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EMM-17-801 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, EMM-17-801 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, EMM-17-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: EMM-17, drug delivery, Quercetin, Cytotoxicity, Zeolite.

Introduction

Recently, developing effective therapeutics become as an urgent demand due to its major impact on the patient's quality of life. Accumulated studies have been devoted to finding the effective therapeutic agents (Wen et al., 2015; Cao et al., 2020). Quercetin as a natural derived flavonoid with prominent pharmacological values is applied for treatment of a broad arrange of diseases from diabetes to breast cancer and asthma. In the last decade, the applications of quercetin have attracted attention in increasing oral treatment due to its multifunction including antioxidant, antibacterial, anti-inflammatory and antineoplastic activities. The low bioavailability of quercetin limited its clinical application (Khursheed et al., 2020). Hence, in order to address this issue, great efforts have been made in developing drug delivery systems for Qurcetin (Wang et al., 2020; Gang et al., 2012).

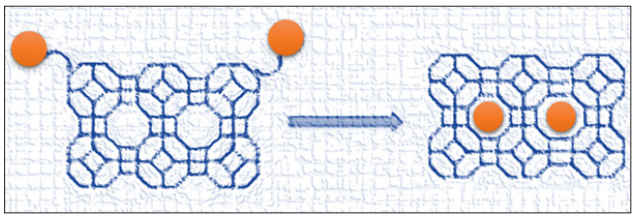

Figure 1: Placement of drug in the structure of Zeolite.

In pursuit of enhancing the specificity and efficacy of traditional anticancer drugs, Zeolites and zeolitic imidazolate frameworks (ZIFs) are considerate as a drug carrying nanoplatforms. Zeolites and mesoporous silicates could be encapsulated different ions and molecules (i.e., proteins) which lead to its pharmacological application (Hao et al., 2021).

For instance, in an attempt, Khodaverdi et al. used zeolites to release indomethacin and ibuprofen in a sustained and controlled manner and reduced adverse effects commonly accompanying oral administrations of NSAIDs (Khodaverdi et al., 2014).

EMM-17 (ExxonMobil Material-17), as an easy to prepare, highly accessible, catalytically active zeolite have been introduced (Weston et al., 2019). Encapsulate of Quercetin using zeolite could be an effective idea (Cai et al., 2019). In present work, the drug loading capacity of EMM-17 for Quercetin as an anticancer drug was evaluated. Upon exposure by EMM-17 -Quercetin the in vitro cytotoxicity against cancer cells were assessed.

The purpose of this project with Quercetin

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 (Zarei et al., 2020). 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 (Rojas et al., 2017). 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 (Song et al., 2019). 5-florouracil (doxorubicin) is anticancer drugs which is able to induces cytotoxic and increase DNA damage (Tawfik et al., 2017). Although, 5 FU frequently applied, developed drug resistance and severe side effects affected its clinical application (Mhaidat et al., 2014). Encapsulate of doxorubicin using various DDS could be an effective idea (Cai et al., 2019). In present work, the drug loading capacity of zsm-5 for doxorubicin as an anticancer drug was evaluated. Upon exposure by zsm-5-5Fu 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 zeolite.

EMM-17 is stable to calcination to remove the OSDA and can be reproducibly synthesized in the presence of fluoride using common, inexpensive reagents over a wide Si/Al range from 15 to infinity, enabling the catalyst acidity to be tailored to almost any petrochemical application. Unlike OSDAs for many new zeolite structures, the OSDAs for EMM-17 are prepared in one simple alkylation step, making EMM-17 an easy to prepare, highly accessible, catalytically active zeolite. Zeolites containing odd numbered channel sizes are rare, and this is the first confirmed example of a 3D 11-ring aluminosilicate zeolite with a pore size in between those of the commercially important 10- and 12-ring zeolites such as ZSM-5 and Zeolite-Y, respectively. Catalysts prepared from EMM-17 exhibit significantly higher activity for catalytic isomerization with no loss in selectivity than current state of the art catalysts. Catalytic isomerization of linear to branched alkanes is a critical component of commercial dewaxing, allowing for the improvement of cold flow properties of hydrocarbon fuels and lubricants through selective hydro isomerization of normal paraffins (Tawfik et al., 2017).

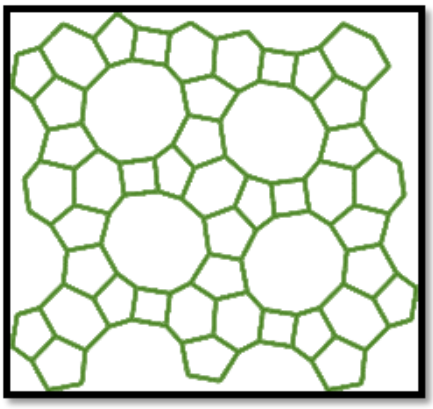

Figure 2: Simulated and simplified structure of zeolite EMM-17

Quercetin

Quercetin is a flavonoid widely distributed in nature. Cao et al. (2020) the name has been used since 1857, and is derived from quercetum (oak forest), after the oak genus Quercus. Wang et al. (2020) and Gang et al. (2012) it is a naturally occurring polar auxin transport inhibitor.

Quercetin is one of the most abundant dietary flavonoids, (Cao et al., 2020; Khursheed et al., 2020) with an average daily consumption of 25–50 milligrams. Khodaverdi et al. (2014) 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. Cai et al. (2019) one study found that organically grown tomatoes had 79% more quercetin than non-organically grown fruit (Zarei et al., 2020). Quercetin is present in various kinds of honey from different plant sources (Rojas et al., 2017).

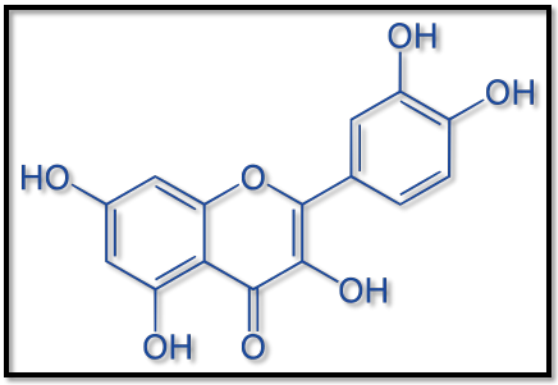

Figure 3: Structure of Quercetin

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. Song et al. (2019) 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 flavanoid 3′-hydroxylase. Eriodictyol is then converted into dihydroquercetin with flavanone 3-hydroxylase, which is then converted into quercetin using flavonol synthase (Song et al., 2019).

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 (Cao et al., 2020). Quercetin forms the glycosides quercitrin and rutin together with rhamnose and rutinose, respectively. Likewise guaijaverin is the 3-O-arabinoside, hyperoside is the 3-O-galactoside, isoquercitin 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 (Tawfik et al., 2017). 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 (Mhaidat et al., 2014). This enzyme hydrolyzes the glycoside quercitrin to release quercetin and L-rhamnose. It is an enzyme in the rutin catabolic pathway (Cai et al., 2019).

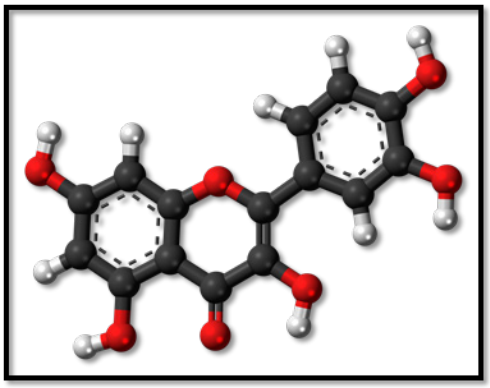

Figure 4: Graphical Structure of quercetin

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 (Fechete et al., 2012). Following dietary ingestion, quercetin undergoes rapid and extensive metabolism that makes the biological effects presumed from in vitro studies unlikely to apply in vivo (Dąbrowski, 2001; Shahabuddin et al., 2020; Khan & Ghoshal, 2000). Quercetin supplements in the aglycone form are far less bioavailable than the quercetin glycoside often found in foods, especially red onions (Cao et al., 2020; Weston et al., 2019). Ingestion with high-fat foods may increase bioavailability compared to ingestion with low-fat foods (Weston et al., 2019) and carbohydrate-rich foods may increase absorption of quercetin by stimulating gastrointestinal motility and colonic fermentation (Cao et al., 2020).

Metabolism

In rats, quercetin did not undergo any significant phase I metabolism (Liu et al., 2021). 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 (Liu et al., 2021). A methyl metabolite of quercetin has been shown in vitro to be more effective than quercetin at inhibiting lipopolysaccharide-activated macrophages (Khan & Ghoshal, 2000). Compared to other flavonoids quercetin is one of the most effective inducers of the phase II detoxification enzymes (Weston et al., 2019). Quercetin is a strong inhibitor of the cytochrome P450 enzymes CYP3A4 and CYP2D6 (Dhand et al., 2014). 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 (Dąbrowski, 2001). 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 (Hartman & Czyz, 2020; Paez-Ribes et al., 2019). Quercetin activates or inhibits the activities of a number of proteins in vitro. For example, it is a nonspecific protein kinase enzyme inhibitor (Dąbrowski, 2001).

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 (GRN No. 341 (Quercetin)". US Food and Drug Administration. 22 November 2010. Retrieved 27 October 2021).

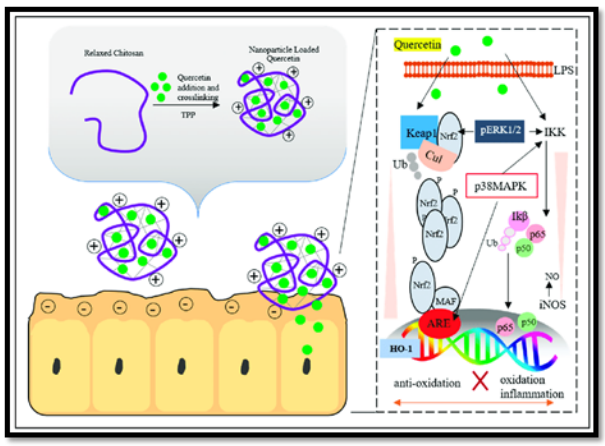

Figure 5: Schematic diagram of loading quercetinon nanoparticles

Health claims

Quercetin has been studied in basic research and small clinical trials (Cao et al., 2020; Yang et al., 2015; Gross, 2009; Miles et al., 2014). While supplements have been promoted for the treatment of cancer and various other diseases, (Cao et al., 2020; D'Andrea, 2015) there is no high-quality evidence that quercetin (via supplements or in food) is useful to treat cancer (Ades, 2009) or any other disease (Cao et al., 2020; European Food Safety Agency [EFSA], 2011). 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 (King, 2017; Pace, 2018). 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",(King, 2017; Pace, 2018) 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 (Andres et al., 2018). 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 (Andres et al., 2018).

Zeolite

Zeolites are a group of crystalline materials made up of evenly sized pores and tunnel systems. When purifying VOCs and hydrocarbons, we use a synthetic hydrophobic zeolite. When the contaminated air passes through the material, the hydrocarbons are adsorbed. The material can adsorb a certain amount of hydrocarbons before needing to be regenerated (Fechete et al., 2012; Dąbrowski, 2001).

A smaller flow of hot air is then directed through the material so that the hydrocarbons release from the zeolite in a higher concentration. This enables more cost-effective incineration. One of its strengths is that it is non-combustible–meaning it can withstand very high temperatures (Shahabuddin et al., 2020). This means that we are also able to purify volatile hydrocarbons such as fumes emitted from vulcanization, plastic smoke and styrene, all of which require very high temperatures during regeneration. The resistance to high temperatures and the structure of the material also allows the zeolite to be completely regenerated – meaning that the VOCs completely release from the zeolite when heated. This means that the system maintains its high purification rate year after year and that the material does not have to be replaced, which gives it a long lifespan and a minimal need for maintenance (Khan & Ghoshal, 2000). Our systems have an availability of over 99% and a lifespan exceeding 25 years. Combining the benefits of zeolite with our 30 years of experience in working with air purification gives our customers a supremely sustainable and customized system with low operating costs and high availability.

A new catalytically active zeolite, designated EMM-17 (ExxonMobil Material-17), with a 3-dimensional 11×10×10-ring topology has been discovered from high throughput experiments while evaluating a family of new organic structure directing agents (OSDAs), 1-alkyl-4-(pyrrolidin-1-yl)pyridin-1-ium hydroxide. The framework structure was determined by model building techniques and confirmed by diffraction calculations. The EMM-17 structure is a random intergrowth of two polymorphs which have a 3-dimensional arrangement of intersecting 11×10×10-ring pores. EMM-17 is stable to calcination to remove the OSDA and can be reproducibly synthesized in the presence of fluoride using common, inexpensive reagents over a wide Si/Al range from 15 to infinity enabling the catalyst acidity to be tailored to almost any petrochemical application. Unlike OSDAs for many new zeolite structures, the OSDAs for EMM-17 are prepared in one simple alkylation step making EMM-17 an easy to prepare, highly accessible, catalytically active zeolite. Zeolites containing odd numbered channel sizes are rare and this is the first confirmed example of a 3-dimensional 11-ring aluminosilicate zeolite with a pore size in between those of the commercially important 10- and 12-ring zeolites such as ZSM-5 and Zeolite-Y respectively. Catalysts prepared from EMM-17 exhibit significantly higher activity for catalytic isomerization with no loss in selectivity than current state of the art catalysts. Catalytic isomerization of linear to branched alkanes is a critical component of commercial dewaxing, allowing for the improvement of cold flow properties of hydrocarbon fuels and lubricants through selective hydroisomerization of normal paraffins (Weston et al., 2019).

The complex crystal structure of EMM-17 polymorphs A and B containing a unique 10(12)×10(12)×11-ring channel system were directly solved using continuous rotation electron diffraction data. Polymorph C and a large number of structural defects were observed at the atomic resolution by integrated differential phase-contrast scanning transmission electron microscopy. EMM-17 exhibits excellent kinetic separation ability for C6 alkane isomers. In this study, we successfully solve polymorphs A and B of zeolite EMM-17, which can only crystallize in sub-micrometre-sized crystals while containing complex stacking disorders, from the three-dimensional (3D) electron diffraction (ED) data. This is the first time that the atomic structure of this polymorph has been ab initio solved, and the result reveals a unique 10(12)×10(12)×11-ring channel system. Moreover, we acquire the first atomic-resolution images of EMM-17 using integrated differential phase-contrast scanning transmission electron microscopy. The images allow us to directly observe polymorphs B and C and discover a large number of local structural defects. Based on structural features unravelled from the reciprocal-space 3D ED data and real-space images, we propose a series of energetically feasible local structures in EMM-17. We also demonstrate that the unique porous structure of EMM-17 enables efficient kinetic separation of C6 alkane isomers ((Liu et al., 2021).

Results and discussion

Characterization

Synthesis

The chemical structure of the EMM-17 was characterized with different analytical methods such as FTIR, PXRD, and FESEM.

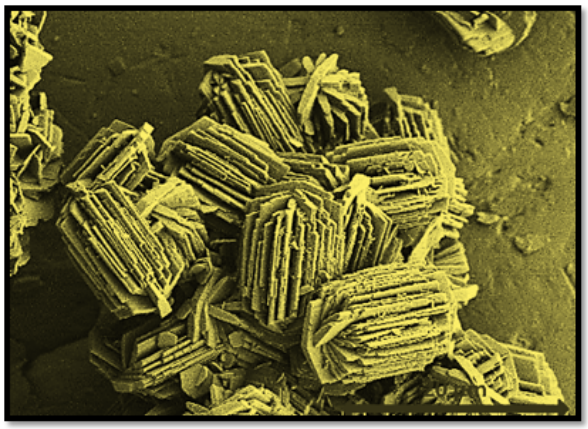

Figure 6 : SEM picture of EMM-17 prepared with OSDA3 showing rolodex morphology.[22]

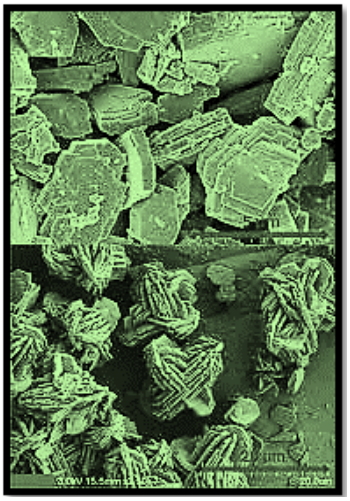

Figure 7: EMM-17, a New Three-Dimensional Zeolite with Unique 11-Ring Channels and Superior Catalytic Isomerization Performance [22]

Drug loadings and release

The EMM-17 with the proper size and the accessible porosity could be applied for loading and release of Quercetin. Under physiological condition (pH 7.4), the loading capacity of EMM-17 was examined. The results displayed high drug loading efficiency (DLE) 65% and drug loading capacity (DLC) (86%) by UV–Vis spectroscopy. The results of release profiles of EMM-17 - Quercetin indicated sustained for 72 h despite with an initial rapid release.

Cytotoxicity assay

In pursuit of evaluate the in vitro cytotoxicity of the EMM-17-, Quercetin drug, and EMM-17-/ Quercetin against A549 cell lines, MTT assay was performed. The obtained results of the cell viability assay exhibited that EMM-17- Quercetin and Quercetin drug could able to inhibit cell growth time and dose-dependently. Based on results, drug loaded EMM-17 and free drug Quercetin revealed more growth inhibition after 48 h compared to that of the EMM-17- on A549 cells. Considering this results, The EMM-17s with low toxicity could be used effectively for drug delivery of Quercetin in the future (Liu et al., 2021).

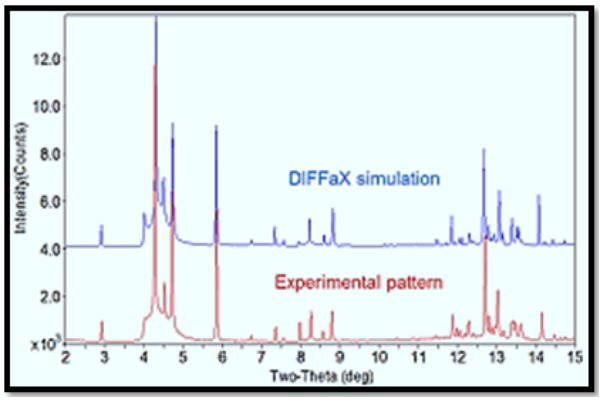

Figure 8: DIFFaX simulated diffraction patterns for intergrowths of EMM-17 simulation and experimental[22]

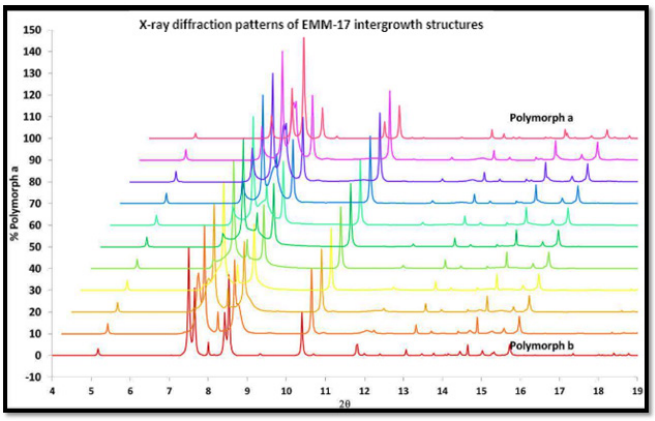

Figure 9 : DIFFaX simulated diffraction patterns for intergrowths of EMM-17 polymorphs A and B at successive 10% intergrowth intervals. The bottom scan is 100% polymorph B and the top scan is 100% polymorph A [22]

Conclusion

In this study, EMM-17- 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 EMM-17 -Quercetin, higher growth inhibition than those for EMM-17- and Quercetin drug against A549cells was determined. Collectively, EMM-17- Quercetin may could be a promising anticancer drug delivery system in the future.

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