

Uio-67-Quercetin As a drug delivery platform for Quercetin

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Abstract

The drug delivery application of Zeolites as a drug carrying platforms have been investigated due to their unique structures which can encapsulated different ions and molecules. In present study, UIO-67 was successfully prepared by applied for delivery of Quercetin. Using variety of analytical methods containing FTIR, FESEM, and EDS the synthesized nanostructure was characterized. Based on the in vitro cytotoxicity results, Uio-67-Quercetin was able to increase cytotoxicity compared to that of Quercetin on A549 cancerous cells indicating the remarkable role of this drug delivery system.

Keywords:Uio-67, drug delivery, Quercetin, Cytotoxicity, MOF

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Fig1. Placement of drug in the structure of MOF.

1. Introduction

Cancer as the most prevalent diseases worldwide is one of the main public health concerns. In spite of intensive efforts for treatment of cancer, the necessity of developing effective agents isn't ignorable [1]. Designing an ideal drug delivery system for targeting cancer cell is considered as a hot topic in life science research. MOFs with crucial features including high drug loading capacity, high surface area, as well as tunable pore size is used for drug delivery intensively[2]. MOFs plays an important role as an carriers in drug delivery because they are non-toxic as well as the uptake of drugs and getting across the cell membrane has been facilitated via controlling the size of MOFs[3].

Quercetin is anticancer drugs which is able to induces cytotoxic and increase DNA damage[4]. Although, Quercetin frequently applied, developed drug resistance and severe side effects affected its clinical application [5]. Encapsulate of Quercetin using various DDS could be an effective idea[6]. In present work, the drug loading

capacity of i for Quercetinas an anticancer drug was evaluated. Upon exposure by UiO-67-Quercetin the in vitro cytotoxicity against cancer cells were assessed.

Finally but contrary to the original goal of this project, which was to use a muff, because of the simpler and faster synthesis, we carried out this project with a MOF.

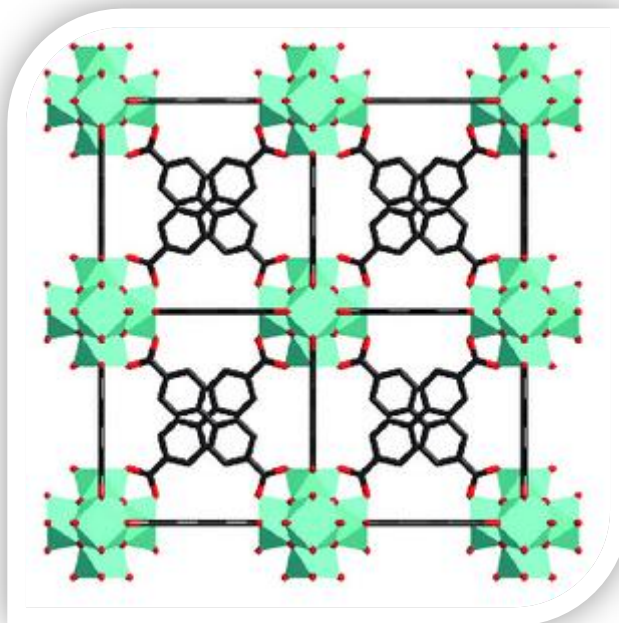


Fig2. Placement of Structures of UiO-67[26]

UiO-67 is a Zirconium-based metal-organic framework that features larger pore sizes compared to UiO-66. This is due to the longer structure of BPDC (UiO-67) as compared to BDC (UiO-66).

The structure and properties of two new UiO-67-type metal-organic frameworks, along with their linker synthesis and powder and single crystal synthesis, are presented. The new MOFs, UiO-67-Me and UiO-67-BN, are based on 3,3'-dimethylbiphenyl and 1,1'-binaphthyl linker scaffolds, and show a much higher stability to water than the thoroughly investigated UiO-67, which is based on the biphenyl scaffold. On the basis of structure models obtained from single crystal X-ray diffraction, it is seen that these linkers are partly shielding the Zr cluster. The new materials have higher density than UiO-67, but show a higher volumetric adsorption capacity for methane. UiO-67-BN exhibits excellent reversible watersorption properties, and enhanced stability to aqueous solutions over a wide pH range; it is to the best of our knowledge the most stable Zr-MOF that is isostructural to UiO-67 in aqueous solutions.

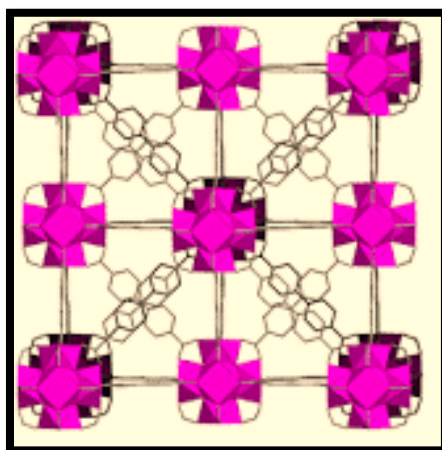


Fig3. Placement of Structures of UiO-67

Application

- ❖ Gas adsorption and storage:
 - Carbon dioxide (CO₂)
 - Hydrogen (H₂)
 - Methane (CH₄)
- ❖ Neutralisation/detoxication of chemical warfare agents (nerve gas)
- ❖ Catalyst
- ❖ Biomolecular motor
- ❖ Biomedical imaging

Properties

Formula: Zr₆O₄(OH)₄(BPDC)₆
Surface area: up to 1970+ m²/gr (BET)

NanoComposite

Nanocomposite is a multiphase solid material where one of the phases has one, two or three dimensions of less than 100 nanometers (nm) or structures having nano-scale repeat distances between the different phases that make up the material. [7]

The idea behind Nanocomposite is to use building blocks with dimensions in nanometre range to design and create new materials with unprecedented flexibility and improvement in their physical properties. In the broadest sense this definition can include porous media, colloids, gels and copolymers, but is more usually taken to mean the solid combination of a bulk matrix and nano-dimensional phase(s) differing in properties due to dissimilarities in structure and chemistry. [8]

The mechanical, electrical, thermal, optical, electrochemical, catalytic properties of the nanocomposite will differ markedly from that of the component materials. Size limits for these effects have been proposed.

1. <5 nm for catalytic activity
2. <20 nm for making a hard magnetic material soft
3. <50 nm for refractive index changes
4. <100 nm for achieving superparamagnetism, mechanical strengthening or restricting matrix dislocation movement [9].

Nanocomposites are found in nature, for example in the structure of the abalone shell and bone. [10] The use of nanoparticle-rich materials long predates the understanding of the physical and chemical nature of these materials. Some researchers investigated the origin of the depth of color and the resistance to acids and bio-corrosion of Maya blue paint, attributing it to a nanoparticle mechanism. From the mid-1950s nanoscale organo-clays have been used to control flow of polymer solutions (e.g. as paint viscosifiers) or the constitution of gels (e.g. as a thickening substance in cosmetics, keeping the preparations in homogeneous form). By the 1970s polymer/clay composites were the topic of textbooks, although the term "nanocomposites" was not in common use. [11]

In mechanical terms, nanocomposites differ from conventional composite materials due to the exceptionally high surface to volume ratio of the reinforcing phase and/or its exceptionally high aspect ratio. The reinforcing material can be made up of particles (e.g. minerals), sheets (e.g. exfoliated clay stacks) or fibers (e.g. carbon nanotubes or electrospun fibers). [12] The area of the interface between the matrix and reinforcement phase(s) is typically an order of magnitude greater than for conventional composite materials. [13] The matrix material properties are significantly affected in the vicinity of the reinforcement. Some scientists be aware that with polymer nanocomposites, properties related to local chemistry, degree of thermoset cure, polymer chain mobility, polymer chain conformation, degree of polymer chain ordering or crystallinity can all vary significantly and continuously from the interface with the reinforcement into the bulk of the matrix. This massive quantity of reinforcement surface area means that a relatively small amount of nanoscale reinforcement can have an observable effect on the macroscale properties of the composite. [14]

MOF

Metal-organic frameworks (MOFs) are a class of compounds consisting of metal ions or clusters coordinated to organic ligands to form one-, two-, or three-dimensional structures. They are a subclass of coordination polymers, with the special feature that they are often porous. The organic ligands included are sometimes referred to as "struts" or "linkers", one example being 1,4-benzenedicarboxylic acid (BDC).

More formally, a metal-organic framework is a coordination network with organic ligands containing potential voids. A coordination network is a coordination compound extending, through repeating coordination entities, in

one dimension, but with cross-links between two or more individual chains, loops, or spiro-links, or a coordination compound extending through repeating coordination entities in two or three dimensions; and finally a coordination polymer is a coordination compound with repeating coordination entities extending in one, two, or three dimensions.[1]

In some cases, the pores are stable during elimination of the guest molecules (often solvents) and could be refilled with other compounds. Because of this property, MOFs are of interest for the storage of gases such as hydrogen and carbon dioxide. Other possible applications of MOFs are in gas purification, in gas separation, in water remediation,[2] in catalysis, as conducting solids and as supercapacitors.[3]

The synthesis and properties of MOFs constitute the primary focus of the discipline called reticular chemistry (from Latin reticulum, "small net").[4] In contrast to MOFs, covalent organic framework (COFs) are made entirely from light elements (H, B, C, N, and O) with extended structures.

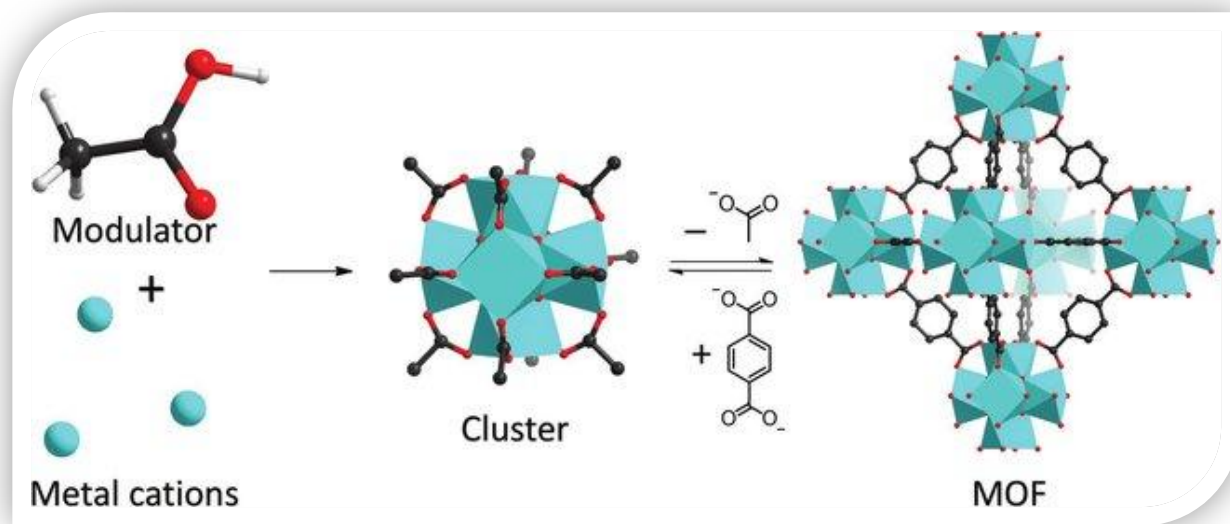


Fig4. Representative modulated synthesis [26]

Structure

MOFs are composed of two major components: a metal ion or cluster of metal ions and an organic molecule called a linker. For this reason, the materials are often referred to as hybrid organic–inorganic materials; however, this terminology has recently been explicitly discouraged.[1] The organic units are typically mono-, di-, tri-, or tetravalent ligands.[6] The choice of metal and linker dictates the structure and hence properties of the MOF. For example, the metal's coordination preference influences the size and shape of pores by dictating how many ligands can bind to the metal and in which orientation.

Classification of hybrid materials based on dimensionality					
		Dimensionality of Inorganic			
		0	1	2	3
Dimensionality of Organic	0	Molecular Complexes	Hybrid Inorganic Chains	Hybrid Inorganic Layers	3-D Inorganic Hybrids
	1	Chain Coordination Polymers	Mixed Inorganic-Organic Layers	Mixed Inorganic-Organic 3-D Framework	
	2	Layered Coordination Polymer	Mixed Inorganic-Organic 3-D Framework		
	3	3-D Coordination Polymers			

To describe and organize the structures of MOFs, a system of nomenclature has been developed. Subunits of a MOF, called secondary building units (SBU), can be described by topologies common to several structures.

Each topology, also called a net, is assigned a symbol, consisting of three lower-case letters in bold. MOF-5, for example, has a pcu net.

Attached to the SBUs are bridging ligands. For MOF's, typical bridging ligands are di- and tricarboxylic acids. These ligands typically have rigid backbones. Examples are benzene-1,4-dicarboxylic acid (BDC or terephthalic acid, biphenyl-4,4'-dicarboxylic acid (BPDC), and the tricarboxylic acid trimesic acid.

Synthesis

General synthesis

The study of MOFs developed from coordination chemistry and solid state inorganic chemistry, especially the zeolites. Except for the use of preformed ligands, MOFs and zeolites are produced almost exclusively by hydrothermal or solvothermal techniques, where crystals are slowly grown from a hot solution. In contrast with zeolites, MOFs are constructed from bridging organic ligands that remain intact throughout the synthesis.[8] Zeolite synthesis often makes use of a "template". Templates are ions that influence the structure of the growing inorganic framework. Typical templating ions are quaternary ammonium cations, which are removed later. In MOFs, the framework is templated by the SBU (secondary building unit) and the organic ligands. A templating approach that is useful for MOFs intended for gas storage is the use of metal-binding solvents such as N,N-diethylformamide and water. In these cases, metal sites are exposed when the solvent is evacuated, allowing hydrogen to bind at these sites. Four developments were particularly important in advancing the chemistry of MOFs.

(1) The geometric principle of construction where metal-containing units were kept in rigid shapes. Early MOFs contained single atoms linked to ditopic coordinating linkers. The approach not only led to the identification of a small number of preferred topologies that could be targeted in designed synthesis, but was the central point to achieve a permanent porosity.

(2) The use of the isorecticular principle where the size and the nature of a structure changes without changing its topology led to MOFs with ultrahigh porosity and unusually large pore openings.

(3) Post- synthetic modification of MOFs increased their functionality by reacting organic units and metal-organic complexes with linkers.

(4) Multifunctional MOFs incorporated multiple functionalities in a single framework.

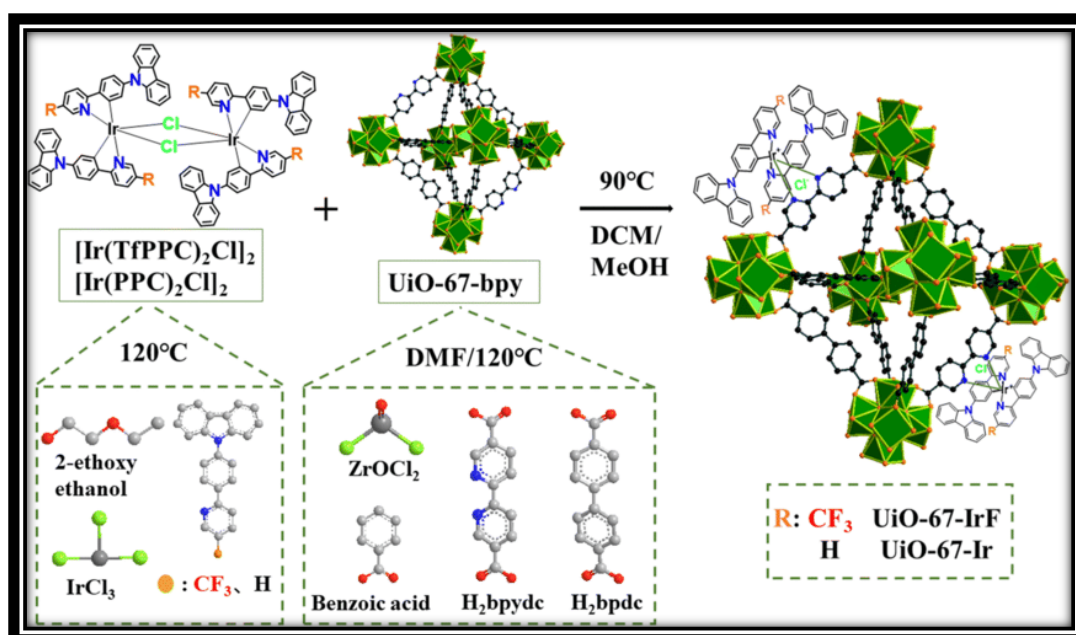


Fig5. Synthesis routine for UiO-67-IrF [28]

Since ligands in MOFs typically bind reversibly, the slow growth of crystals often allows defects to be redissolved, resulting in a material with millimeter-scale crystals and a near-equilibrium defect density. Solvothermal synthesis is useful for growing crystals suitable to structure determination, because crystals grow over the course of hours to days. However, the use of MOFs as storage materials for consumer products

demands an immense scale-up of their synthesis. Scale-up of MOFs has not been widely studied, though several groups have demonstrated that microwaves can be used to nucleate MOF crystals rapidly from solution. This technique, termed "microwave-assisted solvothermal synthesis", is widely used in the zeolite literature, and produces micron-scale crystals in a matter of seconds to minutes, in yields similar to the slow growth methods. Some MOFs, such as the mesoporous MIL-100(Fe), can be obtained under mild conditions at room temperature and in green solvents (water, ethanol) through scalable synthesis methods.

A solvent-free synthesis of a range of crystalline MOFs has been described. Usually the metal acetate and the organic proligand are mixed and ground up with a ball mill. $\text{Cu}_3(\text{BTC})_2$ can be quickly synthesised in this way in quantitative yield. In the case of $\text{Cu}_3(\text{BTC})_2$ the morphology of the solvent free synthesised product was the same as the industrially made Basolite C300. It is thought that localised melting of the components due to the high collision energy in the ball mill may assist the reaction. The formation of acetic acid as a by-product in the reactions in the ball mill may also help in the reaction having a solvent effect in the ball mill. It has been shown that the addition of small quantities of ethanol for the mechanochemical synthesis of $\text{Cu}_3(\text{BTC})_2$ significantly reduces the amounts of structural defects in the obtained material.

A recent advancement in the solvent-free preparation of MOF films and composites is their synthesis by chemical vapor deposition. This process, MOF-CVD,[19] was first demonstrated for ZIF-8 and consist of two steps. In a first step, metal oxide precursor layers are deposited. In the second step, these precursor layers are exposed to sublimed ligand molecules that induce a phase transformation to the MOF crystal lattice. Formation of water during this reaction plays a crucial role in directing the transformation. This process was successfully scaled up to an integrated cleanroom process, conforming to industrial microfabrication standards.[20]

Numerous methods have been reported for the growth of MOFs as oriented thin films. However, these methods are suitable only for the synthesis of a small number of MOF topologies. One such example being the vapor-assisted conversion (VAC) which can be used for the thin film synthesis of several UiO-type MOFs.[21]

High-throughput synthesis

High-Throughput (HT) methods are a part of combinatorial chemistry and a tool for increasing efficiency. Basically, there are two synthetic strategies within the HT-methods: On the one hand the combinatorial approach, here all reactions take place in one vessel, which leads to product mixtures and on the other hand the parallel synthesis, here the reactions take place in different vessels. Furthermore, a distinction is made between thin films and solvent-based methods.[22]

Solvothermal synthesis can be carried out conventionally in a teflon reactor in a convection oven or in glass reactors in a microwave oven (high-throughput microwave synthesis). The use of a microwave oven changes, in part dramatically, the reaction parameters. In addition to solvothermal synthesis, there have been advances in using supercritical fluid as a solvent in a continuous flow reactor. Supercritical water was first used in 2012 to synthesize copper and nickel-based MOFs in just seconds.[23] In 2020, supercritical carbon dioxide was used in a continuous flow reactor along the same time scale as the supercritical water-based method, but the lower critical point of carbon dioxide allowed for the synthesis of the zirconium-based MOF UiO-66.[24]

High-throughput solvothermal synthesis

In high-throughput solvothermal synthesis, a solvothermal reactor with (eg) 24 cavities for Teflon reactors is used. Such a reactor is sometimes referred to as a multiclav. The reactor block or reactor insert is made of stainless steel and contains 24 reaction chambers, which are arranged in four rows. With the miniaturized Teflon reactors, volumes of up to 2 mL can be used. The reactor block is sealed in a stainless steel autoclave; for this purpose, the filled reactors are inserted into the bottom of the reactor, the Teflon reactors are sealed with two Teflon films and the reactor top side is put on. The autoclave is then closed in a hydraulic press. The sealed solvothermal reactor can then be subjected to a temperature-time program. The reusable Teflon film serves to withstand the mechanical stress, while the disposable Teflon film seals the reaction vessels. After the reaction, the products can be isolated and washed in parallel in a vacuum filter device. On the filter paper, the products are then present separately in a so-called sample library and can subsequently be characterized by automated X-ray powder diffraction. The informations obtained are then used to plan further syntheses.

Reversible hydration and dehydration

During drying it comes to the removal of free and bound water from the crystal grid, which is then counterbalanced back in contact with materials such as stored grain and feed, pet litter, in flue gas to prevent condensation and the like. [19] Clinoptilolite stabilize moisture at a low dose of volume and avoid the adverse effects of water. [20]

Metal-organic frameworks (MOFs) are organic-inorganic hybrid crystalline porous materials that consist of a regular array of positively charged metal ions surrounded by organic 'linker' molecules. The metal ions form nodes that bind the arms of the linkers together to form a repeating, cage-like structure. Due to this hollow structure, MOFs have an extraordinarily large internal surface area.

Researchers have synthesized MOFs that feature a surface area of more than 7800 square meters per gram. To put this into context, if you could lay out the available surface area in a teaspoon of this material (around a gram of solid), it would cover an entire soccer field. MOFs offer unique structural diversity in contrast to other porous materials uniform pore structures; atomic-level structural uniformity; tunable porosity; extensive varieties; and flexibility in network topology, geometry, dimension, and chemical functionality. This allows researchers the successful control of framework topology, porosity, and functionality.

MOFs unique structure design and tunability – crystalline porous materials that are composed of both organic and inorganic components in a rigid periodic networked structure– is not readily accessible in conventional porous materials, e.g., purely inorganic zeolites. By making the MOF from different metal atoms and organic linkers, researchers can create materials that selectively absorb specific gases into tailor-made pockets within the structure. MOFs therefore offer great potential for their effective integration and exploration in various sensing applications. MOFs can be put together arbitrarily like Lego bricks and outperform every previously known class of material in terms of flexibility.

Short history and Background of MOFs

The physicochemical properties of materials are governed by the synergistic effects of structures and compositions, and MOFs are fascinating examples of how the unique structure of hollow-structured materials can provide a whole raft of advantageous features. Among them are enhanced surface-to-volume ratio; low density; microreactor environment; higher loading capacities; and reduced transmission lengths of mass and charge.

Consequently, the preparation of hollow structures for technological applications has long been a popular research field for chemists and materials scientists. However, the synthesis of porous or hollow-structured materials with controllable – and especially complex – structures and certain composition in a controlled manner has always been a challenge for scientists.

Enter MOFs – crystalline hybrid materials created from both organic and inorganic molecules via molecular self-assembly. Pioneered in the late 1990s ("Design and synthesis of an exceptionally stable and highly porous metal-organic framework") by Prof. Omar Yaghi at UC Berkeley, MOFs have become a rapidly growing research field. So far, more than 90,000 different MOF structures have been reported and the number grows daily. Though exciting, the sheer number of MOFs is actually creating a problem: It researchers propose to synthesize a new MOF, how can they know if it is truly a new structure and not some minor variation of a structure that has already been synthesized? To address the issue, researchers are using machine learning to develop a 'language' for comparing two materials and quantifying the differences between them.

MOF Applications

Numerous applications in many fields are being developed that exploit MOFs' cage-like structure, such as gas storage and separation, liquid separation and purification, electrochemical energy storage, catalysis, and sensing. In addition to direct applications, MOFs have been used as unique precursors for the construction of inorganic functional materials with unparalleled design possibilities, such as carbons, metal-based compounds, and their composites.

Currently, carbonaceous materials are attracting much interest for their extensive applications including adsorption, catalysis, batteries, fuel cells, supercapacitors, and drug delivery and imaging. In addition, some sensors are also one of the important applications of carbonaceous materials, because they are closely related to human health.

There are varieties of approaches for the preparation of these carbon materials, but among them, directly carbonizing from organic precursors is the most frequently used method to prepare nanoporous carbons due to its flexibility and simplicity. These materials present certain drawbacks, though, such as low surface areas, disordered structures, and non-uniform sizes, which will greatly limit their applications. However, researchers found that carbon materials derived from metal-organic frameworks (MOFs) could overcome these limitations.

Quercetin

Quercetin is a flavonoid widely distributed in nature.[2] The name has been used since 1857, and is derived from quercetum (oak forest), after the oak genus *Quercus*. [4][5] It is a naturally occurring polar auxin transport inhibitor.

Quercetin is one of the most abundant dietary flavonoids, [2][3] with an average daily consumption of 25–50 milligrams. [7] In red onions, higher concentrations of quercetin occur in the outermost rings and in the part closest to the root, the latter being the part of the plant with the highest concentration. [9] One study found that organically grown tomatoes had 79% more quercetin than non-organically grown fruit. [10] Quercetin is present in various kinds of honey from different plant sources. [11]

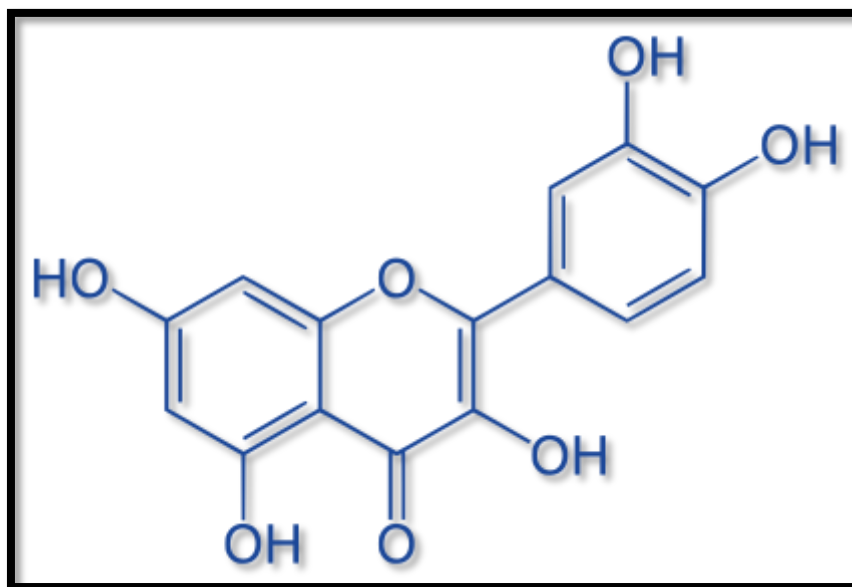


Fig3. Structure of Quercetin

Biosynthesis

In plants, phenylalanine is converted to 4-coumaroyl-CoA in a series of steps known as the general phenylpropanoid pathway using phenylalanine ammonia-lyase, cinnamate-4-hydroxylase, and 4-coumaroyl-CoA-ligase. [12] One molecule of 4-coumaroyl-CoA is added to three molecules of malonyl-CoA to form tetrahydroxychalcone using 7,2'-dihydroxy-4'-methoxyisoflavanol synthase. Tetrahydroxychalcone is then converted into naringenin using chalcone isomerase. Naringenin is converted into eriodictyol using flavanone 3'-hydroxylase. Eriodictyol is then converted into dihydroquercetin with flavanone 3-hydroxylase, which is then converted into quercetin using flavonol synthase. [12]

Glycosides

Quercetin is the aglycone form of a number of other flavonoid glycosides, such as rutin (also known as quercetin-3-O-rutinoside) and quercitrin, found in citrus fruit, buckwheat and onions. [2] Quercetin forms the glycosides quercitrin and rutin together with rhamnose and rutinose, respectively. Likewise quajaverin is the 3-O-arabinoside, hyperoside is the 3-O-galactoside, isoquercetin is the 3-O-glucoside and spiraeoside is the 4'-O-glucoside. CTN-986 is a quercetin derivative found in cottonseeds and cottonseed oil. Miquelianin is the quercetin 3-O-β-D-glucuronopyranoside. [13] A number of taxifolin (also known as dihydroquercetin) glycosides also exists. Isoquercetin is the 3-O-glucoside of quercetin.

Rutin degradation pathway

The enzyme quercitrinase can be found in *Aspergillus flavus*. [14] This enzyme hydrolyzes the glycoside quercitrin to release quercetin and L-rhamnose. It is an enzyme in the rutin catabolic pathway. [15]

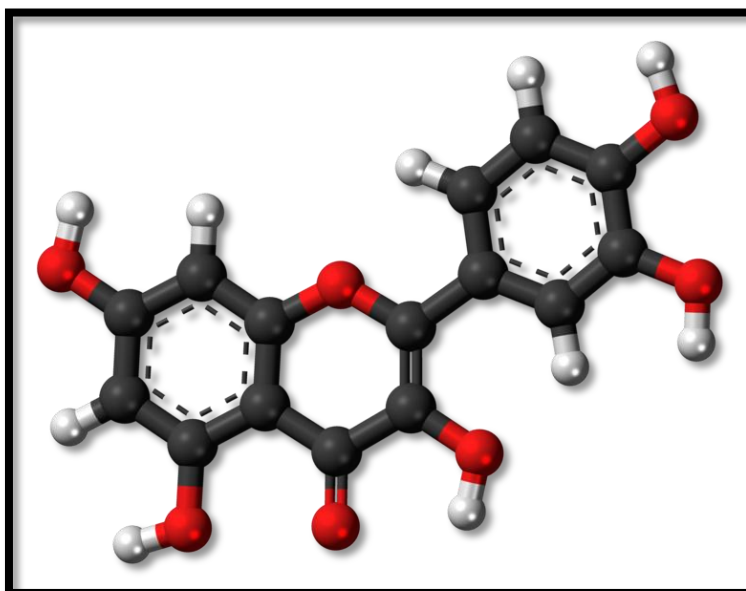


Fig4. Graphical Structure of quercetin

Pharmacology

Pharmacokinetics

The bioavailability of quercetin in humans is low and highly variable (0–50%), and it is rapidly cleared with an elimination half-life of 1–2 hours after ingesting quercetin foods or supplements.[16] Following dietary ingestion, quercetin undergoes rapid and extensive metabolism that makes the biological effects presumed from in vitro studies unlikely to apply in vivo.[17][18][19] Quercetin supplements in the aglycone form are far less bioavailable than the quercetin glycoside often found in foods, especially red onions.[2][20] Ingestion with high-fat foods may increase bioavailability compared to ingestion with low-fat foods,[20] and carbohydrate-rich foods may increase absorption of quercetin by stimulating gastrointestinal motility and colonic fermentation.[2]

Metabolism

In rats, quercetin did not undergo any significant phase I metabolism.[21] In contrast, quercetin did undergo extensive phase II (conjugation) to produce metabolites that are more polar than the parent substance and hence are more rapidly excreted from the body. In vitro, the meta-hydroxyl group of catechol is methylated by catechol-O-methyltransferase. Four of the five hydroxyl groups of quercetin are glucuronidated by UDP-glucuronosyltransferase. The exception is the 5-hydroxyl group of the flavonoid ring which generally does not undergo glucuronidation. The major metabolites of orally absorbed quercetin are quercetin-3-glucuronide, 3'-methylquercetin-3-glucuronide, and quercetin-3'-sulfate.[21] A methyl metabolite of quercetin has been shown in vitro to be more effective than quercetin at inhibiting lipopolysaccharide-activated macrophages.[19] Compared to other flavonoids quercetin is one of the most effective inducers of the phase II detoxification enzymes.[22] Quercetin is a strong inhibitor of the cytochrome P450 enzymes CYP3A4 and CYP2D6.[23] Drugs that are metabolized by these pathways may have increased effect.

Pharmacological research

Quercetin has been reported to inhibit the oxidation of other molecules and hence is classified as an antioxidant in vitro.[17] It contains a polyphenolic chemical substructure that stops oxidation in vitro by acting as a scavenger of free radicals. Quercetin has been shown to inhibit the PI3K/AKT pathway leading to downregulation of the anti-apoptotic protein Bcl-w.[24][25] Quercetin activates or inhibits the activities of a number of proteins in vitro. For example, it is a nonspecific protein kinase enzyme inhibitor.[17]

Food safety

In 2010, the FDA acknowledged high-purity quercetin as GRAS for use as an ingredient in various specified food categories at levels up to 500 milligrams per serving.[26]

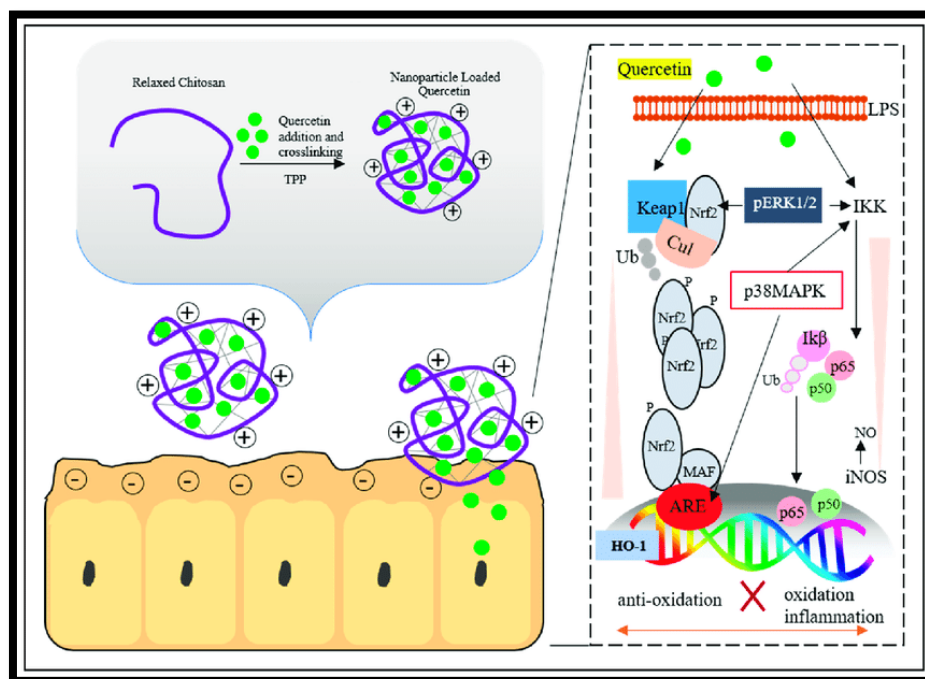


Fig5. Schematic diagram of loading quercetinon nanoparticles

Health claims

Quercetin has been studied in basic research and small clinical trials.[2][27][28][29] While supplements have been promoted for the treatment of cancer and various other diseases,[2][30] there is no high-quality evidence that quercetin (via supplements or in food) is useful to treat cancer[31] or any other disease.[2][32] The US Food and Drug Administration has issued warning letters to several manufacturers advertising on their product labels and websites that quercetin product(s) can be used to treat diseases.[33][34] The FDA regards such quercetin advertising and products as unapproved – with unauthorized health claims concerning the anti-disease products – as defined by "sections 201(g)(1)(B) and/or 201 (g)(1)(C) of the Act [21 U.S.C. § 321(g)(1)(B) and/or 21 U.S.C. § 321(g)(1)(C)] because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease",[33][34] conditions not met by the manufacturers.

Safety

There has been little research into the safety of quercetin supplementation in humans, and the results are insufficient to give confidence that the practice is safe. In particular, there is a lack of safety information on the effect of quercetin supplementation for pregnant women, breastfeeding women, children, and adolescents. The hormonal effects of quercetin found in animal studies raise the suspicion of a parallel effect in humans, particularly in respect of estrogen-dependent tumors.[35] Quercetin supplementation can interfere with the effects of medications. The precise nature of this interaction is known for some common medicines, but for many, it is not.[35]

Results and discussion

Characterization

The chemical structure of the Uio-67-quercetin was characterized with different analytical methods such as XRD, SEM & TEM.

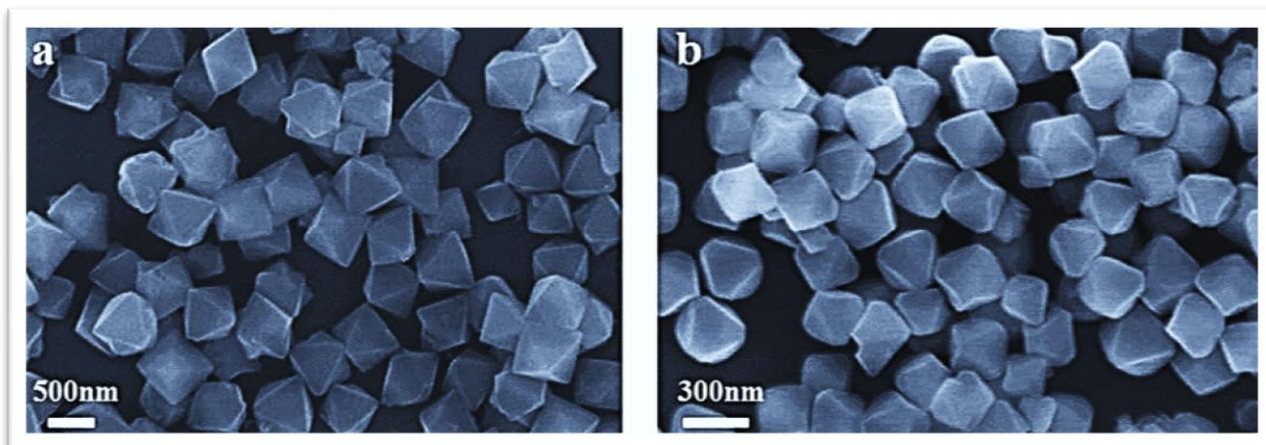


Fig6. TEM image of UiO-67-querctin

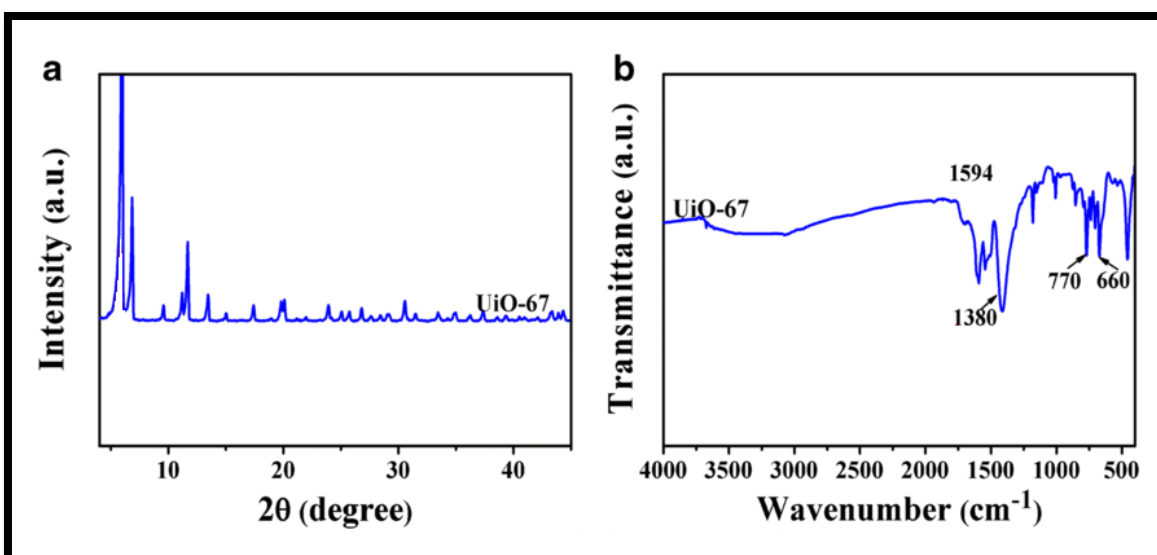


Fig7. (a) XRD and (b) FT-IR patterns for UiO-67.

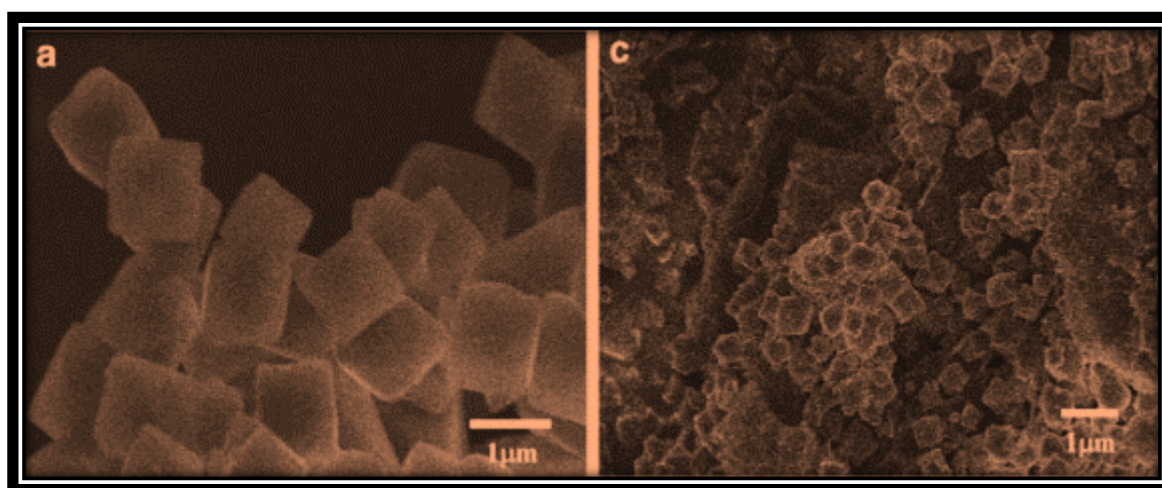


Fig8. SEM images of UiO-67 samples obtained Quercetin:
(a)UiO-67, (c) UiO-67-querctin.

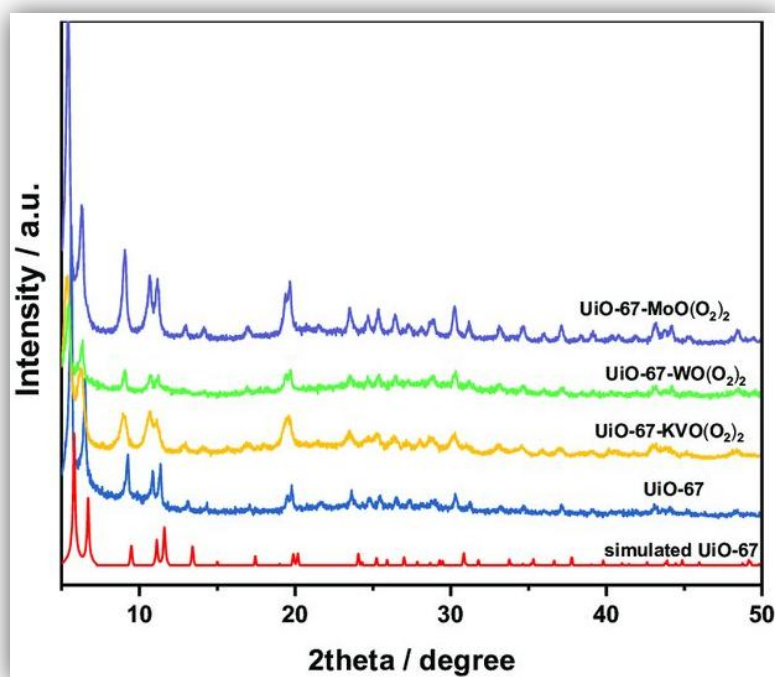


Fig 9.XRD patterns of the simulated UiO-67 and the synthesized UiO-67, UiO-67-MoO(O₂)₂, UiO-67-WO(O₂)₂, and UiO-67-KVO(O₂)₂. [29]

Drug loadings and release

The MOF- with the proper size and the accessible porosity could be used for loading and release of Quercetin. The loading capacity of UiO-67 under physiological condition (pH 7.4) was investigated. The results showed high drug loading capacity (DLC) (90%) and drug loading efficiency (DLE) 70% by UV-Vis spectroscopy. The results of release profiles of UiO-67-Quercetin revealed sustained for 72 h despite with an initial rapid release.

Cytotoxicity assay

In order to determine the in vitro cytotoxicity of the UiO-67, Quercetin drug, and UiO-67-Quercetin HT-29 cell lines, MTT assay was conducted. The obtained results of the cell viability assay showed that UiO-67-Quercetin and Quercetin drug inhibited cell growth in a time and dose-dependent manner while the UiO-67 showed less growth inhibition after 48 h compared to drug loaded UiO-67 and free drug Quercetin. Based on this results, one may conclude that MOFs with low toxicity could be used effectively for biological applications in the future [3].

3. Conclusion

In this study, UiO-67 as a drug carrier was used for delivery of Quercetin. The obtained nanostructure poses spherical morphology with an average diameter of 20 nm. The high loading capacity (86%) and sustained drug release behavior was observed. Moreover, upon exposure by UiO-67-Quercetin, higher growth inhibition than those for UiO-67 and Quercetin drug against A549 cells was determined. Collectively, UiO-67-Quercetin may be a promising anticancer drug delivery system in the future.

Outlook for MOFs

The numerous advantages of MOFs, foremost their high surface area and modular composition, place them at a multidisciplinary crossroads. For good reason, MOFs are one of the most active research fields today, with aspects of their fundamental and applied properties permeating into disciplines as varied as electronics, chemical engineering, and optics. Whereas this Outlook does not attempt to delineate the developments and potential in all these areas, we have introduced some of the exciting prospects related to continued synthetic advances in the field. We further elaborated on three applied areas where MOFs are primed to excel: in challenging gas

separations, as porous electrical conductors, and in heterogeneous catalysis. These examples are not exhaustive, but present subtleties that are applicable and relevant to many other applications of MOFs. The challenges and opportunities in these select applications, which span both the traditional and the modern aspects of the field, are illustrative of the continually expanding interest and bright future for MOF chemistry.

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