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Natural Spore and Pollen Microcarriers: Processing and Advanced Drug Delivery*

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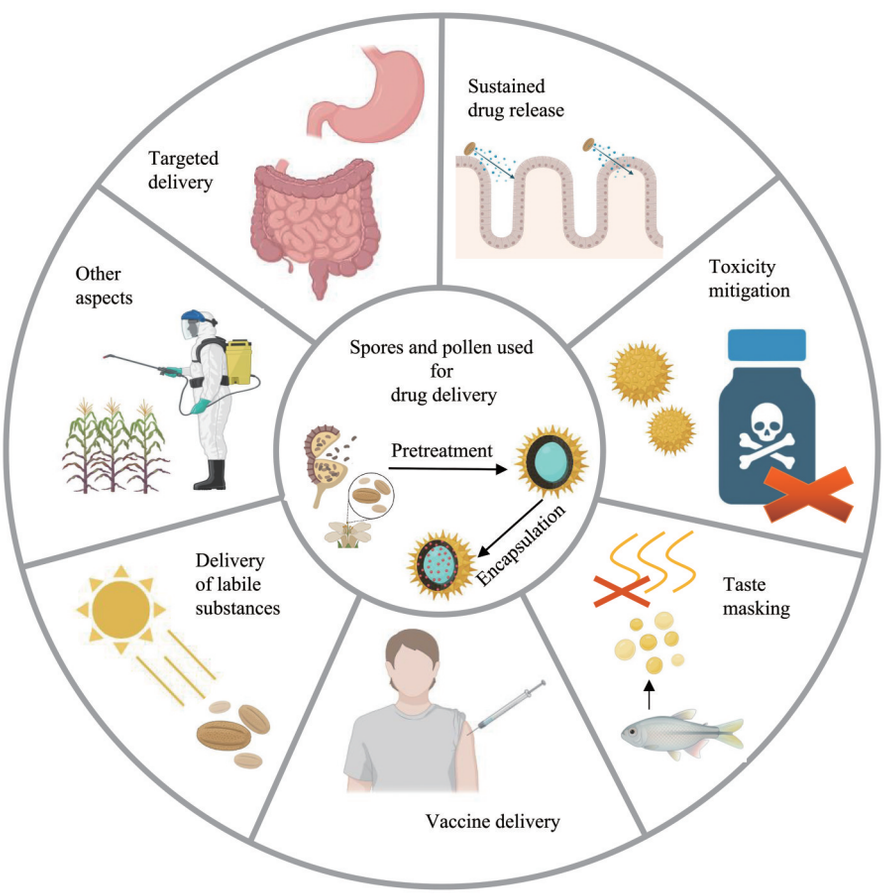
Graphical abstract



Abstract Spores and pollen, as ubiquitous organisms found in nature, possess a remarkable core-shell structure and intricate surface morphology. These tiny particles are notable for their dimensional uniformity, sustainable utilization, environmental friendliness, porosity, amphiphilicity, and strong adhesive properties. In addition, they display excellent biocompatibility and biodegradability, which significantly enhances the stability and targeting of drugs within the body. Spores and pollen can be extracted

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using methods such as acidic solutions, alkaline solutions, or enzyme treatments to obtain sporopollenin, which is an extremely resilient and chemically inert complex biopolymer. The sporopollenin extracted through this process removes the original bioactive substances, such as cell nuclei, enzymes, and DNA, providing greater drug loading capacity and containing no potential allergens or immunogens, thus further enhancing its drug loading capacity and improving safety in therapeutic applications. Due to these beneficial attributes, spores, pollen and sporopollenin have gained widespread use in a variety of drug delivery systems, such as targeted delivery, sustained drug delivery, toxicity mitigation, flavor masking, vaccine delivery, delivery of labile substances, and other applications. This review introduces the types of natural spores and pollen commonly used in drug delivery systems, including their main components, common effects, and uses in drug delivery systems, and so on. It subsequently summarizes novel optimization methods in their processing, such as physical treatment, surface modification, and chemical modification, which enable higher drug loading efficiency, stability, and targeting, among other benefits. Additionally, this paper reviews the research progress and applications of natural spores, pollen, and sporopollenin in drug delivery systems, while also touching on some innovative research content, such as novel nanomotor microcarriers developed based on pollen. Based on these research findings, we further elaborate on the advantages of spores, pollen, and sporopollenin in drug delivery systems. For example, they have high stability and drug loading capacity, good adhesion, excellent targeting, and are easy to modify functionally. Currently, they show promising prospects in the fields of targeted drug delivery, sustained-release drug delivery, as well as the delivery of drugs that are effective but slightly toxic, and are often used in research on the treatment of diseases such as cancer and inflammation. We have also highlighted the challenges they face in various applications and identified some issues that need to be addressed, including difficulties in large-scale production, the need to improve extraction and purification processes, and the existence of a low but still noteworthy risk of allergies, in order to fully leverage their potential in drug delivery applications. According to current research, although spores, pollen, and sporopollenin face some unresolved issues in clinical drug delivery, they still have great potential overall and are expected to become a new generation of green drug delivery platforms. In the future, further research into their unique physical and chemical properties and structural characteristics will help develop more efficient and stable drug delivery systems to meet diverse treatment needs. We believe that continued exploration of natural spores, pollen, and sporopollenin will drive this emerging field to achieve continuous breakthroughs and progress, ultimately making an important contribution to the cause of human health.

Key words drug delivery system, natural microcarriers, spore, pollen, sporopollenin

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Drug delivery systems are pivotal in biomedical research, serving as critical tools to enhance therapeutic efficacy while minimizing side effects. Spores and pollen, as renewable natural resources, have garnered significant attention in drug delivery due to their environmental sustainability, structural stability, and biocompatibility. These natural microcarriers utilize plant-derived microstructures to encapsulate or adsorb drugs, enabling targeted release through biological processes.

Spores typically consist of a spore wall and inner cytoplasm. The spore wall exhibits a multilayered structure, divided into an inner layer primarily composed of cellulose and an outer layer formed by sporopollenin. Spores are naturally abundant, easily harvested, and scalable, making them sustainable resources for large-scale drug delivery systems. Through some advanced treatments, it is also possible to achieve targeted transportation of drugs, continuous drug delivery, and so on.

Pollen, the male reproductive cells of plants, is rich in nutrients and demonstrates excellent biocompatibility. It is one of the most stable structures in nature, capable of surviving in harsh environments for millions of years. Pollen grains exhibit a variety of shapes and sizes, and their environmental friendliness, structural stability, biocompatibility, and monodispersity have attracted increasing attention. In recent years, numerous studies have been conducted on their innovative applications, which are now widely used for drug delivery.

Sporopollenin is the primary biopolymer that makes up the outer wall of spores and pollen, polymerized from carotenoids and phenolic compounds. It is renowned for its exceptional stability, heat resistance, and durability against mechanical and non-oxidative chemical stresses. Often called the “diamond of biopolymers”, it is one of the most resilient organic materials in the plant kingdom. Sporopollenin demonstrates outstanding

mechanical stability, even when compared to many carbon materials and synthetic polymers[1-2]. Its unique cross-linked structure of the outer wall of sporopollenin endows it with remarkable properties, including high temperature tolerance, amphiphilicity, non-toxicity, resistance to acids and bases, chemical stability, and biocompatibility, which enable it to preserve drug potency and stability while protecting against environmental challenges, making it a promising candidate for controlled drug delivery and release systems[3].

The available reviews on spores and pollen mainly summarize their drug delivery functions, and some of them also review their properties and application prospects. However, there has been a lack of systematic elaboration of modern treatments and new applications for spores and pollen in recent years. Thus, we have reviewed the commonly used drug-carrying spores and pollen in recent years and their novel processing treatments and new applications in the field of drug delivery.

1 Spores

1.1 Prevalent spore−based delivery system

1.1.1 *Ganoderma lucidum* spores

Ganoderma lucidum (*Ganoderma lucidum* (Curtis) P. Karst.) is a fungus belonging to the Ganodermataceae family. As a natural herbal medicine, it has various medicinal properties, such as replenishing Qi, calming the mind, relieving coughs and asthma, and lowering blood pressure and blood sugar. *Ganoderma lucidum* spores (GLS) are the reproductive cells produced in the later stages of the fruiting body's growth. They contain numerous bioactive components, including polysaccharides, triterpenoids, and sterols. GLS has broad application prospects in the medical field and is considered a precious natural medicinal resource[4]. A simplified diagram of the structure of GLS and their scanning electron microscope image are shown in Figure 1.

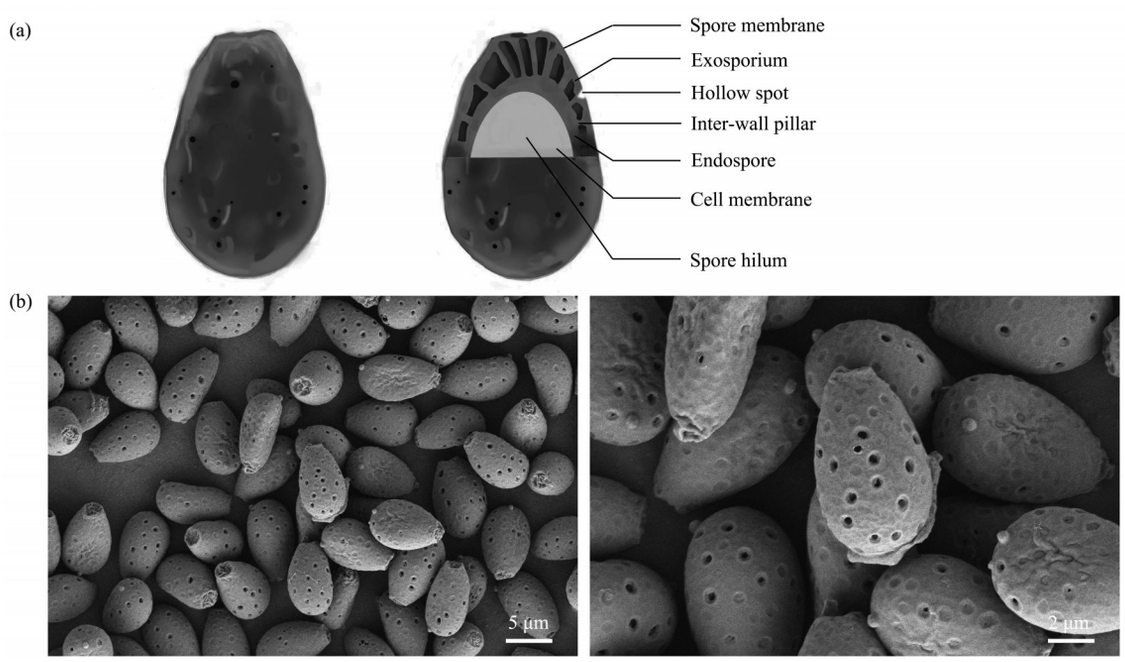

Fig. 1 The schematic diagram shows the structure (a) and scanning electron microscope images (b) of natural GLS

1.1.2 *Lycopodium clavatum* spores

Lycopodium (*Lycopodium japonicum* Thunb.), also known as "tendon-relaxing grass", is a perennial plant of the *Lycopodium* genus. It possesses medicinal properties such as relaxing tendons and promoting blood circulation, dispelling wind and cold, eliminating dampness and toxins, as well as diuretic effects and regulating menstrual flow. *Lycopodium clavatum* spores (LCS) contain various phytochemicals, including flavonoids, alkaloids, and volatile oils, which impart pharmacological activities such as diuretic, hormone-like, antibacterial, and

anti-inflammatory effects. The microencapsulation technology of LCS allows these active ingredients to be more stably preserved and efficiently absorbed and utilized in the body.

LCS exhibits significant drug-loading capacity due to its unique microparticle characteristics and internal cavity structure, making it a promising candidate for further research as a drug delivery carrier. The robust and porous shell structure of LCS enables efficient drug loading and release, enhancing drug targeting and efficacy. Appropriate chemical modifications can further improve the drug-loading capacity of LCS while maintaining its biocompatibility and biodegradability.

Lycopodium spores have broad application prospects in the medical field, particularly in drug delivery systems. As summarized in Table 1, various drugs loaded into sporopollenin microcapsules extracted from natural *Lycopodium* spores have demonstrated significant improvements in efficacy and reductions in side effects.

Table 1 Applications of natural *Lycopodium* spore drug delivery systems

Loaded drug	Mechanism of efficacy	Application	Reference
Acetylsalicylic acid	26.70% loading capacity and 53.40% encapsulation efficiency; enhanced bioavailability with reduced side effects	Controlled and sustained drug delivery platform	[5]
Ibuprofen	97.10% encapsulation efficiency; 88.10% retention in simulated gastric fluid (45 min), 85.20% release in PBS (pH 7.4, 5 min)	Gastrointestinal-targeted release	[6]
Diclofenac sodium	Mitigated hepatotoxicity by reversing elevated serum biomarkers (aminotransferase, alkaline phosphatase, bilirubin) and proinflammatory cytokines; restored antioxidant activity	Prevention of drug-induced liver injury	[7]
5-Fluorouracil	49.00% encapsulation efficiency *via* vacuum-assisted loading; pH-responsive release in gastrointestinal conditions	Gastrointestinal cancer therapy	[8]
Folic acid	8.63% loading capacity and 21.60% encapsulation efficiency; dual functionality in sustained release and UV protection	Photostable nutrient delivery	[9]
Therapeutic peptides/proteins	Alginate-coated sporopollenin microcapsules protected against gastric degradation; triggered release in intestinal alkaline media	Two-stage oral delivery system	[10]

1.2 Processing optimization

GLS has potential applications in drug delivery systems due to their large internal cavity, thermal stability, non-toxicity, and uniform size. Conversely, natural GLS have extremely hard double walls, *i. e*., sporopollenin inner wall and chitin outer wall, which makes it difficult for drug molecules to penetrate the inner cavity effectively, and the drug loading mainly relies on surface adsorption, with a low drug loading capacity, which restricts its application. Nowadays, ultrasonication, milling, acid or alkali treatment, and enzymolysis are mostly used to partially or completely destroy the structure of the spore wall in order to intensify its loading capacity and loading efficiency. Zhao *et al*. [11] found that significant morphological changes, such as rupture, fracture, and disintegration of GLS, were observed by SEM after ultrasound treatment. It was concluded that the best sporocarp-breaking performance was achieved at an ultrasonic power density of 23.7 W/cm^2, a duty cycle of 100% and a treatment time of 90 min. In combination with ultrasound in the ice bath, the efficiency of embryo breaking can be further increased by almost 30%. It is confirmed that the ice bath combined with sonication can deliver GLS components more efficiently and is an economical technique for producing high-quality GLS from broken spore skin. Currently, ultrasonication has been widely used to optimize the treatment of spores. In addition, GLS powder is naturally hydrophobic and prone to agglomeration, with weak dispersion in aqueous media, affecting the uniformity of drug loading and drug delivery. Liao *et al*. [12] pretreated GLS with iturin A to increase its porosity. Subsequent treatment with KOH or HCl enhanced the hydrophilicity or hydrophobicity of the spores, respectively, and a porous GLS carrier with selective affinity was designed to carry hydrophilic or hydrophobic drugs. Modified GLS carriers have increased specific surface area, enhanced porosity, and open internal cavities, resulting in high selectivity and high drug-carrying capacity. These carriers are

characterized by selective drug affinity, high drug loading, sustained release, and gastrointestinal adhesion, providing a novel method for the fabrication of oral carriers.

LCS have many advantages over other spores in terms of drug loading; they are highly homogeneous and have a very small particle size, high uniformity of drug loading, and are convenient to process. In continuation, LCS has a unique single-layer ultra-thick sporopollenin wall with high chemical and physical stability. The purified *Pinus sylvestris* spores also have the advantages of relatively low biological activity and immunogenicity, and low immunization risk. Even so, the deployment of LCS in drug-carrying is also faced with drawbacks such as more difficult wall-breaking. Therefore, LCSs are relatively more difficult to handle, and most of the macromolecules are encapsulated in natural LCS. Mundargi *et al*.[13] accomplished the encapsulation of macromolecules into natural LCS by three different microencapsulation techniques-passive, compression, and vacuum loading. Among them, maximum encapsulation was realized using vacuum loading, and the encapsulation of macromolecules was confirmed by laser scanning confocal microscopy. And its research points out that all developed formulations are highly uniform in size and have a well-defined micro-ridge structure. This study provides ideas for the encapsulation and treatment of more natural spores, showing the promising future of natural spores in the field of drug delivery.

2 Pollen

2.1 Prevalent pollen−based delivery system

2.1.1 Sunflower pollen

Sunflower pollen, extracted from the flower buds of sunflowers (*Helianthus annuus*), is a high-yielding and genetically stable natural resource. The potential advantages of natural sunflower pollen as a drug delivery carrier include: (1) oral safety; (2) unique microstructure with uniform particle size distribution and internal cavities; and (3) rough surface structure with mucosal adhesion properties[14]. Sunflower pollen also contains various bioactive components, such as vitamins, amino acids, and trace elements, which can regulate endocrine functions and enhance immunity, further enhancing its advantages as a drug delivery system. The microcapsule structure of sunflower pollen can be modified or engineered to meet specific drug delivery needs. The shell of sunflower pollen can be designed to be responsive, changing its permeability or stability based on environmental conditions such as temperature and pH, thereby controlling the rate and mode of drug release. These properties make sunflower pollen a versatile and efficient drug delivery carrier with broad application prospects.

2.1.2 Natural pine pollen

Natural pine pollen is primarily derived from the dried pollen of Masson pine (*Pinus massoniana*) or other species within the same genus. Pine pollen is rich in nutrients such as proteins, amino acids, polysaccharides, and minerals[15], which exhibit antioxidant, anti-inflammatory, and antibacterial activities, further enhancing its potential as a drug delivery system. Pine pollen also contains various vitamins, phospholipids, and enzymes, earning it the title of “natural micronutrient bank”. Pine pollen has attracted widespread attention due to its rich nutrient content, bioactive components, and pharmacological effects. Its unique multi-cavity structure and sporopollenin properties give it excellent composite loading capacity.

2.1.3 Ragweed pollen

Ragweed (*Ambrosia artemisiifolia* L.) is an annual herbaceous plant in the Asteraceae family, native to North America and now widely distributed in most temperate regions worldwide. Ragweed pollen is derived from this plant. Due to its high yield, wide distribution, and suitable particle shape and size, ragweed pollen is an ideal candidate for drug delivery systems.

Ragweed pollen contains various phytochemicals, including flavonoids, phenols, and sesquiterpenes, which provide rich functionalities and characteristics for its use as a drug delivery carrier. Ragweed pollen has certain immunogenic properties, stimulating the immune system to produce immune responses, which is significant in studying its impact on human health.

2.1.4 Rapeseed pollen

Rapeseed (*Brassica campestris* L.) is a major oil crop with a wide cultivation area and long flowering period, resulting in high pollen yield. Its chemical composition is complex, containing proteins, amino acids, sugars, lipids, and vitamins. Rapeseed pollen

contains various active substances, such as flavonoids and polysaccharides, which exhibit antioxidant, anti-inflammatory, immune-regulating, and cardiovascular disease-preventing effects. Furthermore, rapeseed pollen demonstrates exceptional biocompatibility and controlled biodegradability, making it an ideal candidate for drug delivery systems. Its inherent physicochemical properties enable sustained drug release while minimizing systemic toxicity, thereby addressing critical challenges in pharmaceutical formulations.

2.2 Processing optimization

Natural pollen exhibits high biocompatibility and biodegradability, with its distinctive porous architecture conferring suitability as a drug carrier. The rigid sporopollenin-based exine can protect encapsulated therapeutics against degradation in harsh biological environments (*e. g.*, gastric acid). Additional advantages include abundant sourcing, cost-effectiveness, and inherent ligand-mediated targeting potential. On the other hand, like spores, they are potentially immunogenic and difficult to standardize, while the production and purification processes are more complex, and the stability of drug loading and control of drug release furthermore need study.

A large number of studies have been conducted to optimize the treatment of pollen. For example, surface modification or chemical modification can improve the interaction between pine pollen and drug molecules, enhancing drug loading efficiency and stability. By using simple vacuum and passive loading techniques, natural pine pollen is able to efficiently encapsulate a variety of molecules, including proteins, organic dyes, and pharmaceuticals, into pollen microcapsules[16]. This technology demonstrates the potential of natural pine pollen as a multifunctional molecular carrier in drug delivery systems and innovative therapeutic microdevices. Cheng *et al.*[17] noted that the distribution of phenolic compounds in pine pollen could be altered by ^{60}Co irradiation and ultrafine grinding wall-breaking treatment, resulting in differences in antioxidant activity and α-glucosidase inhibition. On this premise, it was found that without decreasing the phenolic compound content and α-glucosidase inhibitory capacity, the antioxidant activity of pine pollen could be enhanced by ultramicro-milling wall-breaking treatment after irradiation with appropriate doses of ^{60}Co. These findings provide a technological foundation for advancing pine pollen utilization in nutraceutical formulations.

The presence of a thin waterproof layer of naturally occurring lipid compounds in pine pollen results in reduced permeability. Prabhakar *et al.*[18] found that it is possible to improve pollen surface wetting by removing surface-adherent lipid compounds, exposing the nano-channel structure in the pollen shell, and enhancing the water uptake capacity of the entire pollen structure. Natural pollen has also been explored for multi-therapeutic agent loading to treat diverse pathologies. Leveraging the architectural features of *Pinus massoniana* pollen, researchers developed a novel dual-molecule encapsulation approach *via* integrated vacuum-assisted passive loading; moreover, they realized the spatially controlled encapsulation of both molecules in different compartments of a single microparticle carrier[16]. This technology epitomizes a facile yet potent dual-payload strategy, providing robust support for deploying natural pine pollen in function-tailored drug delivery and innovative therapeutic microdevices.

3 Sporopollenin extraction and functionalization

Sporopollenin is an extremely tough, resistant, and chemically inert complex biopolymer on the outer walls of plant spores and pollen. The chemical backbone of sporopollenin consists mainly of polyhydroxyaliphatic components and polyketide-derived aliphatic α-pyrone elements, but its exact structure is elusive due to its extreme chemical inertness[19]. Intact spores and pollen contain biologically active substances such as nuclei, enzymes, DNA, *etc*., which are potential allergens or immunogens that may trigger allergic reactions when introduced into the organism, severely limiting the safety of their application in the field of drug delivery. In contrast, sporopollenin drug delivery uses purified sporopollenin empty shells. During the extraction of sporopollenin, the internal biologically active substances are completely removed, leaving only the inert shell, which greatly reduces the immunogenicity and allergenicity of the drug-carrying material, making it safer to use for drug delivery. At the same time, the internal cavity of Sporopollenin provides a

larger drug-carrying space. In addition, there are natural differences in the size, shape, and internal structure of individual spores and pollen from natural sources, which are not conducive to standardized production. Sporopollenin removes the complex internal biological structure and is relatively more reproducible as a drug carrier. Sporopollenin also has the ability to regulate drug release more precisely. In conclusion, sporopollenin has a broader perspective in the field of drug delivery compared to spores and pollen, and a large number of studies have been conducted using a variety of different methods for extracting sporopollenin.

Earlier studies used alkaline or acid solution treatments (Figure 2) and physical methods to extract sporopollenin. A balanced protocol of reflux acid hydrolysis with 85% phosphoric acid at 70°C for 5 h resulted in maximized particle yield, efficient protein removal, and good preservation of cage microstructure. Bovine serum albumin has been successfully and efficiently encapsulated into dandelion sporopollenin outer capsules ((32.23± 0.33)% efficiency)[20]. However, harsh reagents (*e.g.*, strong acids and/or bases) may alter the microscopic structure of pollen grains. Enzymatic digestion is another method of obtaining sporopollenin. The use of different sequences of enzymes, such as proteases, lipases, amylases, pectinases, cellulases, and hemicellulases, removes the genetic components of pollen grains and cellulose lining, and this method avoids the use of strong acids, which, in combination with it, prevents some undesirable effects. A study was conducted involving the enzymatic treatment of pollen from three plant species, followed by an analysis of the spectral fluorescence characteristics post-treatment. The results indicate that enzymatic treatment does not alter the chemical structure of sporopollenin. Although the digestion of adjacent components may potentially influence sporopollenin fluorescence emission, such effects are likely minimal and difficult to detect. The few methods that have been developed to extract sporopollenin normally involve long and laborious processes and are not scalable to other pollen types. To this end, Ageitos *et al*.[9] submitted a simplified scheme to fabricate stable and pristine hollow pollen microcapsules. The sporopollenin derived from this method has a low protein content, a textured surface with nanopore morphology, and a low product density. And the optimized process has been validated in varied pollen samples and produced sporopollenin microcapsules for the first time from hemp plants. Owing to the relatively biologically inert interface of spore powder outer membrane capsules, surface modification is an effective strategy to convert them into better biocompatible materials for biological applications. Optimizing the treatment by coating with iron ions and tannic acid can make it have better cell adhesion performance[21], enhance the effect of sporopollenin and expand its application range. The act of incorporating sporopollenin treatment into the original carriers also adjusted the hydrophilicity, antimicrobial and antioxidant properties of the substrate to some extent[22]. The finding is expected to upgrade the performance of many carriers.

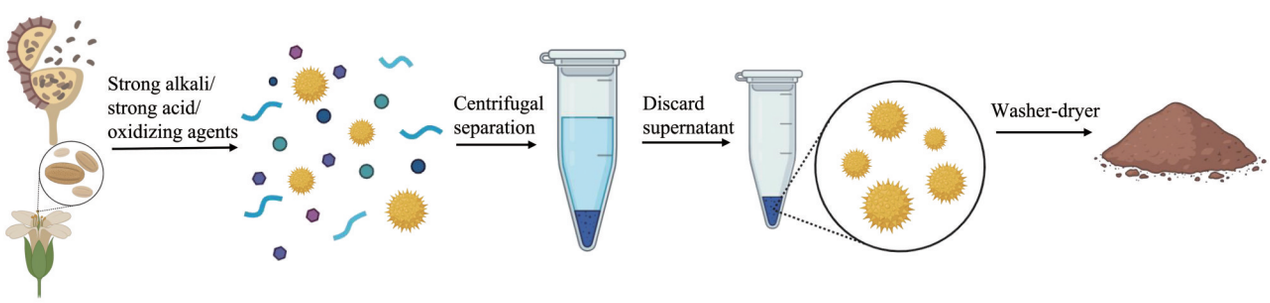

Fig. 2 Chemical extraction of sporopollenin

Overall, the different treatments resulted in significant differences in the chemical composition of the residual sporopollenin, which some studies have argued may stem from the failure to completely remove labile compounds or alter the chemical structure of sporopollenin. Jardine *et al*.[23] reported

that enzyme/solvent treatments were effective in removing labile compounds but may affect biopolymers in sporopollenin; KOH treatments were suitable for small samples but did not completely remove carbohydrates and lipids; H_2SO_4 and HF-Py treatments tend to require longer treatment times, and H_2SO_4 treatments altered the chemical structure of sporopollenin, among others. In summary, it is of critical importance to select the appropriate method for obtaining sporopollenin and use the same treatments for processing to ensure that comparisons are made with like samples. Various methods can also be used to optimize the structure of sporopollenin for better application.

In addition, there are still some issues to be resolved regarding the further application of spore powder. There is currently very limited research on the sensitization risk of sporopollenin residues. Most studies have focused on the biosynthesis, structural analysis, or separation methods of sporopollenin, while fewer studies have been conducted on its allergenicity. Although no direct evidence currently exists to suggest that it is allergenic, further research is needed to assess its potential risks due to its chemical stability and possible coexistence with other allergens[24]. Future research should focus on the behavior of sporopollenin under different environmental conditions, the nature of its metabolites, and its potential impact on humans and animals. Moreover, under the present technical path, large-scale production of pure sporopollenin faces significant yield and cost constraints and is currently limited to research on cutting-edge drug delivery systems. The main obstacles lie in high raw material costs, complex and inefficient extraction processes, difficulties in scaling up, and enormous waste disposal costs, among other issues. We believe that future breakthroughs may lie in the development of milder, more efficient, and environmentally friendly extraction processes, or in achieving efficient biosynthesis, that is, producing large quantities of sporamin or its key structural units through synthetic biology methods[25]. This is the most promising path to scaling up, but it is still in the early stages of research. In addition, attempts to extract sporopollenin economically from waste from other large-scale production processes (such as certain highly refined products with extremely high pollen yields) could also significantly reduce raw material costs.

4 Applications in drug delivery systems

4.1 Targeted delivery

4.1.1 Intestine-targeted delivery

Intestinal-targeted drug delivery requires resistance to the highly acidic, hostile environment of the stomach and degradation by various enzymes in the digestive tract, as well as a certain degree of biocompatibility to avoid interference from the bacterial flora. Natural spores and pollen have high stability and biocompatibility as carriers, which are promising for enteral delivery. Its surface contains phenolic groups, carboxyl groups, *etc*., which play a key role in achieving pH-dependent drug release. It can help achieve targeted intestinal release. In the highly acidic environment of the stomach, the groups are all in a neutral, hydrophobic state and are released very slowly, protecting the drug from degradation by stomach acid or premature release. In the neutral to weakly alkaline environment of the intestine, the group carries a negative charge and is hydrophilic, significantly accelerating release and ensuring that the drug is released at the effective absorption site in the small intestine[26]. This is a commonly used strategy for oral colon-targeted drug delivery. Furthermore, specific enzymes abundant in the intestine also contribute significantly to targeted drug delivery in the intestine.

Under their strikingly monodisperse size distribution, mechanical robustness, and efficient encapsulation, a broad range of plant spores and pollens shows great potential as oral drug carriers, especially for biomolecules and drugs that require targeted delivery. Phosphate-optimized sunflower spore powder ectoplasmic capsules for efficient loading of bovine serum albumin. Vacuum-encapsulated tablets inhibit protein release for up to 2 h in a simulated gastric environment, while 100% release is attained within 8 h under intestinal conditions for precise protection of bioactivity[27]. Similarly, sunflower pollen-derived microspheres are double-coated with eudragit and ascorbyl palmitate, which can respond to increased intestinal pH and esterase enrichment to target drug release and adherence to the site of inflammatory bowel disease injury, enabling intestinal targeted delivery and helping to withstand the hostile environment of the stomach, and dramatically improving the efficiency of

hemostasis and tissue repair[28]. Wu *et al*.[29] prepared soluble mixtures of glycerol monostearate and nobiletin by high-temperature ultrasound to fulfill a supersaturated state of nobiletin. Further encapsulation using alginate hydrogel to control its release under simulated gastrointestinal conditions showed that the sunflower pollen particles exhibited a nobiletin loading capacity of (770±40) mg/g. The synergistic interaction of glyceryl monostearate and alginate hydrogel effectively delays the release of nobiletin, ensuring slow gastric release and prolonged intestinal absorption.

It has been demonstrated that hollow GLS loaded with Fe_3O_4 nanoparticles can be prepared as magnetic GLS, which reveal high drug-carrying capacity, superior utilization efficiency, and low toxicity. As an example, the maximum drug loading of 5-fluorouracil in magnetic GLS reached 250.23 mg/g. The cumulative release rates of 5-fluorouracil in physiological buffer and hydrochloric acid solution reached 80.11% and 67.14% after 48 h, respectively. This validates the feasibility of GLS as a vehicle for controlled, targeted drug delivery[30]. Alongside this, Alshehri *et al*.[31] successfully injected acetaminophen into porous natural sporopollenin microcapsules derived from date pollen. They engineered an oral drug delivery system by coating microcapsules with natural polymer composites. *In vitro* release studies showed a maximum drug loading capacity of 97.2% at pH 6.0. The cumulative release rate of acetaminophen was more than tripled when the pH was increased from 1.4 to 7.4.

For protein/peptide drug delivery, a two-stage drug delivery system was developed by Sudareva *et al*.[10] The first layer consists of the outer wall of rod-shaped *Staphylococcus* spores and includes the target. Alginate microparticles serve as a second layer that protects the peptide from gastric acid and enzymes and slowly releases the target in alkaline intestinal media. In conjunction with this, the introduction of the peptidase inhibitor follicle-like protein into the alginate envelope prevents enzymatic degradation of peptides in the intestinal medium. The system makes possible drug-targeted loading in the gut while providing effective, sustained drug release. Other researchers have successfully harvested sporopollenin microcapsules from natural LCS, encapsulated them with metformin, and encapsulated them in calcium alginate microspheres, achieving sustained release and significantly higher bioavailability of metformin[32].

Inspired by natural pollen, Wang *et al*.[33] prepared polymer particles with controlled surface roughness, strong adhesion to intestinal mucosa, good biocompatibility, high drug-carrying efficiency, and controlled release kinetics, which are well-matched to intestinal targeted drug delivery. Comparably, ragweed pollen microcapsules encapsulating bovine serum albumin and incorporating enteric polymers achieved selective release in the intestine[34]. Further, surface modification, drug loading, and release mechanisms of LCS have been studied thoroughly. Mohammed *et al*.[5] constructed a platform for controlled and sustained drug delivery by extracting high-quality sporopollenin microcapsules from natural LCS and successfully loading acetylsalicylic acid into LCS microcapsules. LCS microencapsulation technology significantly improves drug bioavailability while reducing unwanted drug release in the gastrointestinal tract, thus minimizing acetylsalicylic acid side effects. The study further illustrated clearly that microencapsulation reduces the non-essential release of drugs in the gastrointestinal tract, mitigates side effects, and boosts efficacy.

Summarily, there are numerous innovative points in recent research on natural carrier-targeted intestinal drug delivery: (1) intelligent response design, using the Eudragit-esterase system to achieve precise drug release at the site of intestinal inflammation; (2) functionalization modification, such as the use of magnetic nanoparticle loading and polymer coating, to enhance targeting; (3) multi-layer protection system, such as the use of alginate-sporopollenin composite carriers combined with enzyme inhibitors to comprehensively counteract digestive enzyme degradation.

4.1.2 Stomach-targeted delivery

Gastric-targeted drug delivery requires carriers with an adhesion mechanism to prolong gastric mucosal retention, and natural pollen and spores are advantageous in the field of gastric drug delivery due to their excellent mechanical stability, high drug loading, multifunctional drug loading capacity, and surface modifiability. Yet, in comparison with intestinal targeting, natural spore and pollen carriers need to solve more problems in gastric targeting, for instance, oversize limiting their penetration, lack of precision in retention-release control, *etc.*, as well as

the problem of acidic inactivation. More recent attempts have also been made in research; for example, Cai *et al*.[35] developed a new type of micro-motor based on the pollen of traditional Chinese medicine. By incorporating an asymmetrically sputtered Mg layer on one side of the pollen grains, the Mg layer can react with hydrogen ions to produce a large number of hydrogen bubbles to propel the micro-motor when the motor is exposed to gastric juices. And attributed to its autonomous movement and unique spiny structure, the micro-motor can actively move inside the stomach and adhere to the surrounding tissues, prolonging its retention in the gastric mucosa (Figure 3). The study verified that the micro-motor could effectively deliver berberine hydrochloride with good efficacy in a mouse model of gastric ulcer. This project provides a cutting-edge theory for the targeted drug delivery of herbal pollen to the stomach. The core value of pollen/spore as a gastric-targeted carrier lies in the antacid protection and high drug delivery, but on account of the above mentioned drawbacks, in the short term, it is more applicable to the scenarios of localized long-lasting effects (*e.g*., the repair of gastric ulcers), and for the systematic delivery of the drug, more in-depth studies are required.

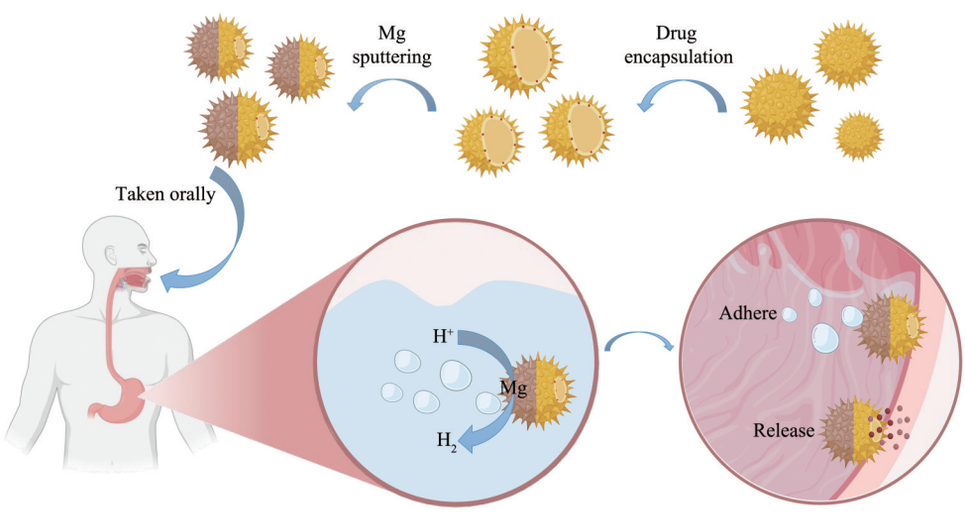

Fig. 3 Preparation of pollen micro−motors as an oral drug delivery system for gastric diseases and their working mechanism in the stomach

4.2 Sustained drug release

Natural spores and pollen, with their singular microstructures (including porous cavities, spiny surfaces) and bioadhesive properties, are emerging as innovative slow-release platforms for breaking through bottlenecks in localized drug delivery. Its slow-release mechanism mainly includes. (1) Sporopollenin has an extremely complex porous structure, and drug molecules can be loaded into these structures[36]. The large specific surface area provides abundant drug adsorption sites. These microstructures form a physical barrier to the outward diffusion of drug molecules, which must travel along these winding paths to be released into the external environment. This effectively slows down the diffusion rate, which is the basis of slow release. (2) Sporopollenin has excellent chemical stability and mechanical strength[37]. This implies that it is not easily broken down or destroyed in the body, ensuring that the drug-loaded particles can maintain their porous structure for a long time in physiological environments (such as the digestive tract and body fluids), effectively delaying drug release. (3) Sporopollenin is mainly composed of long-chain aliphatic polymers and aromatic compounds cross-linked together, giving its surface a natural hydrophobicity. Therefore, hydrophilic drug molecules need to overcome hydrophobic environments in order to diffuse out, which can also regulate the release rate. Besides, surface modification can also change its hydrophilicity and hydrophobicity, which can control the loading and release behavior of

drugs with different properties[19].

In the field of bladder cancer treatment, Hu *et al*. [38] passively loaded pirarubicin by sequential degreasing and acidolysis of sunflower pollen, and the encapsulation efficiency could reach (45.3±1.43)% by utilizing the inherent microscale core-shell structure and spiny surface morphology of sunflower spore powder ectoplasmic capsules (SECs). Moreover, there is also vigorous adhesion to the bladder mucosa after repeated urination, and the drug encapsulated in SECs maintains its concentration in the bladder for upwards of 5 h. In a mouse model of *in situ* bladder cancer, SECs heightened the effect of intravesical chemotherapy with pirarubicin by 38%. This dual-function design of "adhesion-retarded release" has proved to be effective in solving the core problem of short drug retention time in bladder perfusion therapy, and suggests that natural sunflower pollen is expected to be a promising new material for fostering continuous drug delivery therapy. In the domain of skin inflammation treatment, Wang's team[39] designed a natural ascorbic acid-integrated pollen delivery system by loading ascorbic acid into defatted sunflower pollen husks. The results revealed that the pollen shells integrated with bittersweet exhibited strong adhesion and sustained drug release ability, effectively alleviated the symptoms of allergic contact dermatitis (edema, crusting, weight loss, itching), and demonstrated its potential in the treatment of inflammatory dermatoses. Next, in oral anticancer delivery, the encapsulation of the anticancer drug imatinib mesylate by European birch pollen sporopollenin microcapsules demonstrated the long-lasting property of slow release of 65% of the drug in 24 h (complete release in 1 h in the control group), which provides a cutting-edge concept for oral chemotherapy[40]. To optimize gut-targeted slow release, the researchers continued to formulate a brand-new system. Huang *et al*. [41] were inspired by peony pollen to form fresh multilobed microparticles (MPs), which demonstrated excellent adhesion performance by virtue of a larger contact area compared to spherical MPs. Researchers encapsulated the anti-inflammatory drug dexamethasone in a hydrogel matrix and demonstrated that this system executes gradual drug delivery and reliable anti-inflammation in a rat model of inflammatory bowel disease. The results point to the fact that such bionic multilobed MPs are perfect carriers for gastrointestinal drug delivery, combining strong adhesion and long-lasting controlled release. Mundargi *et al*. [8] prepared an oral controlled-release formulation of 5-fluorouracil based on natural LCS. Utilizes vacuum loading technology for maximum package efficiency up to a maximum of 49%. Homogeneous Eudragit RS 100 coating on spores loaded with 5-FU for controlled 5-FU release under simulated gastric (pH 1.2) and intestinal (pH 7.4) conditions as long as 30 h.

In brief, the core strengths of slow-release mechanisms for natural spores and pollen are as follows: (1) structural strengths, with the natural cross-linked sporopollenin layer of pollen/spores forming a diffusion barrier, like birch sporopollenin slowing the release of 65% of the drug for 24 h; (2) prolonged duration of action through adhesion, for instance micrometer-sized spicules or bionic multilobed structures to enhance tissue retention; (3) synergistic control of slow-release by coating, such as the Eudragit coating in response to environmental changes to achieve regulated dosing. Together, these analyses validate the promise of natural spores and pollen to break through the time-limited barriers of traditional delivery and provide a new carrier platform for long-acting treatments of localized lesions.

4.3 Toxicity mitigation

Natural spore and pollen loaded drugs have also been trialed for drug detoxification due to the sporopollenin outer wall that isolates the drug from direct contact with tissues and its slow-release effect that avoids excessive concentrations of toxic drugs, and phenolics that actively neutralize free radicals. To exemplify, the main limitation of diclofenac sodium (DIC) therapy is the adverse effects it causes. Meligi *et al.* [7] discovered that loading DIC in natural lithopone spore powder (LCS) microcapsules is forecast to significantly attenuate its hepatotoxicity. It was revealed that DIC-loaded LCS could potently regulate DIC-induced abnormal elevation of serum aminotransferases, alkaline phosphatase, total bilirubin, and pro-inflammatory cytokines. Researchers also conducted liver function tests on mice and found that the microcapsules exhibited a certain degree of liver protection. Based on previous studies, it is inferred that the mechanism is that carotenoids in the side chain structure of sporopollenin act as physical quenchers of singlet oxygen and remove other reactive oxygen species. In

addition, sporopollenin biopolymers contain covalently bound conjugated phenolic compounds, such as ferulic acid, coumaric acid, and cinnamic acid, all of which have antioxidant activity. Besides, the delivery system restored the DIC-induced decrease in antioxidant enzyme activity, attenuated DNA damage, and ameliorated liver histopathological abnormalities. This test validates that natural spores and pollen can be used as a reliable delivery platform with a higher safety profile and warrants further exploration in clinical studies. Its ability to inhibit toxicity has also been attempted for pesticide delivery, as researchers have produced a structurally stable, uniform-sized controlled-release microcapsule for delivery of the highly effective broad-spectrum herbicide Pendimethalin, using Japanese wolfsbane spores as a natural carrier. The technology targets mitigating the risk of phytotoxicity associated with its overuse. Experiments have shown that a 15% concentration of spore microcapsules significantly reduced oxidative stress in rice seedlings and improved safety compared to conventional formulations[42]. Its good herbicidal efficacy and limited ecological risk highlight the potential of *Lycopodium* spores and even spores in herbicide carrier applications.

According to the analysis of existing research, the core mechanisms of natural sporopollenin in inhibiting drug toxicity include: precise delivery to reduce damage to healthy tissues or organs; attachment to the target site, prolonging retention time and reducing the frequency of administration to prevent damage caused by excessive drug concentration; and the wall layer of sporopollenin contains natural antioxidants that can neutralize harmful free radicals in drugs. The carrier has now been used in lots of applications such as detoxification of tumor chemotherapeutic drugs, protection of the gastrointestinal tract, and brain-targeted detoxification of neurological drugs. Compared to current competitors in the field (*e.g*., liposomes and polymer micelles), spore powder has higher safety and moderate production costs, leading to promising clinical breakthroughs.

4.4 Taste masking

Humans can distinguish between unpalatable flavors at low concentrations, making it hard to ingest some nutritionally valuable but unpalatable food supplements. Currently, natural spores and pollen are also being tried out for taste masking applications. Early on, some researchers encapsulated fish oil with sporopollenin and experimentally demonstrated its success in achieving flavor masking. Diego-Taboada *et al*. [6] encapsulated ibuprofen with sporopollenin (SEC) harvested from LCS and assayed an encapsulation efficiency of 97.1% and no change in the morphology of encapsulated ibuprofen with solid crystals. SEC is non-toxic to human endothelial cells, does not contain allergenic protein epitopes, and is able to resist the gastric environment. In a double-blind trial of 10 human volunteers, SEC was verified to offer significant flavor masking to encapsulated ibuprofen.

The chief merit of plant spores and pollen as flavor-masking drug carriers is the exceptional physical protection supplied by the natural sporopollenin barrier. However, the allergen problem is the most unavoidable drawback of its clinical application, which must be completely solved by reliable and efficient desensitization technology. In addition, large-scale production, cost control, and precise regulation of release behavior are all challenges to be faced. As it stands, there are fewer recent studies on natural spores and pollen in flavor masking. We consider that its development is mainly limited by the lack of odor masking efficiency and difficulty in controlling safety, as well as facing strong competition from synthetic materials. While it is still far from widespread use, continued innovation could revolutionize the field in the future.

4.5 Vaccine delivery

Spores and pollen, especially pollen, have natural immunostimulatory components, and their use as vaccine carriers can decrease the addition of exogenous adjuvants. Studies have proven that chemically treated ragweed pollen can be converted into allergen-free carriers and genetically engineered to carry vaccine proteins. Oral vaccine formulations can be made up by mixing vaccine antigens with ragweed pollen. Alongside encapsulating antigens within the pollen core, a small amount of antigen can be adsorbed on the pollen surface. This treated ragweed pollen formulation stimulates mucosal and systemic immune responses[43]. The unique internal chambers and rigid structure in the outer wall of the pollen not only stabilize the protein structure but also exhibit external morphological advantages such as strong mucosal adhesion, making it particularly

appropriate for nasal mucosal drug delivery. The Chrysanthemum pollen outer wall-based vaccine delivery system enhances protein-antigen stability and boosts adjuvant and antigen co-delivery efficiency while realizing mucosal retention. By precisely regulating particle size and surface charge, the system offers control of *in vivo* distribution and release kinetics[37]. Researchers successfully loaded squalene (Squ) and protein antigen (OVA) onto wild chrysanthemum sporopollenin (Spo) to form a water-in-oil-in-water (w/o/w) emulsion, designing wild chrysanthemum sporopollenin as an adjuvant and carrier for vaccines (Figure 4).

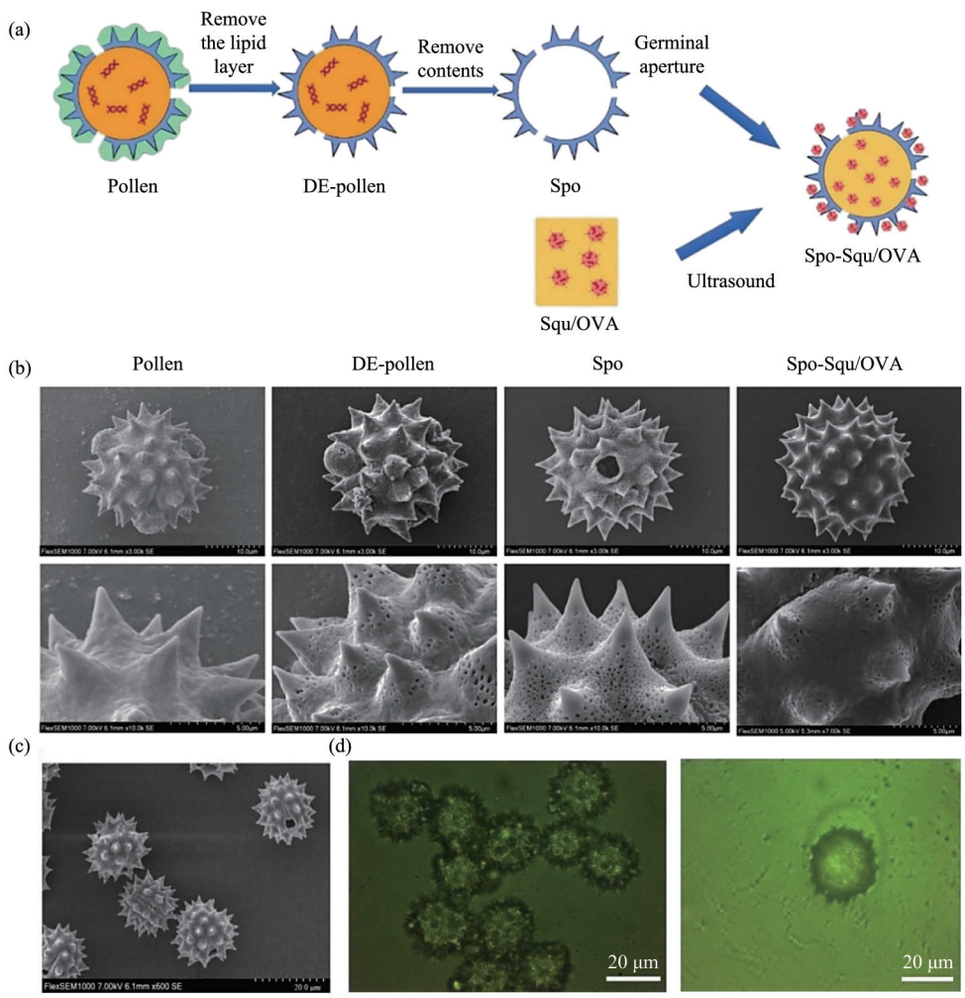

Fig. 4 Preparation process of Spo−Squ/OVA and the shape and morphology of sporopollenin carrier

(a) Schematic diagram of Spo-Squ/OVA preparation process flow chart. (b) SEM images of pollen, DE-pollen, Spo and Spo-Squ/OVA samples at different magnifications. (c) Morphology of Spo under SEM. (d) Morphologies under Spo-Squ/OVA fluorescence microscope. Reproduced with permission from refenrence [37] (CC BY 4.0).

In recent years, sporopollenin has also been employed in a cutting-edge immunotherapy for lung cancer. Overexpression of antiphagocytic molecules in tumor-associated macrophages contributes to tumor cells evading phagocytic capture by associated macrophages. Study of an innovative inhalable microparticle based on spiked sunflower sporopollenin pheromone capsules designed to reprogram macrophages associated with lung cancer treatment. These microparticles utilize sunflower sporopollenin as a delivery vehicle to specifically knock down anti-phagocytic genes on tumor-associated macrophages[44]. This study provides a new and advanced idea for tumor treatment and is one of

the very promising applications of sporopollenin.

Using natural spores and pollen for vaccine delivery can partially address some of the current challenges in this field, including better stability and efficient activation of mucosal immunity. Currently, this carrier has been used in scenarios such as oral nucleic acid vaccines and multi-valent mucosal vaccines, offering irreplaceable advantages. Yet, natural spores and pollen as vaccine carriers also face many controversies. For example, pollen has the risk of residual allergens, and mRNA vaccines and other competitors also pose challenges to its development. Based on existing achievements, we believe that the current carrier has broader prospects for delivery in oral/mucosal vaccines, and it may also be used in the future to manufacture multi-valent vaccine carriers, programmable smart carriers, and so on.

4.6 Delivery of labile substances

Plant spores and pollen have also been examined for the delivery of unstable materials, achieving some progress. Folic acid (FA), an essential vitamin for life, is susceptible to degradation by pH, heat, ultraviolet, and sunlight, resulting in reduced bioavailability. It is critical to develop systems that can aptly secure and deliver such unstable substances. Some experiments have utilized robust rod-shaped lithopone spore powder (LCS) microcapsules to encapsulate FA. The conclusions showed the following facts of LCS. (1) Enhanced stability: LCS microcapsules significantly improved the photostability of FA under UV or sunlight irradiation and effectively resisted environmental degradation. (2) Controlled delivery: FA from LCS microcapsules exhibits pH-dependent controlled and sustained release properties, ensuring predictable and long-lasting delivery. (3) Biocompatibility: *in vitro* experiments have confirmed that the preparation is safe and biocompatible with human skin fibroblasts[45]. The photoprotective and sustained delivery properties of LCS microcapsules are perfectly suited for the delivery of unstable substances (*e.g*., FA), opening up a wide range of applications in oral/topical drug delivery and the food industry. Barrier *et al*. [46] extracted sporulated outer capsules (SECs) of LCS as a microencapsulated carrier with protective potential, particularly adept at encapsulating and stabilizing vulnerable materials. The SECs in the study displayed excellent protection against highly unstable substances: polyunsaturated oils, which are easily oxidized, and equally sensitive enzymes (*e. g.*, streptavidin-horseradish peroxidase, sHRP, and alkaline phosphatase ALP) were ideally encapsulated. And no oxidation of the oil or denaturation and inactivation of the enzyme was observed in the subsequent full recovery of these materials. This survey clearly exhibits for the first time that SECs are capable of microencapsulating a wide group of unstable materials without inducing deleterious changes (*e.g*., oxidation or denaturation), highlighting their great potential as universal safeguard carriers.

4.7 Other aspects

There are plenty of other pioneering applications of natural spore powder. In the antimicrobial field, Yang *et al*. [47] designed a sulfuric acid-treated sunflower sporopollenin exfoliate-derived microcapsule for capturing light and bacteria for antimicrobial photothermal therapy. Experiments showed that the photothermal properties of the sulfuric acid-treated microcapsules were greatly enhanced, with strong bacterial trapping ability for Gram-positive bacteria, which is a good platform for the treatment of bacterial infection diseases. What's more, there are researchers who have designed a biologically safe cryogel hemostatic agent based on the unique microscopic hierarchical structure and non-allergenic chemical composition of plant pollen. The key to the gel's stable macroporous structure without the addition of harmful cross-linking agents is the structure and surface chemistry of the pollen that responds rapidly to water/blood stimulation, triggering a shape memory effect in as little as 2 s, resulting in superior hemostatic performance in the treatment of deep incompressible wounds, such as the mouse liver penetration model, that are simply removable after application[48]. Even further expanding the boundaries of its applications, a variety of natural and non-toxic pollen grains (*e.g*., dandelion, pine, lotus, *etc*.) were used to efficiently fabricate platinum-pollen (Pt-pollen) hybrid micro-robots. These micro-robots are not only exceptionally mobile, which significantly improves the performance of removing heavy metal pollutants from water, but can also be used as carriers to load the anti-cancer drug Adriamycin, realizing the dual functions of environmental remediation and drug delivery[49]. Yekan Motlagh *et al*. [50] also utilized spore powder/zinc oxide as a catalyst for sonic catalytic treatment of 3 organic compounds. After 120 min of the

sonophotocatalysis, it was observed that its degradation efficiency for all three compounds was higher than that of other processes. And due to its stability, the catalyst is reusable after 4 consecutive cycles. Hence, spore-pollen holds promise for environmental remediation, an idea confirmed in a new study by Yang *et al*. [36]. There is already substantial evidence that spore-pollen can be used to remediate water pollution. More interestingly, this innovative idea based on natural spore pollen extends to agriculture as well. Xiang *et al*. [51] innovatively utilized the unique porous surface and highly homogeneous particle size of LCS to develop them into intelligent controlled-release pesticide microcarriers. They loaded the fungicide fluxapyroxad onto spores and further extended the efficacy by calcium carbonate modification. The prepared microcapsules not only exhibited slow-release properties but also supplemented calcium ions in acidic environments (*e. g*., rhizoctonia-occurring soils), and the preventive efficacy was significantly better than that of commercially available formulations in rhizoctonia control experiments for cabbage. This work not only opens up a new way for the development of eco-friendly slow-release pesticides, but also introduces a new perspective on on-demand precision application based on the characteristics of pests, which fully highlights the broad application prospects of phytosporidium from emergency medical care to targeted delivery, environmental remediation, and even AI agriculture.

5 Conclusion and perspective

Spores and pollen, as vital reproductive cells in the biological world, not only play a crucial role in nature but also demonstrate immense potential in the medical field. For spores, their robust outer shells and internal cellular structures provide protection for drugs and stabilize their properties. Encapsulating drugs within spores to form spore microcapsule drug delivery systems not only improves drug stability but also achieves targeted delivery, offering novel approaches for treating diseases such as cancer and inflammatory conditions. Pollen, with its diverse morphological and structural characteristics, has been utilized to develop various innovative drug delivery systems. Leveraging pollen's natural forms and biocompatibility enables sustained release and targeted delivery of drugs, providing more effective solutions for managing chronic diseases, wounds, and other conditions.

In conjunction with existing studies, spores, pollen and sporopollenin have many advantages as natural carriers for drug delivery systems: firstly, they are highly biocompatible, which reduces the risk of biotoxicity. Subsequently, it has a strong structural stability, anti-enzymatic, acid and alkali resistance, which can protect the drug activity. Furthermore, it has good size and loading potential, and its micron-sized particle size and hollow structure are suitable for encapsulating drugs for targeted delivery. Not only that, this natural carrier also has a very good potential for functionalization, which can effectively improve its multi-faceted properties through a variety of novel modifications, such as surface modification, controlled release design and co-delivery, making it more suitable for drug delivery. The drug-carrying application scenarios of spores, pollen as well as sporopollenin have also been better expanded, and in addition to the biomedical field, they are also better used in the agricultural field and even in the field of new robots. Yet their further application is constrained by a number of reasons, including difficulties in large-scale production and the need to develop low-cost, high-yield collection and purification processes. Immunogenicity still exists, and deproteinization or synthetic sporopollenin replacement still carries a certain risk of allergy, and better solutions are urgently needed. Precise regulation of drug release kinetics is also required to ensure its release accuracy. Based on the current research, it is known that spores, pollen, and sporopollenin have better prospects for making eco-friendly carriers, interdisciplinary customized functional carriers, and clinical drug delivery, and are expected to become a new generation of green drug delivery platforms. By harnessing the valuable resources of spores and pollen, we anticipate groundbreaking advancements in drug delivery methodologies. Further exploration of their distinctive physicochemical properties and structural features will allow the development of more efficient and stable drug delivery systems tailored to diverse therapeutic needs. As research on spores and pollen continues to deepen, this emerging field will achieve greater breakthroughs and progress, ultimately contributing significantly to the advancement of human health.

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天然孢子/花粉微载体的制备及其在新型药物递送系统中的应用*

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摘要　孢子和花粉作为自然界中广泛存在的微小生物，具有天然的核壳结构和精细的表面形态。它们在尺寸均匀性、可持续利用、环境友好性、多孔性、两亲性和黏附性方面表现出色。此外，它们还具有良好的生物相容性和生物降解性，有效增强了药物的稳定性和靶向性。它们经酸性溶液、碱性溶液或酶处理等方法提取可得到孢粉素，去除了天然孢子和花粉中原有的生物活性物质，如细胞核、酶和DNA，从而获得了更强的载药能力和更高的安全性。基于以上特性，孢子和花粉被广泛应用于载药系统，包括靶向递送、持续给药、抑制毒性、风味掩蔽、疫苗递送、递送不稳定材料等。本文介绍了常见的用于载药的孢子和花粉及其处理方法。利用近期研发的新型处理方法，可使孢子和花粉具有更高的药物负载效率、稳定性和靶向性等。此外，本文综述了近年来孢子和花粉在载药领域的应用，并涉及部分创新研究内容。基于这些研究成果，进一步阐述了孢子、花粉及孢粉素在药物递送系统中的优势。例如，它们具有高稳定性、药物负载能力强、良好的黏附性、优秀的靶向性，且易于功能性修饰。目前，它们在药物递送领域展现出广阔前景。本文还强调了它们在应用时面临的一些挑战，包括大规模生产困难、需要改进提取和纯化过程，以及存在较低但仍需注意的过敏风险，克服这些挑战，将有助于更充分地发掘它们在药物递送应用中的潜力。根据当前研究，尽管孢子和花粉在临床药物递送中仍存在一些未解决的问题，但它们具有巨大潜力，有望成为新一代绿色药物递送平台。

关键词　药物递送系统，天然微载体，孢子，花粉，孢粉素

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