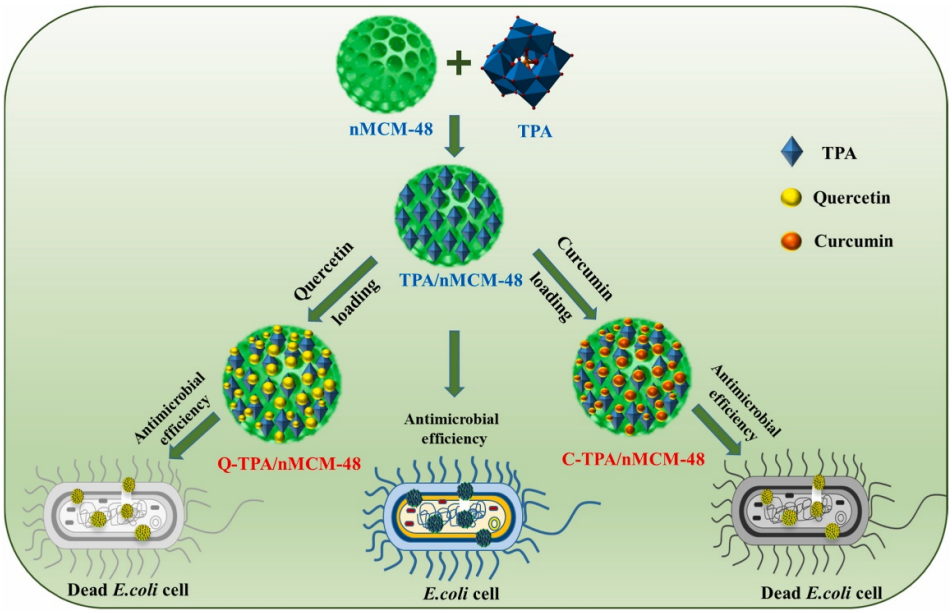

Figure 12. Schematic representation of the synthesis strategy and antimicrobial action of Q-TPA/MCM-48 and C-TPA/MCM-48.

Calcium silicate-based composites attract significant attention from researchers also due to their excellent performance in bone tissue regeneration treatments. To increase their biocompatibility, antimicrobial activity, and anti-inflammatory effect these materials are successfully combined with natural polyphenols such as gallic acid (GA), pyrogallol (PG), and tannic acid (TA). Published date reported the influence of the polyphenols' concentration on the setting time, antibacterial activity against *E. coli* and *S. aureus*, and osteogenic activity on human osteoblast-like cell line MG63 of the obtained samples. The results showed that the loading of polyphenols in calcium silicate greatly enhanced its antibacterial activity, and doesn't have a significant effect on the osteogenic activity (MG63 cells) and the cytotoxicity (L929 cells) [64]. It was found that quercetin-containing mesoporous calcium silicate carriers obtained by polycaprolactone-assisted 3D printing process possess great bioactivity and mechanical properties for the promotion of osteogenesis in mesenchymal stem cells. The mesoporous calcium silicate scaffold loaded with quercetin exhibits greater results in *in vitro* tests for cell proliferation, cytotoxicity, and immunofluorescence staining for mesenchymal stem cells in comparison with the non-loaded composites. This novel approach for the preparation of efficient materials for bone tissue regeneration at room temperature could be used instead of bone-related proteins which remain bioactive only at low temperatures [65]. In another study genistein (GN) was used to enhance the cells' (MC3T3-E1) response (adhesion, proliferation, differentiation, and gene expressions) *in vitro* and to promote osteogenesis *in vivo* of mesoporous magnesium-calcium-silicate/polyetheretherketone composite with potential application in bone regeneration. The obtained composite contains 40 wt% mesoporous magnesium-calcium-silicate loaded with genistein, and it was prepared by a cold pressing and sintering method. Based on a comparative study it can be concluded that the presence of genistein stimulated the cell responses *in vitro* and significantly improved osteogenesis and enhanced osseointegration of the parent composite [66].

Silica materials modified with metal oxides were used as carriers not only for one isolated molecule but for polyphenolic extracts as well. The stability of extracts from grape pomace was enhanced by their encapsulation in pure mesoporous silica type MCM-41 and decorated with ZnO (Zn-MCM-41) or MgO (Mg-MCM-41) analogues. The stability of free and encapsulated extracts was studied for evaluation of their radical scavenger activity in time, assessed by DPPH method. The encapsulated extracts demonstrated similar antioxidant capacity up to 5 months, whereas the free extracts showed a decrease of their activity over time due to the degradation. The best

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cytocompatibility was obtained for Zn-MCM-41 encapsulated extract, which makes it a promising candidate for incorporation in cosmetic or nutraceutical formulations [67].

Additionally, NH_2-modified silica could be applied as a layer around magnetic iron oxide nanoparticles as a core in order to obtain inorganic composites (average particle size 50 nm) with application as adsorbents for flavonoids extracted from Licorice (*Glycyrrhiza uralensis Fisch*.) root. A comparative study showed greater affinity and faster attainment of the adsorption equilibrium of the flavonoids to the silica-iron oxide particles instead of the commercial absorbents. The higher purity of the enriched extract and the easy desorption of flavonoids from these adsorbents make them promising in magnetic separation technology for natural products [68].

In a few recent studies different approaches for using polyphenol-metal complexes in combination with porous silica in controlled drug delivery were demonstrated. The polyphenol's ability to form complexes with metal ions is used to form trigger-sensitive coatings around the silica particles. These new types of composite materials possess excellent stability and biocompatibility in a physiological environment. The high specific surface area of silica porous nanoparticles allows the loading of a significant amount of biologically active molecules, while the coating of metal-polyphenolic networks assures the photothermal and pH-responsive properties. The nature of these carriers makes them promising candidates for applications in photothermal and pH-sensitive therapy.

In these cases, the formation of a complex of tannic acid (TA) with metal ions (Fe^{3+}, Al^{3+}) was applied in order to encapsulate drug-loaded silica particles. The preparation of such systems usually requires the following steps: i) synthesis of the silica carrier; ii) loading the bioactive substance in the pores of the carrier; iii) encapsulation of the loaded particles in polyphenol-metal framework by self-assembly process. Results for the delivery system of fucoxanthin (natural carotenoid) based on Fe_3O_4-SiO_2-TA nanoparticles obtained by the above-described procedure offer magnetic and pH-dependent targeted delivery. The improved water dispersion and biocompatibility, as well as inhibited growth of human colon cancer cells (HCT116) and low cytotoxicity against mouse fibroblast cells (L929) were shown from obtained formulations compared to free fucoxanthin [69]. The same strategy for encapsulation of the anti-tumor drug doxorubicin resulted in an improvement in the effectiveness of the treatment and superior biocompatibility [70]. In these systems, by controlling the thickness of the coating of the polyphenol-metal network the photothermal performance of the obtained delivery system can be easily tuned, which makes these materials promising candidates not only for pH-dependent therapy but also for photothermal therapy [71]. Another example for similar system was design on the basis of polyacrylic acid-coordinated Mn^{2+} and F^- co-doped nanoscale hydroxyapatite coated with metal-polyphenol network. The coating of pH-sensitive tannic acid (TA)-Fe^{3+} complex improves the biocompatibility of the delivery system, increase the stability of the hydroxyapatite carrier, preventing the burst release of the loaded drug (Doxorubicin) before reaching the target (tumors) and greatly enhanced the drug loading and encapsulation efficiency. After phagocytosis by HeLa cells the obtained delivery system degrades rapidly while continuously release the loaded antitumor drug (Doxorubicin), TA, and Mn^{2+} ions. The released Mn^{2+} ions have the ability to bind to proteins with leads to enhanced magnetic resonance contrast. The developed pH-sensitive and magnetic resonance imaging active delivery system showed great potential for tumor diagnosis and therapeutic synergy [72].

4. Conclusions and Final Remarks

Recent advancements in the development of novel tools to enhance quality of life are driving research towards engineering of highly effective materials for diagnostic and therapeutic applications. The unique properties of mesoporous silica materials make them ideal for designing delivery systems of biologically active compounds. Used as carriers mesoporous silica can be a solution of some serious drawbacks of bioactive molecules, like polyphenols, such as low solubility, burst release and fast metabolism before the target organ/tissue is reached, inability to internalize the target cells, fast degradation, etc. Rapid progress in developing new porous silica has resulted in materials with diverse particle sizes, shapes, pore structures, and surface properties. Comparative

studies were conducted to identify the most suitable carriers for specific biologically active compounds. The data indicate that pore structure and size significantly influence drug loading effectiveness and can affect the kinetics of drug release. These parameters are determined by steric and diffusion factors, including the size of the adsorbate molecules, their ability to form crystals, and their solubility. Both the loading capacity and release behavior are also greatly influenced by the surface chemistry of the porous silica carrier and the loaded molecules. The easy-to-modify silica surface allows enhancing the affinity of the adsorbate molecules to the carrier by introducing specific selective species, such as organic groups or metal ions. By increasing the potential for ionic, electrostatic, or hydrogen bond interactions, the loading efficiency and release properties of the delivery system can be improved. The results indicate that an increased number of specific surface groups leads to higher adsorption efficiency. However, due to the complexity of creating an effective delivery system, no strict rules can be established for the optimal pore structure or surface modification.

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