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Sources, synthesis, physicochemical and functional properties of *Monascus* pigments and their encapsulation strategies for food applications

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ABSTRACT: *Monascus* pigments (MPs), derived from *Monascus* fermentation, exhibit excellent biological activities and exceptional coloring capabilities. However, their broader application in the food industry is significantly hindered by their susceptibility to environmental degradation and the potential risk of citrinin contamination. This review provides a comprehensive overview of the sources, biosynthesis pathways, extraction methodologies, physicochemical properties, and functional characteristics of MPs. Moreover, we critically evaluate current MP delivery systems, highlighting their limitations in achieving controlled release within complex food matrices. To overcome these challenges, this paper proposes a forward-looking research framework, emphasizing that the rational integration of stimuli-responsive smart materials and 3D printing technology enhances the functional stability of MPs. Furthermore, this review underscores the critical interplay between upstream fermentation regulation (to minimize citrinin) and downstream smart encapsulation (to maximize stability). By bridging safe, efficient extraction with precise, controlled release, this proposed system aims to establish a comprehensive technical ecosystem, ultimately facilitating the high-value utilization of MPs in modern food applications.

Keywords: *Monascus* pigments; Stability; Biological activity; Extraction technology; Delivery system

1. Introduction

The growing demand for natural functional food components has positioned *Monascus* pigments (MPs), natural colorants with a millennia-long history of application, at the forefront of food industry research ^[1]. They exhibit excellent coloring properties and demonstrate diverse biological activities, including antibacterial, antioxidant, hypolipidemic, anti-inflammatory, and hypoglycemic effects ^[2, 3]. The coloring capacity and biological activities of MPs remain key areas of interest. However, despite their substantial promise, the broader commercial application of MPs is severely hindered by two primary bottlenecks. First, safety concerns arise from the potential co-production of citrinin during fermentation, a nephrotoxic mycotoxin known to induce kidney cell death at concentrations as low as 50 $\mu\text{mol/L}$ ^[4, 5]. Second, MPs suffer from inherent instability; they are highly sensitive to environmental stressors such as light, heat, and pH fluctuations, making them prone to rapid degradation and discoloration ^[6]. To circumvent these challenges,

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extensive research has focused on enhancing their safety and stability. For instance, citrinin production can be effectively mitigated by regulating pH or incorporating NaCl during the fermentation process^[7]. Furthermore, optimizing other process parameters, such as medium composition, temperature, and magnetic field strength, can similarly minimize citrinin levels, strategies that will be systematically discussed in subsequent sections.

The common methods to enhance the stability of MPs include chemical modification, the addition of color protectants, and encapsulation^[8,9]. However, chemical modification and the addition of color protectants often face challenges such as complex processing, the need for safety assessments, or conflicts with the current consumer preference for “clean label” trends. Advanced delivery systems offer a highly promising approach to overcoming these challenges. By encapsulating MPs within a robust protective barrier, these systems effectively shield the pigments from adverse environmental factors. This encapsulation not only significantly enhances their stability and bioaccessibility but also provides the added benefits of improving sensory attributes (such as flavor and texture) and extending shelf life^[10]. Furthermore, the materials used to prepare the delivery system are typically biomacromolecules such as proteins or polysaccharides, which possess a high degree of safety^[11]. Emulsions, hydrogels, microcapsules, liposomes, and nanoparticles are currently the most common delivery systems, providing greater opportunities for the widespread application of MPs. For example, encapsulating MPs within zein-lecithin nanoparticles has significantly prolonged the shelf life of MPs compared to unloaded MPs^[12]. Therefore, it is critical to develop an effective delivery system to improve the stability of MPs. In the past five years, review articles on MP-related research have primarily focused on fermentation processes and the pigments themselves^[13-15]. Their application in functional foods, cosmetics, and pharmaceuticals remains confined to ‘additive use’, lacking integration with modern delivery technologies such as pH- or reactive oxygen species (ROS)- responsive systems.

This review aims to transform MPs from a promising raw material into a reliable functional food substance by integrating upstream fermentation regulation (achieving high yields and low toxicity) and downstream application innovation (through excellent delivery systems). Specifically, this review will focus on balancing the synthesis regulation strategies of high-yielding pigments and low-citrinin toxins and analyze the stability and biocompatibility limitations of existing delivery systems in practical food applications. Moreover, this review illustrates how to achieve controlled release of MPs in target environments through smart material design, providing a theoretical basis and technical perspectives to promote the safe and high-value application of MPs.

2. Sources, production, and extraction technologies of MPs

2.1 Sources and production of MPs

MPs are derived from the secondary metabolites produced by *Monascus* during the process of growth and metabolism. There are mainly two fermentation methods: solid-state fermentation (SSF) and liquid-state fermentation (LSF).

2.1.1 SSF

SSF is a relatively conventional fermentation method. SSF involves inoculating *Monascus purpureus* onto solid culture media enriched with carbon sources (such as rice, millet, and other grains) and nitrogen sources, then cultivating it under appropriate temperature, humidity, and aeration conditions ^[16]. *Monascus spp.* grows via its mycelium and secretes multiple extracellular enzymes to break down and use nutrients in the medium, undertaking primary and secondary metabolism. During this process, the fungus metabolically synthesizes various polyketide secondary metabolites ranging from orange-red to purple-red in hue, namely MPs. SSF substrate provides nutrients and serves as a carrier and support structure ^[17]. Its pore structure facilitates mycelial spread, oxygen transfer, and heat dissipation, thereby promoting the biosynthesis and accumulation of MPs. The extraction process ultimately yields a product rich in MPs ^[18]. Although *Monascus* has traditionally preferred white rice as its primary substrate due to its high starch content, recent studies indicate that alternative starch-rich crops, such as maize, wheat, and sorghum, show significant application potential ^[19]. Beyond traditional grains, utilizing inexpensive agri-food waste provides an economically viable and scalable alternative to costly synthetic pigments ^[17]. For example, the *Monascus purpureus* M630 strain, generated via room-temperature plasma mutagenesis, demonstrates high efficiency in submerged fermentation for MP production using rice straw hydrolysate as a substrate. Furthermore, this strain exhibits robust tolerance to inhibitory compounds inherent in the hydrolysate, such as furfural and 5-hydroxymethylfurfural, thereby highlighting the viability of rice straw hydrolysate as a cost-effective alternative substrate ^[20]. Beyond substrate selection, the choice of fermentation mode significantly impacts MP production. Compared to LSF, SSF generally achieves higher pigment yields. However, MP accumulation during SSF is highly sensitive to environmental factors such as moisture content, pH, and temperature. Furthermore, conventional SSF processes face substantial industrial bottlenecks: they lack effective online monitoring methods, are highly time- and space-intensive, and present significant challenges regarding process control and batch-to-batch consistency ^[14].

2.1.2 LSF

Modern production is mainly derived from LSF, involving the cultivation of *Monascus purpureus* strains in a liquid medium enriched with carbon sources (such as glucose or malt extract) and nitrogen sources, subjected to deep-layer aeration and stirring ^[21]. During this process, the microbial cells disperse uniformly throughout the liquid phase as free hyphae or spores. They undergo growth and metabolism through efficient absorption of dissolved nutrients, simultaneously secreting and synthesizing MPs (primarily polyketide compounds). The key control parameters include dissolved oxygen levels, temperature, pH, and stirring rate, ensuring optimal metabolic pathways for efficient pigment synthesis and secretion. LSF environment offers uniformity and high mass/heat transfer efficiency, facilitating precise control and large-scale production. High-purity MPs are ultimately obtained by separating the mycelium and extracting them from the fermentation broth or from the mycelium itself ^[22]. Compared with SSF, LSF offers several advantages, including simplified parameter manipulation, shorter fermentation times, larger processing batches, and greater scalability ^[23]. In summary, the choice of fermentation method needs to balance the goals: SSF can be

considered when pursuing higher pigment yield. LSF is a better choice considering process control and large-scale, stable production.

2.2 Optimization of key fermentation parameters

As a natural polyketide secondary metabolite, optimizing key parameters in the fermentation process of MPs are essential to improve pigment yield and reduce citrinin [24]. The primary optimization parameters can be categorized into three aspects: (1) culture medium optimization, such as nitrogen and carbon sources, (2) fermentation process optimization, such as pH and temperatures, and (3) novel fermentation techniques such as low-frequency magnetic fields (LF-MF), gene recombination, and gene editing techniques.

2.2.1 Culture medium optimization

During the fermentation process, the nutrient composition and properties of the medium influence the activity of the microorganisms and consequently the yields of MPs [25]. The use of nitrogen sources affects the composition of MPs, and different nitrogen sources yield distinct MPs colors [26]. Currently, the common nitrogen sources used in the production of MPs include proteins, peptones, and nitrates. For example, Orak et al. employed chicken feather peptone as the sole nitrogen source for MPs production, achieving higher yields of *Monascus* red pigments (MRPs) and *Monascus* orange pigments (MOPs) than with the addition of fish peptone and protease peptone [27]. Moreover, as chicken feather peptone is extracted from waste feathers, it offers a more cost-effective solution. Moreover, research indicates that organic nitrogen sources (such as yeast and peptone extract) generally promote pigment synthesis more effectively than inorganic nitrogen sources (such as sodium nitrate) and can inhibit citrinin production [28]. During the fermentation of MPs, nitrogen sources enhance MPs yield by influencing microbial growth and metabolic enzyme synthesis, whereas carbon sources affect MPs yield through alternative mechanisms. Carbon sources are the foundation for energy and material, influencing the growth, metabolic pathways, and product synthesis of *Monascus*. The type of carbon source influences the pathways of pigment synthesis. While rapidly utilized carbon sources (such as glucose and sucrose) promote *Monascus* growth, prolonged exposure to high glucose concentrations may inhibit pigment-synthesizing enzyme activity, thereby inhibiting pigment production. Conversely, slowly utilized carbon sources (such as starch or maltose) provide a stable metabolic flux, continuously promoting pigment accumulation, which makes them more suitable for SSF or LSF of *Monascus*, prolonging the synthesis period of secondary metabolites and enhancing pigment yield [29].

2.2.2 Fermentation process optimization

pH is a key parameter in the fermentation process of MPs. It has been shown that the optimal pH range is weakly acidic, where acidic conditions inhibit citrinin production and enhance pigment stability [7]. Both excessively low and high pH levels inhibit mycelial growth and reduce pigment yield. As reported by Chen [30], on a glucose-peptidone medium at pH 6.5, pigment secretion was promoted, and pigment yield increased. Moreover, the activity of key enzymes (such as polyketide synthase (PKS) and oxidoreductase) for the synthesis of MPs in *Monascus purpureus* depends on a specific pH environment, and deviation from the

optimal pH range reduces enzyme efficiency [31]. In addition to enhancing pigment yield, pH also regulates citrinin production, such as under extremely low pH conditions (≤ 2.5 -3.0) where the biosynthetic gene cluster for citrinin is completely inhibited, thereby blocking its production, and promotes the accumulation of orange and yellow pigments [32]. However, this method can control citrinin production but yields lower pigment levels. Temperatures are one of the critical parameters regulating microbial growth and fermentation processes. Different temperatures also affect pigment color and yield [33]. For example, a study demonstrated that raising the fermentation temperature from 30 °C to 35 °C shifted the primary pigment from Y1 to Y3 and Y4. This finding was attributed to the elevated temperature, which promoted the expression of relative pigment biosynthesis genes such as MpFasA2, MpFasB2, mppB, and mppE [34]. This is consistent with the findings reported by Babitha [17], who indicate that the optimal fermentation temperature for MPs is around 30 °C. In summary, the appropriate fermentation conditions (pH and temperature) are crucial for enhancing MPs yield.

2.2.3 Fermentation techniques optimization

In addition to conventional methods for optimizing fermentation process parameters, novel fermentation techniques have been used to increase MPs yield and reduce citrinin production. LF-MF (< 300 Hz) is a novel approach that promotes sodium ion influx and activates the HOG-MAPK signaling pathway. It also upregulates global regulatory genes (veA/laeA), thereby specifically enhancing pigment synthesis gene expression (pksPT/pigR) and inhibiting streptomycin genes (pksCT/ctnA), ultimately influencing pigment yield and reducing the content of citrinin [35]. In addition, LF-MF can influence pigment yield by modulating intracellular electron transport and free-radical reactions. Liao et al. found that LF-MF (50Hz, 1.6mT) ROS signaling in *Monascus purpureus* during early fermentation significantly enhanced red yeast pigment yield by upregulating antioxidant systems (such as SOD and GSH) and specifically modulating the expression of pigment synthesis genes, including the polyketide synthase gene pksPT, whilst inhibiting the synthesis of monacolin [36]. In addition to regulating ROS responses, magnetic fields can also control citrinin production by modulating intracellular and extracellular iron levels. Yang et al. confirmed that applying a 1.6 mT magnetic field for two days during the early fermentation stage of *Monascus purpureus* promoted intracellular iron efflux, reduced iron content, and thereby increased pigment yield while decreasing citrinin production [37]. In addition, genetic recombination technology has been widely used as an effective method for regulating the *Monascus* fermentation process. Ghosh reported the selection of the red yeast fusional clone F2-19 through multiple rounds of genetic recombination, achieving a significant 67% to 76% increase in yellow, orange, and red pigment yields compared to the original strain [38]. High-performance liquid chromatography analysis confirmed that the fermentation products of this strain are rich in multiple beneficial active compounds, with the key safety indicator, citrinin, not detected, thereby fundamentally eliminating contamination risks while achieving highly efficient yield enhancement. In addition to genetic recombination, gene-editing techniques are used to regulate citrinin production. Liu et al. identified that industrial strains of *Monascus purpureus* producing food coloring pigments are frequently contaminated with the nephrotoxic mycotoxin citrinin, which remains challenging to address through conventional methods [39]. By optimizing CRISPR/Cas gene-editing

technology, they successfully deleted the 15 kb citrinin synthesis gene cluster. This approach yielded stable homozygous mutants that eliminated the toxin while increasing pigment yield by 2-5%. The above study suggests that multiple factors influence MPs production, and that a combination of multi-parameter synergistic optimization and advanced monitoring techniques will significantly increase MPs yield and reduce citrinin production.

In addition, beyond yield enhancement, advanced synergistic extraction methodologies play a pivotal role in refining the purity of the pigment isolates. By effectively minimizing competitive impurities through selective extraction, these green technologies significantly reduce steric hindrance and unwanted chemical interference during the subsequent encapsulation process, thereby substantially increasing the MPs loading capacity and encapsulation efficiency (EE) of the delivery systems.

2.3 Biosynthetic pathway of MPs

To enhance the yield of MPs and reduce the production of citrinin, a detailed understanding of the MPs biosynthesis pathway is crucial. It has been demonstrated that the metabolic synthesis of MPs results from multiple pathways, among which the polyketone pathway is one of the most primary ^[40]. Figure 1 illustrates the polyketide synthetic metabolic pathways of MPs under different environmental conditions and their regulatory mechanism. Critically, the biosynthetic pathways for MPs and citrinin are closely linked and competitive. The biosynthetic pathways for the secondary metabolites of *Monascus purpureus* (MPs and citrinin) both utilize the condensation of acetyl-CoA and malonyl-CoA as substrates ^[41]. Environmental factors such as changes in fermentation conditions affecting the oxidation-reduction potential (ORP), ethanol, H₂O₂, or pH across the membrane can enhance cell membrane permeability, promote the fatty acid synthase (FAS), and increase pigment yield ^[42, 43]. Concurrently, LF-FM can promote the release of intracellular pigments into the extracellular environment, thereby alleviating feedback inhibition ^[37]. High-salinity stress can also mitigate inhibition through stress responses, thereby significantly enhancing MPs yield ^[44]. In addition, activation of the cAMP signaling pathway further promotes pigment synthesis ^[45]. Meanwhile, pH and light conditions regulate pigment composition: acidic conditions favor the formation of yellow pigments, while alkaline conditions promote the synthesis of red pigments. Different light qualities can also modulate the proportions of pigment components. MPs synthesis generally involves the formation of chromophores and β -keto acids catalyzed by PKS and FAS, respectively. These subsequently combine under esterase action to produce MOPs. The MOPs subsequently undergo an amination reaction to convert into MRPs, ultimately forming *Monascus* yellow pigments (MYPs) through the action of a reductase. Understanding this competitive relationship is fundamental for devising strategies to decouple the pathways and achieve the dual goal of high MPs yield and low citrinin contamination.

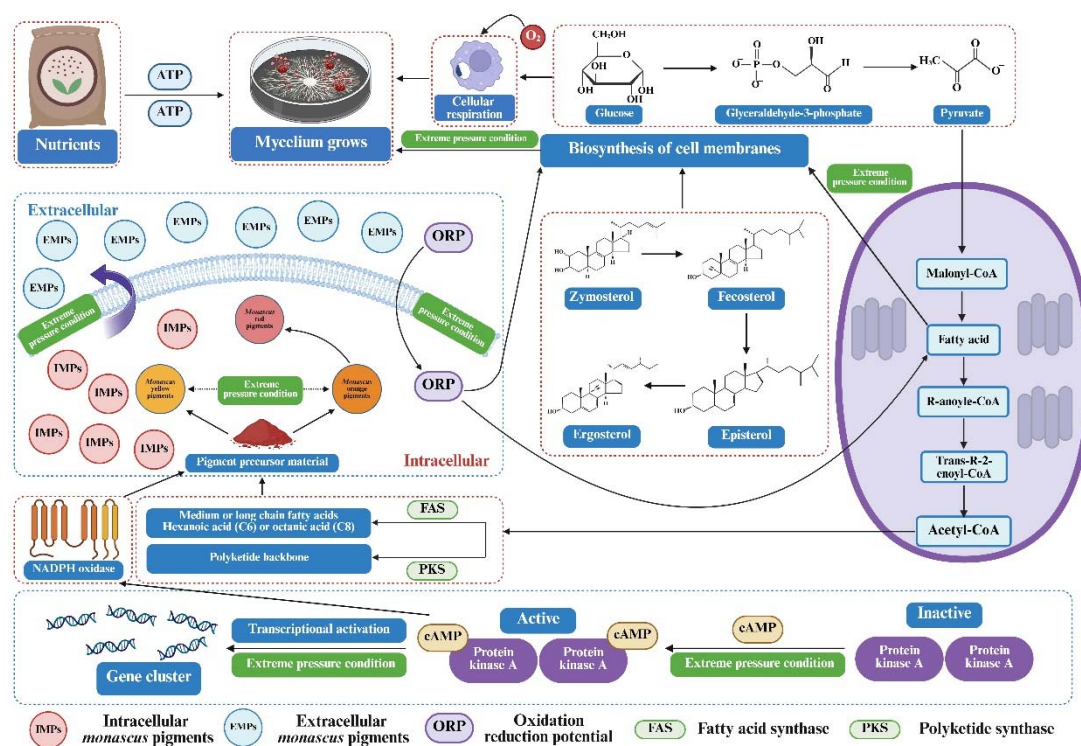


Figure 1: Synthetic metabolic pathway of MPs. MPs are primarily synthesized through the polyketide pathway. This pathway uses acetyl-CoA as its initial substrate, which PKS catalyzes to progressively form a polyketide backbone through condensation reactions. Meanwhile, FAS synergistically introduces medium-chain fatty acid side chains, collectively constituting the pigment precursor. These precursors undergo cyclisation, oxidation, and modification reactions, ultimately converting into three pigment classes: red, orange, and yellow. Environmental factors (such as pH, light, LF-FM, and high salinity) can influence pigment composition and yield by regulating the expression of key genes and metabolic fluxes within this pathway.

2.4 Advances in extraction and purification technologies

An appropriate extraction technique is essential to enhance the quality and yield of MPs. The conventional solvent extraction methods, including Soxhlet extraction, water extraction, and distillation extraction, are often limited due to their time-consuming nature, high energy consumption, low efficiency, and environmental pollution [46]. Therefore, some novel green extraction techniques have emerged, including biosurfactant extraction (BE), ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), supercritical CO_2 extraction (SCE), and enzyme-assisted extraction (EAE). Figure 2A shows the different extraction techniques. The advantages and disadvantages of each novel extraction technique are listed in Table 1.

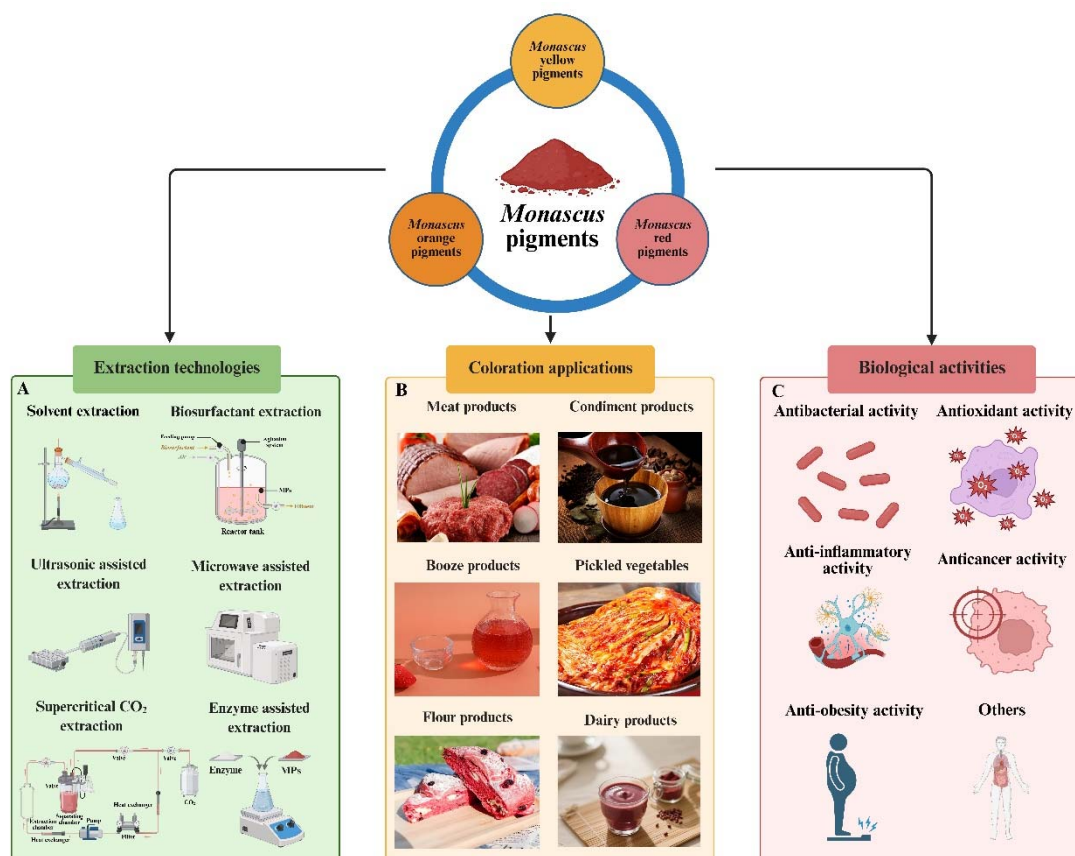


Figure 2: Overview of the categories of MPs and their extraction techniques and functional properties. (A) Extraction techniques, (B) Coloration applications and (C) Biological activities of MPs.

2.4.1 Conventional method

Soxhlet extraction is the simplest and most commonly used solvent extraction (SE) method for MPs. It is widely adopted for its simplicity and low cost, yet its extraction efficiency is sensitive to the type of extraction solvent used [47]. Extraction solvents commonly used in the SE method include ethanol, methanol, benzene, chloroform, and ethyl acetate. For example, Ghosh compared the effects of different extraction solvents on MYPs yield. They found that ethanol yielded the highest extraction rate (1559.8 ± 10.7 AU/g), significantly exceeding those achieved with methanol, hexane, ethyl acetate, and acetone [19]. This finding also indicates that the selection of the extraction solvent is a critical parameter in the Soxhlet extraction process, directly influencing the extraction efficiency of the target compounds. However, conventional extraction methods have several disadvantages, including excessive consumption of organic solvents and energy, as well as incomplete extraction. Moreover, the volatile solvents used in this process pose safety risks and cause environmental pollution, while the high temperatures involved may degrade heat-sensitive bioactive ingredients [48]. Therefore, to enhance the efficiency, safety, and reliability of MP extraction, novel extraction techniques have emerged to overcome the inherent limitations of conventional methods. Many of these innovative approaches are classified as ‘green technologies’ due to their reduced reliance on organic solvents and minimal environmental impact. Representative methods encompass green physical extraction techniques (such as UAE, MAE, and SCE) and bioprocessing methods (such as BE and EAE).

2.4.2 Green physical processing

The UAE relies on mechanical vibration and cavitation effects, which disrupt the cell wall and membrane of *Monascus* rice flour particles, promoting pigment release and thus accelerating contact and mass transfer between MPs and the solvent^[49]. Meanwhile, ultrasonic vibration can also promote solvent penetration and diffusion, further improving the extraction efficiency of MPs^[50]. For example, Yang et al. obtained a high-yield mutant of MPs by treating the *Monascus* strain with ultrasonic mutagenesis, and the production of MPs increased by 29.74% compared to the original *Monascus* strain. The results showed that the UAE could improve the extraction efficiency of MPs^[51]. Moreover, reports indicate that the UAE can precisely regulate system temperatures, making it more suitable for extracting heat-sensitive active substances such as pigments^[52]. However, high ultrasonic power and long processing time should be avoided during the extraction process to prevent damage to the MPs' structure and degradation. Moreover, the synergistic promotion of high-quality, high-yield MPs can be achieved by optimizing the UAE parameters.

MAE combines microwaves with solvent extraction, the microwave energy intensifies molecular motion and solvent-extraction interactions within the field, accelerating diffusion of the extract from cells and boosting extraction efficiency^[53]. However, no reports on studies of MPs extraction using MAE were found, likely due to the requirement for heating during the extraction process, which is not conducive to heat-sensitive pigments such as MPs^[54]. Therefore, future research should focus on temperature control and shortening extraction time while maintaining high extraction efficiency to minimize heat-induced degradation of heat-sensitive pigments.

SCE uses supercritical fluids with unique solvency at critical temperature and pressure for substance separation and extraction; its controllable pressure and temperature regulation can increase MPs yield^[55]. CO₂ is the most commonly used supercritical fluid due to its low critical conditions (31.1 °C and 74 bar), stable chemical properties, and non-toxicity, tastelessness, and non-flammability^[56]. Compared with conventional solvent extraction methods, SCE enables extraction without organic solvents and minimizes their use^[57]. The SCE process is usually conducted at lower temperatures, which effectively prevents the degradation and oxidation of MPs at high temperatures, thereby ensuring the quality and stability of the pigments^[58]. Meanwhile, CO₂ exhibits good selectivity, enabling it to extract the effective components from MPs, reduce impurity introduction, and thereby improve product purity. Moreover, the physicochemical properties of CO₂ do not contaminate the environment or the product, aligning with the safety requirements of the modern food industry. Although efficient extraction of MPs can be achieved by adjusting pressure and temperature, this requires larger machines, which increase cost and severely limit the application of SCE in food processing, thereby explaining the dearth of studies exploring the use of SCE to extract MPs.

2.4.3 Bioprocessing techniques

Biosurfactants are surface-active compounds derived from microbial metabolism, offering advantages including biosafety, low cost, and environmental friendliness, with extraction efficiency primarily dependent on surfactant type and concentration^[59]. The common biosurfactants include sophorolipids, peptidolipids, saponins, and rhamnolipids^[60]. Several studies have shown that the extraction efficiency of MPs by different

types of biosurfactants varies with their molecular structures and properties. For example, anionic rhamnolipids and mixed sophorolipids may improve the extraction of MPs by compounding. As the compounded surfactants synergize, they exhibit superior physical properties and reduce the total amount of surfactant ^[61]. Moreover, the use of biosurfactant and MPs complex also has a positive effect. Yang et al. developed a ginsenoside-MPs fermentation system, and the results showed that ginsenosides promoted the production of MPs and demonstrated stronger regulation of lipid metabolism ^[62]. This synergistic effect increases the yield of MPs and, to a certain extent, improves their stability. Although BE is a good alternative to SE, its typically mixed nature limits its specificity for specific pigments. It is susceptible to environmental factors (e.g., pH, temperature), leading to instability and the potential introduction of impurities that can complicate subsequent purification.

EAE primarily relies on the specific catalytic effects of enzymes. In addition, the EAE method has no solvent residue and mild reaction conditions. It does not require expensive equipment compared to conventional extraction methods and other green extraction techniques such as SE, SCE, UAE, and MAE. It has been reported that probiotics may serve as tools to assist in the EAE of MPs. For example, *Lactobacillus* is a probiotic widely used in MPs extraction for its ability to convert carbohydrates into lactic acid and to produce amylase, protease, and other enzymes. Zhu et al. used lactic acid bacteria to facilitate the fermentation of structured soy protein with MPs, and the results demonstrated that lactic acid bacteria could enhance the production of MPs, which could be extracted to a maximum color value of 34.47 ± 0.91 U/g ^[63]. Although the EAE method has advantages, the requirement for enzymatic reactions, which are highly dependent on temperature and pH, will directly affect enzyme activity and thus extraction efficiency. MPs are pigments that are sensitive to temperature and pH. Therefore, it is crucial to strike a balance between the two to achieve optimal extraction efficiency.

2.4.4 Synergistic extraction

Six extraction methods have been introduced in detail, and the shortcomings of each method have been delineated in the preceding sections. Only one extraction method cannot fully meet the extraction requirements, and the use of combined processing is an effective approach for enhancing extraction efficiency and mitigating safety risks. In the future, combined extraction methods (e.g., enzyme-assisted extraction with ultrasound/microwave, supercritical CO₂ extraction with enzyme) can be used to achieve a synergistic effect, resulting in higher extraction efficiency and yield. For example, ultrasound combined with enzyme pretreatment (e.g., pectinase, cellulase) has been successfully applied to *Camellia oleifera* shell pigments. Enzymes can destroy cell wall structure, and ultrasonic pretreatment can further enhance cell wall disruption and mass transfer. Its results show that the combined method in the extraction time of 77 min and the extraction temperature of 64 °C, under the condition of cellulose concentration of 10 mg/mL, the highest pigment extraction rate of 38.56%, and has the pigment has a better thermal, pH, and light stability as well as a better antioxidant activity ^[64]. However, the combined technology for MPs extraction is still in the exploratory stage, and no research reports have been published. The key issues are how to optimize enzyme type and parameters

to prevent MPs degradation, how to control the extraction temperature to improve stability, and how to evaluate the impact of techno-economic and combined processes on MPs safety, ensuring that citrinin production is reduced. In addition, efficiently and stably integrating different unit operations (e.g., enzymatic hydrolysis, ultrasound, and extraction) into a continuous or semi-continuous automated system is a key challenge to achieving industrialization. Future research should focus on the specific synergy mechanism, process standardization, and amplification effect of the combined extraction.

Table 1 Overview of MPs extraction technologies.

Extraction technology	Principle of extraction	Advantages	Disadvantages	Extraction condition	MPs yield	References
Solvent extraction (SE)	The use of the principles of solvent reflux and siphoning, the solids are extracted by pure solvent each time, thus extracting the pigments	Simple operation, low equipment cost, more complete extraction	Time-consuming, high temperatures may lead to degradation of heat-sensitive substances, solvents may have toxic side effects	Different ethanol concentrations (40, 50, 60, 70, 80 and 95% (v/v)) and temperatures (25 °C and 60 °C)	Ethanol concentration of 95% v/v and temperature of 60 °C resulted in a maximum yield of 1760 µg/g	[65, 66]
Ultrasonic assisted extraction (UAE)	The use of ultrasonic cavitation effect generates mechanical force, destroying the cell wall, enhancing the permeability of solvents and accelerating the dissolution of pigments	Short extraction time, high efficiency, mild conditions, and relatively low energy consumption	May produce free radicals leading to pigment degradation, equipment scale-up limitations, noise pollution	The ultrasonic irradiation was started after 12 h of incubation and irradiated every 6 h for 5 s, 10 s, 30 s, 1 min, 2 min, 5 min, 10 min and 20 min, respectively	MPs yield increased by 29.74%	[51, 67]
Microwave assisted extraction (MAE)	Through microwave heating, the temperature inside the cell rises rapidly, the pressure increases, leading to cell rupture, pigment release	High extraction efficiency, low solvent consumption, high thermal efficiency, and high selectivity	Heating may be uneven, limited penetration depth, high equipment cost, unfriendly to heat-sensitive substances	/	/	[68]
Supercritical CO ₂ extraction (SCE)	Extraction of pigments using the high permeability and solubility of supercritical CO ₂ (SC-CO ₂), with solubility controlled by adjusting temperature and pressure	Green (no organic solvent residue), high selectivity, mild conditions, suitable for heat-sensitive substances and high extraction efficiency	High equipment investment, high operating costs, high voltage operation required	Activated <i>M. Monascus</i> (≥ 10 ⁶ total spores/mL) were inoculated into sterilized coix seed (10 mL/100 g) and fermented for 10 d at 30 °C	The fermentation products were γ-tocotrienol (72.83 µg/g), γ-oryzanol (745.96 µg/g), cochineal lactone (9.65 mg/g) and oleic acid (16.58 mg/100 g)	[69, 70]
Biosurfactant extraction (BE)	The use of biosurfactants (e.g. rhamnolipids and acacia glycolipids complex) to form	High extraction efficiency, good biosafety, no separation	Optimization of surfactant compounding ratio may be required, high	A novel integrated fermentation system (IFS) consisting of	MPs yield of 126.7 U/mL	[71]

	micellar structures to solubilize pigment molecules and disrupt cellular structure	of surfactants required	cost, long-term stability to be studied	sodium octenyl succinate and Triton X-100				
Enzyme assisted extraction (EAE)	The use of enzymes (e.g., α -amylase, cellulase, etc.) to degrade cell wall components (e.g., cellulose, starch) and intercellular substances, destroying structure and releasing pigments	Mild conditions, high specificity, environment friendly, low energy consumption and increase the yield of water-soluble pigments	High enzyme cost, longer reaction time, requires strict control of pH and temperature, and may introduce impurities that increase the difficulty of purification	The mass ratio of TSP to rice starch was 3:2 (w/w) and fermentation at 30 °C for 7 d	70.65 $\pm$ 0.70	U/g	[63, 72]	

3. Physicochemical and functional properties of MPs

3.1 Physicochemical properties

In food processing, the physicochemical properties of MPs directly influence food texture and appearance. MPs have a range of physicochemical properties that determine their function and applications across various fields. Structurally, the core feature of MPs are polyketide-derived, fused quinone-heterocyclic chromophore system with long aliphatic side chains, which is key to their presentation of different colors [73]. The three colors of MPs are classified by maximum absorbance: MRPs (490 - 530 nm), MOPs (460 - 480 nm), and MYPs (330 - 450 nm) [74]. They are structurally closely related and are typically interconverted through redox states of side chains or open/closed loops. The solubility and stability of MPs in water exhibit regular pH-dependent fluctuations, with good solubility in neutral to alkaline conditions and a significant decrease in solubility in acidic conditions (pH < 4.0) or high-salt conditions (salt concentration $\geq$ 5%) [75]. Moreover, the solubility of MPs can be significantly improved by modern fermentation techniques or subsequent modifications (e.g., compounding with amino acids and proteins), which enables their widespread application in aqueous food systems such as beverages, ice cream, and jelly. In addition, as explained in the above section, MPs are unstable under pH and light conditions. The pH instability arises because the chromophore groups (such as conjugated alkenone and phenolic hydroxyl groups) in its structure are prone to protonation or dissociation under acid and alkaline conditions, leading to changes in molecular configuration and disruption of the conjugation system, thus causing fading or discoloration. It is unstable when exposed to light mainly because its molecular polyketone chromophore readily absorbs light energy (especially ultraviolet light), triggering photo-oxidation reactions and free-radical processes, leading to the destruction of the conjugated structure and discoloration [76, 77]. The reasonable avoidance of these factors is conducive to the more effective application of MPs in the food sector.

3.2 Functional attributes and mechanistic insights

MPs have attracted academic attention due to their excellent functional properties and potential applications. Its functional properties are mainly divided across two aspects: (1) coloration; (2) various

biological activities (Table 2). Figure 2B and 2C show the coloration applications and biological activity of MPs.

3.2.1 Coloration

Nitrites are extensively utilized in traditional food processing owing to their versatile functional properties, serving as ubiquitous additives that profoundly influence the sensory quality of meat products. They can effectively inhibit the proliferation of harmful microorganisms, thereby preventing lipid oxidation and spoilage in meat products [78, 79]. Moreover, it can give meat products their desirable pink color and unique flavor characteristics [80]. However, as health concerns increase, the health problems caused by nitrite are gradually being exposed. The formation of carcinogenic nitrosamines resulting from nitrite use in meat products poses severe health risks. Consequently, the search for viable nitrite alternatives has attracted considerable attention in food science research. MPs present a promising solution, as they exhibit exceptional coloring capacity, possess diverse biological activities, and offer a significantly superior safety profile compared to nitrites. In the food industry, MPs are used as food coloring agents in meat products. However, while MPs are widely utilized for coloring meat and other food products, their inherent instability poses significant challenges for practical applications [81]. This review outlines effective approaches to address the aforementioned issues in subsequent sections.

3.2.2 Antimicrobial action and food preservation potential

As a natural antimicrobial agent, MPs can effectively inhibit microbial growth and delay food spoilage, thereby improving food quality and safety. *Bacillus subtilis* is a typical Gram-positive bacterium, and its most prominent structural feature is its ability to form endophytic spores, which is a key structure for its adaptation to harsh environments [82]. *Bacillus subtilis* may cause local infections (such as in the lungs, wounds) or sepsis in immunocompromised individuals (such as AIDS patients, postoperative patients), thereby posing a serious threat to human health [83]. Additionally, the heat-resistant nature of its spores may lead to food spoilage if sterilization is incomplete. Moreover, food quality may be affected despite its inability to produce strong toxins [84]. It was reported that MPs had significant antibacterial ability against Gram-positive bacteria [85]. Due to their excellent antibacterial properties, MPs have shown significant potential for natural preservation and prolonging shelf-life, especially in the application research of perishable foods (meat or milk).

3.2.3 Health-promoting properties: From cellular defense to metabolic regulation

MPs are rich in flavonoids and polyphenols, which possess strong free radical-scavenging ability [86]. Scavenging free radicals can slow down skin aging. Meanwhile, it may have a role in preventing chronic diseases (e.g., cardiovascular diseases) [87]. Studies have shown that MYPs can effectively enhance antioxidant enzyme activity and reduce lipid peroxidation, thereby preventing fatty liver and alcoholic liver injury [88]. Inflammation is a complex physiological defense mechanism that plays a crucial role in the body's defense against pathogen invasion and the repair of tissue damage [89]. The core features of this process include the regulation of cellular release of inflammatory cytokines and the infiltration and recruitment of inflammatory

cells. The imbalance of the homeostatic regulatory mechanisms of the inflammatory cytokine network can lead to obesity, colitis, atherosclerosis, and other chronic inflammatory conditions ^[90]. MPs can inhibit the activation of key inflammatory signaling pathways, such as NF- κ B and MAPK, thereby reducing the production of inflammatory mediators, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), iNOS, and COX-2 ^[91]. Moreover, differences in anti-inflammatory activity between pigments have been reported, and in this study, the MOPs had significantly stronger anti-inflammatory activity than the MYPs, primarily due to structural differences in their hydroxyl group at the C-8 position ^[92]. Notably, there is a close synergy between the antioxidant and anti-inflammatory mechanisms of MPs: by reducing oxidative stress, they indirectly inhibit the initiation of inflammation and suppress it, thereby diminishing the release of reactive oxygen species and breaking the vicious cycle between oxidative stress and chronic inflammation. Based on these studies, MPs exhibit multiple health benefits, including slowing skin aging, preventing chronic diseases, and mitigating alcoholic liver damage by scavenging free radicals, enhancing enzyme activity, and inhibiting the expression of inflammatory factors.

According to the 2022 report of the *International Agency for Research on Cancer*, 9.7 million people have died from cancer ^[93]. MPs have been shown to induce apoptosis in tumor cells through various pathways. It may affect signal transduction pathways in tumor cells, activate apoptosis-associated proteases such as caspases, and promote programmed tumor cell death ^[94]. Although MPs have excellent anticancer properties, their safety issues cannot be ignored. Appropriate human dosage and its effects still need to be further specified through clinical trials. In addition, with the increasing pressure of life, people tend towards high-sugar and high-fat diets to relieve stress, which makes them prone to obesity. In recent years, it has been discovered that MPs and their related components (such as monascins and ankaflavins) may have potential roles in the field of anti-obesity, given their mechanisms involving the regulation of lipid metabolism, inhibition of adipocyte differentiation, improvement of insulin resistance, modulation of intestinal flora, and other physiological processes ^[95, 96]. Moreover, it has been demonstrated that tryptophan and 2-(p-tolyl) ethylamine derivatives in MPs exhibit a strong inhibitory effect on lipases ^[97]. In addition to inhibiting enzyme activity, MPs may also exert anti-obesity effects through other mechanisms. Some studies have suggested that monacolin analogs in MRPs may exert their anti-obesity effects through multiple targets and pathways, particularly by reducing insulin resistance ^[98]. In addition, it has been demonstrated that MPs can enhance intestinal barrier function and reduce fat absorption by regulating the intestinal flora, increasing beneficial flora, and inhibiting pro-inflammatory flora ^[99]. Overall, MPs demonstrate remarkable potential in the field of anti-obesity through multiple mechanisms, including the inhibition of lipase activity, regulation of lipid metabolism, improvement of insulin resistance, and remodeling of intestinal flora.

Based on the above biological activities, MPs have potential applications in several functional food fields, including liver-protecting foods, where their antioxidant and anti-inflammatory properties can help reduce the metabolic burden on the liver ^[100]. In cardiovascular health foods, it regulates lipid metabolism and lowers cholesterol. In weight-managed foods, they reduce fat absorption and accumulation ^[101]. In addition, its

potential anti-cancer properties also provide a direction for the development of functional foods for tumor prevention and adjuvant therapy. However, the current lack of *in vivo* studies, especially in humans, is a significant gap. These studies demonstrate that MPs possess excellent functional properties and considerable potential for applications. However, the poor stability of MPs severely limits their wide application. Therefore, it is critical to improve the stability of MPs.

3.3 Challenges of biological activity in food applications

MPs are natural, functional pigments that have shown promising applications in the food industry due to their diverse bioactivities (e.g., antibacterial, antioxidant, anti-inflammatory). However, although rich in biological activities, poor stability leading to loss of activity during processing and storage, as well as low bioaccessibility, severely limit the full realization of their functional value in food. Therefore, overcoming the inherent instability barrier of MPs and enhancing their bioaccessibility have become key bottlenecks in realizing their full functional potential. To address these key challenges, the design and application of efficient delivery systems become essential. Through appropriate delivery systems (e.g., emulsions, hydrogel, liposomes, nanoparticles), the active ingredients of MPs can be effectively protected from the adverse effects of the processing and storage environments, enhancing their solubility, stability, and targeted absorption *in vivo*, and ultimately realizing the efficient and controllable release of their biological activities in functional foods.

Table 2 Summary of biological activities of MPs reported in the past twenty years

Biological activities	Specific component	Model	Key mechanism	Effect	References
Antimicrobial	MRPs (9-(1-hydroxyhexyl)-3-(2-hydroxypropyl)-6a-methyl-9,9a-dihydrofuro[2,3-h]isoquinoline-6,8(2H,6aH)-dione)	Gram-positive bacteria	Exposure of the peptidoglycan layer on the cell surface of Gram-positive bacteria as a target for the action of pigment molecules	Inhibits the growth of <i>Bacillus species</i> (MBM B-310, 357, 358) and <i>Staphylococcus aureus</i>	[29]
Antimicrobial	Hydrophobic amino acid (e.g., L-Phe, D-Phe, L-Tyr, and D-Tyr)-derived MPs	Gram-positive and Gram-negative bacteria	Influences bacterial oxygen uptake and acts as a broad-spectrum antimicrobial	Minimum inhibitory concentration can be as low as 4-8 µg/mL, which is much better than the original pigment (> 32 µg/mL)	[102]
Antioxidant and anti-inflammatory	<i>Monascus purpureus</i> (MTCC 369) extracted biopigment	Human prostate LNCaP cells	Promotes SOD expression and inhibits GSH-Px expression to regulate oxidative stress, while promoting the secretion of the anti-inflammatory factor IL-10	MPs produced significant cytotoxicity against LNCaP prostate cancer cells, inhibiting cell viability by 79.86% and metabolic activity by 89.86%	[103]
Anti-inflammatory	MOPs (<i>Monaphilols</i> A, B, C, and D)	12-O-tetradecanoylphorbol-13-acetate-induced ear edema in mice	Inhibits lipopolysaccharide-induced iNOS expression, nitric oxide production, and decreases levels of inflammatory factors such as TNF-α, IL-1β, and IL-6	The highest inhibitory activity (IC ₅₀ of 1.0-3.8 µM) and significantly inhibited edema formation at a dose of 0.5 mg/ear in a mouse ear edema model	[92]

Anticancer	MPs	Breast cancer cells 4T1 in mice	Promotes altered expression of apoptosis-related proteins to enhance cyclophosphamide toxicity to breast cancer cells 4T1 (Bcl-2, Bax)	The combination significantly reduced cancer cell survival by about 27% (from 59.6% to 32.4%)	[104]
Anticancer	MPs (Ankaraflavin)	Human cancer cell lines Hep G2 and A549	Ankaraflavin exhibits selective cytotoxicity against liver cancer cells Hep G2 and lung cancer cells A549 by inducing apoptosis	IC ₅₀ was approximately 15 µg/mL, whereas there was no significant toxicity to normal lung fibroblasts MRC-5 and WI-38 at the same concentration	[105]
Anticancer and antioxidant	Coix lacryma fermented by <i>Monascus purpureus</i>	HEP2 laryngeal cancer cells	Fermentation of Coix lacryma by <i>Monascus purpureus</i> promotes an increase in the content of antioxidant components such as tocopherols, γ-glutamin and coix lacryma esters	Tocopherol, γ-glutamine, and Coix lacryma ester content increased about 4-fold, 25-fold, and 2-fold, respectively and IC ₅₀ decreased from 3.67 mg/mL to 2.13 mg/mL	[106]
Anti-obesity	<i>Monascus</i> -fermented products and ankaflavin)	Obese rats caused by a high-fat diet	Down-regulates C/EBPβ, PPARγ, C/EBPα and NPC1L1 expression and decreases HR-LPL activity	MPs significantly reduced weight gain by about 50% in obese rats on a high-fat diet and decreased adipose tissue weight without causing muscle damage.	[107]
Anti-obesity	MRPs	High-fat and high-sugar diet-induced Nonalcoholic fatty liver disease (NAFLD)	MRPs alleviate high-fat, high-sugar diet-induced obesity and NAFLD in mice by modulating the gut microbiota and influencing metabolic pathways such as arachidonic acid metabolism	Significantly reduced body weight gain ($P < 0.01$) and improved metabolic parameters, such as lowering serum triglycerides and total cholesterol	[108]

4. Encapsulation and delivery systems for MPs in food applications

Although MPs have been shown in the above-mentioned introductions to possess excellent functional properties, alongside several green and efficient extraction methods to improve MPs yield, their application as food ingredients is still hindered by their instability and susceptibility to decomposition under external conditions. The Web of Science databases were consulted for the number of publications in the last two decades using the keywords “*Monascus* pigment”, “pigment”, and “delivery”, and “*Monascus* pigment” and “delivery”, respectively, as shown in Figure 3. The data show that the number of publications related to MPs has been on the rise since 2016, with more researchers now considering MPs delivery systems. Delivery systems are key to improving the stability of MPs and maximizing the efficacy of their biological activities in the food system or the human body. Moreover, the delivery system exhibits substantial potential for controlled release, odor masking, enhanced food matrix compatibility, and the introduction of new functionalities. Therefore, it is crucial to select an appropriate delivery system to improve the stability of MPs and thereby expand their application. The comparative performance and food application potential of different delivery systems for MPs are listed in Table 3.

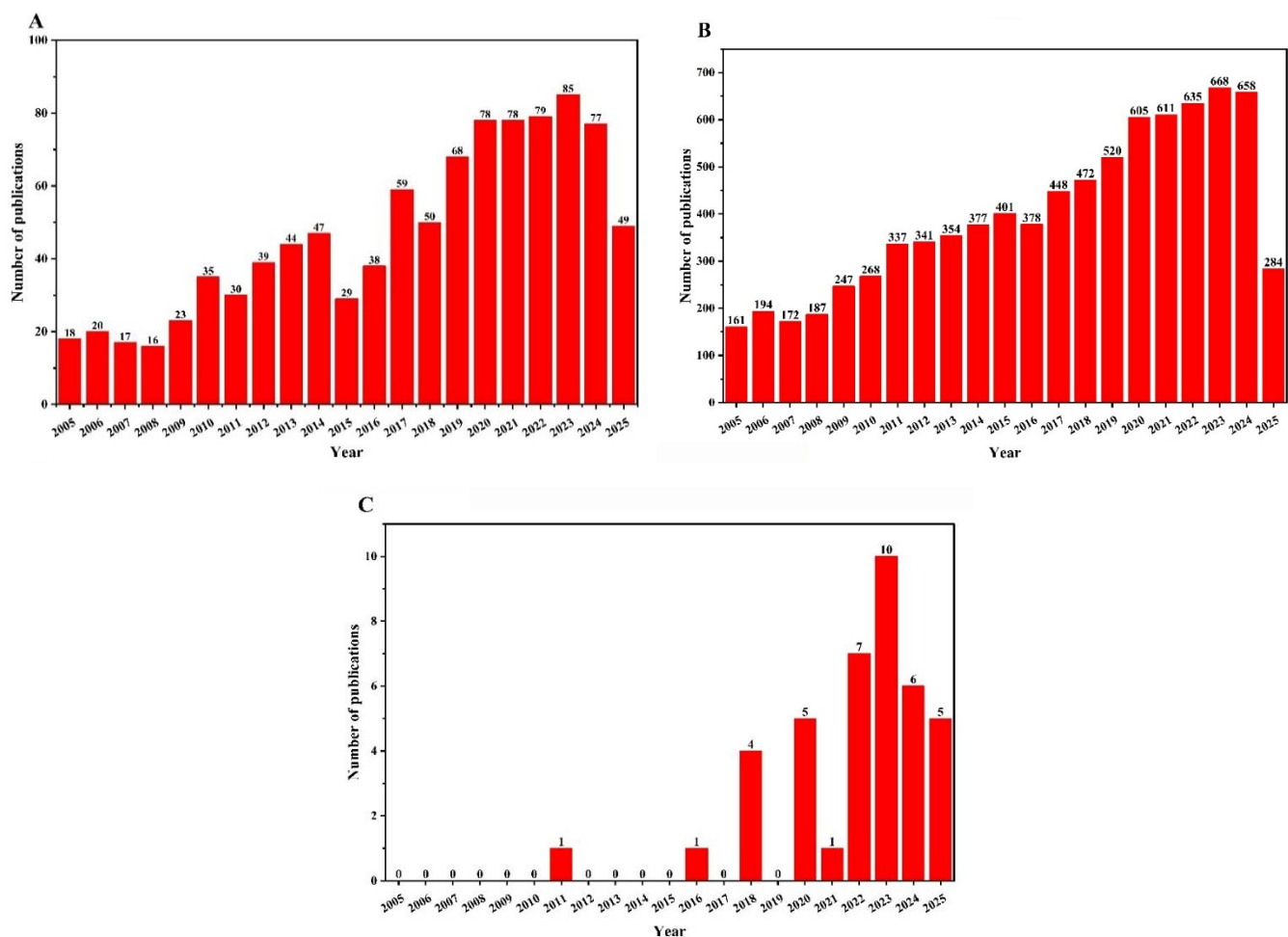


Figure 3: Number of publications in Web of Science databases in the last two decades. (A) The keyword is “*Monascus* pigment”; (B) The keyword is “pigment” and “delivery”; (C) The keyword is “*Monascus* pigment” and “delivery”.

In the food delivery systems, the properties of the delivery systems significantly influence the encapsulation efficacy of bioactive substances. Therefore, during the encapsulation of active substances, the delivery system must be optimized using characterization indicators to select the most appropriate delivery system. In addition, the applications of MPs in the food industry (such as bread, low-fat foods, and jellies) have been outlined, taking into account the characteristics of each delivery system. Figure 4 illustrates the preparation, stability characterization, and release mechanisms of various delivery systems (emulsions, hydrogels, microcapsules, liposomes, and nanoparticles). Importantly, most current evaluations utilizing simulated gastrointestinal digestion primarily assess the bioaccessibility of encapsulated MPs. Consequently, while the delivery systems discussed below exhibit enhanced protective and controlled-release properties *in vitro*, these improvements primarily signify increased bioaccessibility, thereby laying a solid foundation for future *in vivo* efficacy studies.

4.1 Composition-driven customized design of delivery systems.

The structural diversity of MPs, specifically the varying ratios of MRPs, MOPs, and MYPs produced during upstream fermentation, necessitates a tailor-made approach for downstream encapsulation. The rational selection of wall materials and system types should be guided by the specific physicochemical properties of the dominant pigment components:

MRPs often exhibit higher hydrophilicity than certain MYPs, requiring delivery systems that can stabilize across different polarities. For fermentation broths rich in MRPs, water-in-oil (W/O) emulsions or hydrogels formed from hydrophilic biopolymers, are preferred to ensure high EE. Since MYPs and certain unsaturated pigment backbones are particularly sensitive to photo-oxidation and UV degradation, the delivery system must provide a dense physical barrier. For high-yield but highly unstable MYPs fractions, core-shell nanoparticles synthesized with UV-shielding proteins (e.g., zein or ovalbumin) and polyphenols (e.g., rutin or quercetin) can maximize stability through synergistic molecular shielding. The choice of wall material should also consider the specific functional groups of the pigments, such as phenolic hydroxyl groups, which can form hydrogen bonds or electrostatic interactions with specific proteins or polysaccharides, thereby enhancing the structural integrity of the carrier.

By transitioning from one-size-fits-all encapsulation to composition-driven customization, the technical ecosystem of MPs can facilitate spatiotemporally precise release and potentiate bioactivity retention in complex food matrices.

4.2 Emulsions

Emulsions are multiphase dispersion systems composed of two mutually incompatible liquids. The liquid being dispersed is referred to as the dispersed phase (inner phase or discontinuous phase). In contrast, the other liquid is termed the continuous phase (outer phase or dispersing medium) ^[109]. The dispersed phase is uniformly distributed throughout the continuous phase as tiny droplets. Given the difference in the composition of the dispersed and continuous phases, emulsions can be divided into two basic types: Oil-in-water (O/W) and W/O ^[110]. Emulsions are thermodynamically unstable systems and usually require the addition of emulsifiers to improve stability ^[111]. The preparation of W/O emulsion is the most commonly used emulsifier is polyglycerol-polyricinoleate, and emulsion stability is achieved through high-shear shearing and high-pressure homogenization. O/W emulsions are commonly used for encapsulating fat-soluble bioactive substances, and W/O emulsions are commonly used for encapsulating water-soluble bioactive substances ^[112]. Recently, O/W emulsion encapsulated MYPs have attracted academic attention. For example, Li et al. prepared O/W nano-emulsion encapsulating MYPs by phase transition synthesis, which exhibited better pH stability (the minimum relative retention rate is 90%), the highest DPPH radical scavenging ability ($19.47 \pm 0.52\%$), and enhanced hydrolysis ability of lipase ($81.14 \pm 1.73\%$) ^[113]. In addition, for water-soluble pigments, encapsulated MRPs within W/O emulsions ^[114]. Their findings demonstrated that the W/O emulsion enhanced the stability of MRPs under various environmental conditions, including varying reducing-agent concentrations, compared with free MRPs. In addition to encapsulating water-soluble pigments using W/O emulsions, they can also be encapsulated using W₁/O/W₂ emulsions. The unique structural properties of W₁/O/W₂ emulsions offer several advantages in encapsulating bioactive substances, including reduced fat content, controlled release, and extended shelf life compared to conventional W/O emulsions (Figure 4A) ^[115]. Therefore, researchers favor the use of W₁/O/W₂ emulsions for encapsulating MRPs. Alouk et al. demonstrated that the preparation of W₁/O/W₂ emulsions, with guar gum as the inner phase and sodium

caseinate as the outer phase, resulted in smaller particle sizes and higher EE. In addition, the retention rate of double emulsion-encapsulated MRPs increased from $70.4 \pm 0.61\%$ to $86.7 \pm 0.37\%$ compared to free MRPs^[116]. Zheng et al. used a two-step emulsification method to prepare $W_1/O/W_2$ emulsions for encapsulating MRPs, with flaxseed gum as the inner aqueous phase gel and soybean oil as the oil phase. The results showed that the addition of $W_1/O/W_2$ emulsions could reduce the pork fat content from 11.22% to 5.09%, and the polyunsaturated fatty acid content increased from 23.36% to 59.63%^[117]. This result suggests that emulsions can be used as plant-based meat to reduce the fat content of meat products. However, $W_1/O/W_2$ emulsions have a double-layer structure, which brings better release control, but the double-layer emulsions are less readily stabilized than single-layer emulsions and have poor long-term stability. Using protein-polysaccharide binary or protein-polysaccharide-polyphenol ternary complexes will improve the stability of double-layer emulsions. Furthermore, interface engineering optimization can enhance emulsion stability. For instance, selecting appropriate emulsifiers, are typically combining low-molecular-weight surfactants (such as Span 80 or Tween 80) with polymeric complexes, which can further reduce interfacial tension and improve emulsification efficiency. Additionally, employing solid-particle stabilizers such as silica or cellulose nanocrystals as Pickering stabilizers forms irreversible physical barriers at the interface, significantly improving long-term stability. In summary, these results suggest that emulsion-encapsulated MPs are an effective means of improving their stability.

4.3 Hydrogels

Hydrogels are a class of three-dimensional soft materials consisting of cross-linked polymer networks and water, characterized by a network structure^[118]. They thus can be designed to encapsulate, retain, and protect bioactive ingredients after oral administration^[119]. The hydrogel preparation material determines the success of the encapsulation process, the common wall materials include proteins (such as soy protein, fish myofibrillar protein, and scallop protein) and polysaccharides (such as sodium alginate, chitosan, and carrageenan)^[120]. Moreover, cross-linking agents are also essential for the preparation of hydrogels. Furthermore, crosslinking agents are crucial for hydrogel preparation, with Ca^{2+} currently being the most employed crosslinker, such as $CaCl_2$ or $CaCO_3$ (Figure 4B). Li et al. used Ca^{2+} -induced chitosan and sodium alginate to prepare hydrogel microspheres to encapsulate MRPs. The results showed that the hydrogel microspheres exhibited high EE ($70.32\% \pm 0.28\%$), good antioxidant activity, and stability under adverse conditions (heat, light, and storage)^[121]. This demonstrates that encapsulating MPs within a hydrogel with a three-dimensional network effectively addresses their inherent deficiencies in thermal, light, and storage stability. In addition to encapsulating MRPs, hydrogels can also encapsulate MYPs. Zhang et al. used soybean isolate protein and carrageenan to prepare composite hydrogels as delivery systems for MYPs, and the results showed that the composite hydrogels exhibited excellent gel strength and sustained-release properties, enabling controlled MYPs release. Moreover, their research indicates that increasing the concentration of soybean isolate protein promotes the prolonged release of MYPs^[122]. These results indicated that hydrogels prepared from proteins and polysaccharides can help improve the EE and stability of MPs, and, combined

with their water-retaining, thickening, and gelation properties, could be used to develop foodstuffs such as jellies and ice creams. Moreover, the appropriate protein should be selected when preparing a hydrogel jelly, as different proteins have varying gelation properties, resulting in distinct jelly textures.

4.4 Microcapsules

Microcapsules, as a novel encapsulation technique, are increasingly being employed to enhance the application value of active substances in the food industry, such as pigments. Microcapsules are a process in which bioactive components (cores) are encapsulated in natural or synthetic polymers (walls) to protect them from the external environment and significantly improve their stability, typically with diameters ranging from 3 to 800 μm ^[123]. An ideal microcapsule delivery system typically exhibits good biocompatibility, mechanical strength, and a controlled degradation rate ^[124]. There are various methods for preparing microcapsules, and emulsification/internal gelation is a technique based on a W/O emulsion to produce microcapsules with small particle sizes (Figure 4C). Its core mechanism involves the reaction of an organic acid with CaCO_3 , releasing Ca^{2+} , which in turn induces polymer cross-linking to form the capsule wall ^[125]. Compared with microencapsulation techniques such as extrusion, spray drying, and external gelation, emulsification/internal gelation exhibits significant advantages in terms of smaller capsule size, higher EE, reduced risk of leakage, and effectively avoids affecting the biological activity of heat-sensitive MPs due to its mild reaction conditions ^[126]. The particle size and EE of microcapsules are significantly affected by the wall-to-bioactive substance ratio. For example, Zhang et al. prepared microcapsule-encapsulated MRPs using the emulsification/internal gelation technique to investigate the effect of varying the ratios of calcium carbonate to sodium alginate and calcium carbonate to acetic acid on the stability of the microcapsules. The results showed that when the NaCl concentration in PBS was 0.88%, the mass ratio of calcium carbonate to sodium alginate was 3.13, the molar ratio of calcium carbonate to acetic acid was 4.15, and the highest EE was 70.32%. Moreover, the stability of the microcapsule under thermal, pH, metal-ion, and *in vitro* digestion conditions was investigated. The results demonstrated that the construction of a compact core-shell structure via emulsification/internal gelation technology provides a physicochemical barrier across multiple dimensions, including spatial isolation, diffusion control, structural reinforcement, and environmental responsiveness, thereby systematically enhancing pigment stability under the above conditions ^[127]. Most microcapsules are prepared using spray drying or freeze drying, with a wall material encapsulating the core material (MPs) into tiny, powder-like particles ^[128]. Therefore, MPs microcapsules are well-suited for producing instant juice powder, milk tea powder, instant noodle powder packets, and other convenience foods.

4.5 Liposomes

Liposomes are self-assembled, closed bilayer vesicles with a cell membrane-like structure formed in the aqueous phase of amphiphilic phospholipids ^[129]. They have been widely researched for their ability to encapsulate a wide range of active substances in the food industry ^[130]. Due to their amphiphilic nature, they can encapsulate both hydrophilic and hydrophobic bioactive substances ^[131]. Moreover, liposomes have better biocompatibility and biodegradability, making them an ideal delivery system for MPs. For instance, Long et

al. used thin-film ultrasound to prepare liposomes encapsulating MRPs stabilized by soybean lecithin and cholesterol (Figure 4D). The results showed that liposome-encapsulated MRPs significantly improved the stability under different conditions such as pH, heat (the degradation rate decreased by 12.2%), light (the degradation rate decreased by 5.2% for 4 h of light), and metal ions (Ca^{2+} , Cu^{2+} , and Zn^{2+}) environments, the degradation rate of MRPL decreased by 4.3%, 7.1%, and 5%, respectively, in compared to free MRPs [132]. This finding is attributed to the structural properties of liposomes, which form both physical and chemical protective barriers to MRPs, thereby reducing damage to their molecular structure caused by external environmental factors. Moreover, due to their structural properties, which can encapsulate water-soluble and fat-soluble bioactive substances, liposomes offer unique advantages for the development of functional foods. For instance, Dudek et al. used nanoliposomes to encapsulate three pigments, MRPs, MOPs, and MYPs. The prepared nanoliposomes exhibited a low polydispersity index (0.243, 0.187, and 0.202), high surface charge (-21.79, -19.26, and -21.61 mV), and stronger functionality and bioactivity than free pigments [133]. However, most of the raw materials used for preparing liposomes are phospholipids, which are susceptible to lipid oxidation and hydrolysis, potentially leading to structural damage [134]. Therefore, achieving high self-stability is a key parameter for the successful delivery of MPs by liposomes. The more common solution is to modify liposomes with biomolecules, such as proteins and polysaccharides, to improve their stability [135]. However, there is no relevant study on encapsulating MPs yet.

4.6 Nanoparticles

Nanoparticles are a rapidly emerging delivery technology, typically ranging in size from 1 to 1000 nm, used to protect and modulate the release of MPs, thereby improving their stability and bioaccessibility [136]. Biomolecules such as polysaccharides and proteins are often used as wall materials for preparing nanoparticles due to their excellent biodegradability, modifiability, and biocompatibility. Common polysaccharides and proteins include chitosan, pectin, ovalbumin, and zein [137]. Generally, nanoparticles stabilized by a single protein and polysaccharide exhibit low EE and poor stability. The selection of proteins and polysaccharides for the preparation of nanoparticles can improve stability. For example, Yang et al. constructed core-shell composite nanoparticles using ovalbumin, rutin, and octenyl succinic anhydride-modified pectin, effectively encapsulating MPs. This system primarily forms through electrostatic interactions, hydrogen bonding, and hydrophobic interactions. The shell provides protective effects for MPs, significantly enhancing their light, thermal, and storage stability, while also improving their lipase inhibitory and antioxidant activities (Figure 4E) [54]. Researchers also explored other strategies for encapsulating MPs with biomolecules. Huang et al. demonstrated that quercetin-Sn (II)-albumin-chitosan nanoparticles are an effective system for encapsulating MYPs. The results showed that the nanoparticles were formed through layer-by-layer assembly, with a minimum particle size of 251.90 ± 1.15 nm and a maximum surface charge of -50.00 ± 6.56 mV. This system effectively encapsulated MYPs, significantly enhancing their environmental stability, color stability, antioxidant activity, and hypolipidemic activity [138]. In addition to applications in the food industry, nanoparticles can also be employed in pharmaceutical settings due to their nanoscale size, which facilitates

the crossing of biological barriers, such as the blood-brain barrier. For example, Yao et al. demonstrated that nanoparticles loaded with MPs exhibited higher EE and better biocompatibility. Their critical micelle concentration was remarkably low (0.027 ± 0.010 mg/mL), which prolonged the circulation of MPs in the blood. This enhances their uptake by HeLa cells and triggered apoptosis, thereby demonstrating excellent anticancer activity with a tumor inhibition rate of $71.49 \pm 3.53\%$ ^[139]. MPs nanoparticles exhibit excellent bioactivity and are well-suited for producing functional foods with antioxidant, anticancer, and hypolipidemic effects. However, nanoparticles are more prone to agglomeration due to their smaller size. In the future, the research direction for MPs nanoparticles is to prevent particle aggregation, more importantly, and to control the release of MPs into the gastrointestinal tract.

Although the above delivery systems have demonstrated significant protective effects on MPs under ideal laboratory conditions, their performance in complex, real-world food environments remain insufficiently explored. Notably, Section 4.2 has already described the successful application of the $W_1/O/W_2$ emulsions as pork fat substitutes in meat product systems. Furthermore, recent studies have expanded this validation to other food categories. For example, a gelatin-pectin composite hydrogel encapsulating MPs maintains color stability under rigorous thermal (100 °C, 7.5 h) and light (7000 lx, 6 days) stress while effectively suppressing the characteristic off-flavors of MPs (such as fruity, greasy, and musty odors) ^[140]. This is a crucial property for applications in beverages and dairy products with delicate flavors profiles. Meanwhile, spray-dried MP microcapsules incorporated into yogurt and ice cream maintain stable pH, titratable acidity, and color properties during refrigerated storage for 15 to 60 days ^[141]. Overall, these studies confirm the transformative potential of MP delivery systems within real food matrices. However, current evidence is limited to only a few food categories and specific processing conditions (such as baking, pasteurization, and prolonged frozen storage). More importantly, to fully realize the commercial application of MPs delivery systems, it is essential to systematically bridge the significant gap between idealized laboratory conditions and real-world food processing environments through large-scale industrial trials and validation across multiple food matrices.

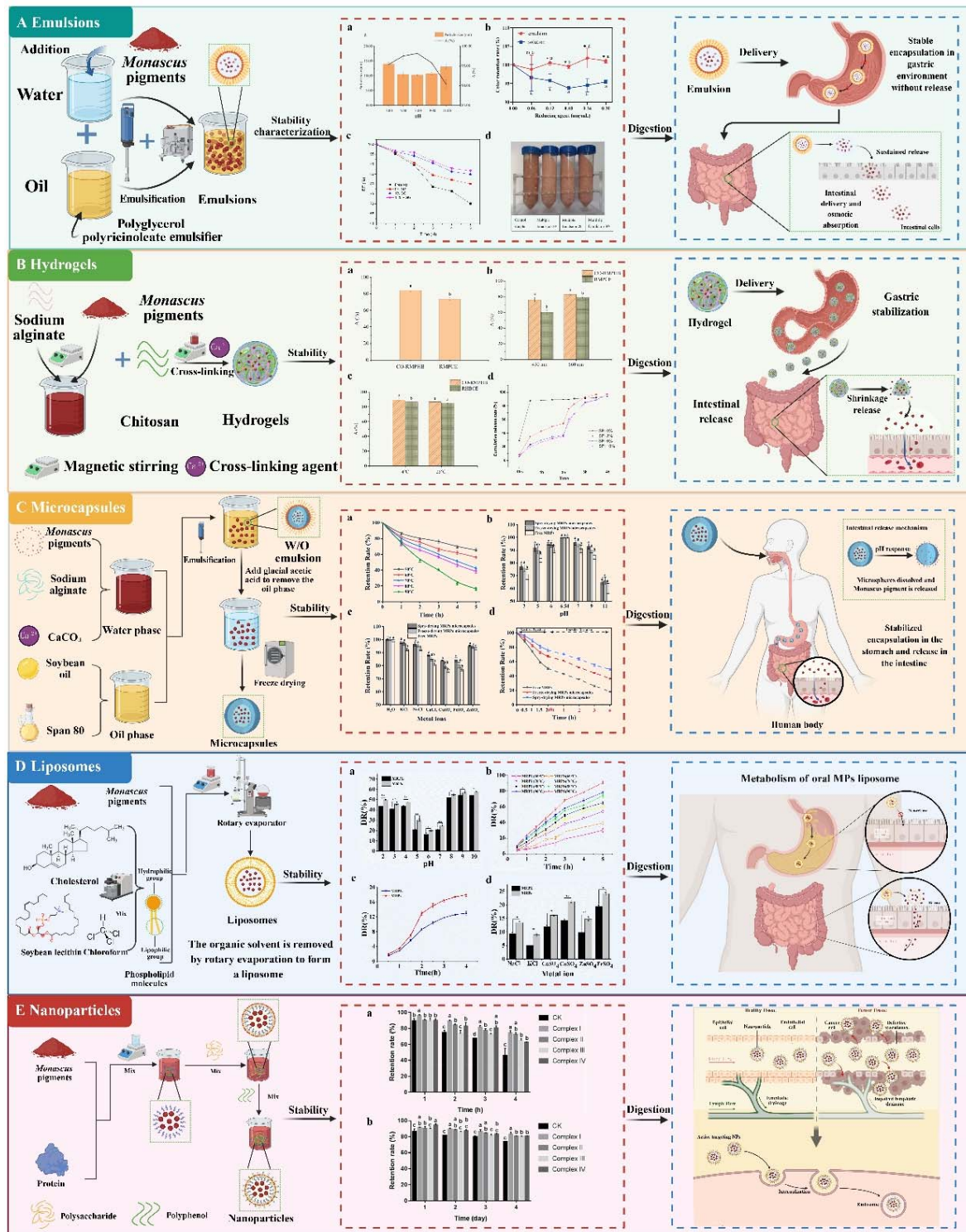


Figure 4: Preparation, stability characterization, and release mechanisms of MPs delivery systems. A: Emulsions (The effect of different condition factors on the stability of MPs emulsions, a: pH; b: reducing agents; c: light; d: MPs contents). Reproduced with permission^[113, 114, 116, 117]. Copyright 2023 and 2025, Elsevier. B: Hydrogels (The effect of different condition factors on the stability of MPs hydrogels, a: temperature; b: light; c: storage; d: soybean isolate protein concentration). Reproduced with permission^[121, 122]. Copyright 2021 and 2024, Elsevier. C: Microcapsules (The effect of different condition factors on the stability of MPs microcapsules, a: temperature; b: pH; c: metal ion; d: *in vitro* simulated gastrointestinal digestion). Reproduced with permission^[127]. Copyright 2023, Elsevier. D: Liposomes (The effect of different condition factors on the stability of MPs microcapsules, a: pH; b: temperature; c: light; d: metal ion). Reproduced with permission^[132]. Copyright 2023, MDPI. E: Nanoparticles (The effect of different condition factors on the stability of MPs microcapsules, a: thermal treatment; b: light treatment). Reproduced with permission^[138]. Copyright 2023, Elsevier.

Table 3 Characteristics of the MPs delivery systems and their potential applications in food.

Systems	Raw materials	Advantages	Disadvantages/Challenges	Conclusions	Applications	References
Emulsions	Soybean oil, polyglycerol polyricinoleate, pea protein isolate, flaxseed gum	Improved pigment stability, designed for controlled release, improved food texture (as a fat replacer)	The stability is easily influenced by temperature, pH, and ionic strength; the safety of some synthetic emulsifiers is questionable; the cost of industrialized production is high	The emulsion reduces the total fat content without affecting the firmness and color retention of the meat product	Low-fat meat products, food coloring, functional foods	[117]
Hydrogels	Chitosan, sodium alginate, CaCl ₂	Good biocompatibility, sustained release properties, significantly improved pigment stability, pH-responsive release	Limited load capacity, mass production may not be efficient, mechanical strength sometimes insufficient	Hydrogel as a carrier for MPs can enhance their stability, exhibit a high EE (73.54 ± 2.16%), and possess certain sustained-release capabilities	Functional foods, active substance carriers	[121]
Microcapsules	Soybean oil, NaAlg, CaCO ₃	High stability (resistance to light, heat, oxygen), prolonged shelf life, easy storage and transportation, easy handling and mass production	Limitations in wall material selection, release rates sometimes not easily controlled, complex coalescence process is relatively complex	Emulsified/internal gel encapsulation of MPs can enhance their stability, with a maximum EE of 70.32 ± 0.28%	Convenience foods, baked goods, solid beverages, pharmaceuticals	[127]
Liposomes	Soybean lecithin, ultra-pure cholesterol, chloroform	Encapsulation of both hydrophilic and hydrophobic components, good biocompatibility and degradability, enhanced pigment stability	Low EE, easy to aggregate and oxidize in long-term storage, high requirements for preparation process	Liposome-encapsulated MPs improve the stability of MPs and exhibit better anticancer activity	Food additives, pharmaceuticals, cosmetics	[132]
Nanoparticles	Rubropunctatin deoxycholate sodium, poloxamer 188, phospholipid	High stability, high bioaccessibility, enhanced bioactivity (e.g., antioxidant, antimicrobial), high cellular absorption	Complex preparation process, higher cost, safety evaluation needs to be more in-depth	Tumor inhibition rate of MPs-encapsulated nanoparticles was as high as 71.49 ± 3.53%	Pharmaceuticals, cosmetics, functional foods	[139]

5. Challenges and future directions

As natural pigments, MPs have a wide range of applications in the food, pharmaceutical, and cosmetic industries due to their unique color properties and excellent bioactivity. However, its industrial production and applications still face multiple challenges. The future lies in technological innovation and industrial synergy to break through bottlenecks and achieve sustainable development.

5.1 Challenges of MPs

The key safety concern for MPs are citrinin contamination. As a nephrotoxic toxin, citrinin can cause significant damage to the human kidney and pose a major threat. The application of MPs products is limited by the presence of citrinin. Therefore, it is crucial to increase the yield of MPs while reducing citrinin content. The production of citrinin is closely related to strain selection, fermentation conditions (e.g., temperature and pH), and the purification process^[14]. The content of citrinin can be controlled within the safety threshold through high-throughput screening of low or no-citrinin-producing *Monascus* strains, optimization of solid/liquid fermentation parameters (e.g., shortening the fermentation cycle, controlling contamination by stray bacteria), and the use of green extraction techniques^[142]. Even for low-yielding strains, it is necessary to establish a comprehensive monitoring system, from raw material selection to the fermentation process and final product, and to implement standardized, highly sensitive testing methods to ensure systematic product compliance.

Beyond technical extraction challenges, the commercialization of MPs are heavily governed by stringent and disparate international regulatory frameworks regarding citrinin safety thresholds. For instance, due to lingering uncertainties regarding genotoxicity and carcinogenicity, the European Commission (Regulation EU 2019/1901) drastically lowered the maximum permitted level of citrinin in red yeast rice supplements from 2,000 µg/kg down to a strict 100 µg/kg. In Asia, where MPs have a profound history of application, regulations remain rigorous; Japan restricts citrinin in *Monascus* pigment additives to 0.2 mg/kg (200 µg/kg), while China's National Food Safety Standard (GB 1886.19-2015) mandates an even stricter limit of 0.05 mg/kg. In the United States, the Food and Drug Administration (FDA) has not broadly granted Generally Recognized as Safe (GRAS) status to MPs as food colorants, maintaining intense scrutiny over their application. Furthermore, while modern biotechnological interventions such as CRISPR/Cas9 and genetic recombination present promising solutions for engineering fundamentally citrinin-free strains, their transition to industrial application faces profound regulatory hurdles. The global acceptance of food additives derived from Genetically modified microorganisms is highly fragmented. The EU subjects such products to rigorous pre-market authorizations and GMO traceability directives, whereas other international bodies may offer regulatory relief only if no recombinant DNA remains in the final purified pigment. Therefore, realizing the full potential of these advanced bioprocesses requires not only scientific innovation but also proactive alignment with global food safety authorities to ensure definitive regulatory compliance.

The stability problem of MPs cannot be ignored. In the previous section, several delivery systems were introduced to encapsulate MPs. Although they improved the stability of MPs to some extent, the existing delivery systems for MPs are susceptible to gastric acid damage, enzymatic degradation, and a lack of targeted release, resulting in low bioaccessibility. Stimuli-responsive delivery systems can be targeted to solve these problems. For example, MPs can be stabilized in the low-pH environment of the stomach by designing pH-responsive materials that are triggered to release when they reach the neutral or weakly alkaline environment of the intestine. At the same time, enzyme-responsive systems can be activated by specific enzymes (e.g.,

trypsin) in the intestine to achieve precise, controlled release. These intelligent delivery strategies protect the biological activity of MPs and improve the absorption efficiency. They also enhance their targeting and stability, significantly increasing the potential of MPs in functional foods. Moreover, the application of MPs in cosmetics (e.g., lipstick, blush) is limited by their hydrophilicity and poor compatibility, requiring the development of lipid-soluble derivatives or nanocarriers to enhance dispersion and stability. In addition, most of the current studies on MPs delivery systems have focused on short-term cellular experiments or weeks of animal experiments aimed at demonstrating their initial efficacy, lacking long-term stability studies. Currently, most delivery systems release active substances through degradation, but for those that are not cleared in time, either completely or partially degraded, their long-term retention in the organ is a source of long-term safety concerns. Therefore, further investigation is required to address the stability issues of MPs and better leverage their bioactivity.

At the molecular level, the design of these smart delivery systems should leverage the specific chemical moieties of MPs, such as the phenolic hydroxyl groups and extended conjugated systems, to facilitate strong intermolecular interactions (e.g., hydrogen bonding and π - π stacking) with stimuli-responsive carriers. Such molecular coupling not only reinforces the structural integrity of the delivery vehicle but also enables a more synchronized response to target environmental triggers, such as intestinal pH shifts or enzymatic activity, ensuring the spatiotemporally precise release of the bioactive.

5.2 Future directions for MPs

The future direction of MPs can be centered around safety, yield, stability, and applications in the food field. (1) Safety. It is necessary to control citrinin pollution through various synergistic strategies, including the selection and breeding of low-toxicity or non-toxicity strains, the optimization of fermentation conditions, the introduction of metabolic engineering to regulate the secondary metabolic pathways, and the development of highly efficient post-extraction and purification processes. In addition, it was found that the *ctnF* gene reduced citrinin production by 34% through alterations to the MPs biosynthetic pathway, while pigment yield decreased by 72%^[143]. Increasing the yield and reducing citrinin content simultaneously, or even eliminating it, still requires comprehensive research. The toxicological evaluation of MPs and their derivatives should be further improved, and more accurate risk assessment models and food safety standards should be established to provide a scientific basis for their safe application; (2) Yield. Fermentation process innovation and green production can be achieved through the combined use of two or more extraction methods, which enables the extraction of bioactive substances without compromising their overall biological properties^[144]. Although no research has been reported on MPs, they have yielded good results in the extraction of other pigments. For example, Lenucci et al. utilized SCE in conjunction with EAE to extract lycopene, and the results demonstrated that the combined treatment group exhibited a 3-fold increase in lycopene yield compared to the uncombined treatment^[145]. Additionally, genetic engineering techniques can also enhance the yield of MPs. When overexpression of the *MpigQ* gene increases the yield of MPs, while deletion decreases the yield of MPs^[146]; (3) Stability. Several delivery systems were introduced earlier. However, issues such as poorly

controlled release and targeting ability occur. Currently, stimuli-responsive systems are a research hotspot, and some groups are being introduced to improve targeting^[147]. Although no relevant studies have been reported on MPs, they have shown good results with other pigments. Sun et al. used the preparation of pH-responsive curcumin hydrogel microspheres, which showed that the release rate of curcumin increased with decreasing pH, exhibiting excellent pH-responsive properties^[148]. However, the presence of citrinin remains a factor that cannot be ignored for MPs, making the achievement of high purity and the thorough removal of citrinin prior to encapsulation a key prerequisite for these advanced delivery systems; (4) Functional foods. People are increasingly pursuing healthy, high-quality, and nutritious dietary lifestyles, and many studies have reported the addition of MPs as functional ingredients in foods such as rice flour, noodles, yogurt, bread, and plant-based meat analogs. Gong et al. isolated and purified water-soluble MYPs and added them to rice flour to prepare a functional rice flour with improved texture and sensory qualities^[2]. Due to their ease of preparation, low cost, and convenient storage, noodles are popular among consumers. However, the nutritional composition of noodles is relatively basic. Li et al. demonstrated that the quality of noodles was significantly improved by adding MPs at levels of $\sim 0.5\%$ to 1.0% ^[149]. 3D printing technology is gaining attention for its ability to personalize and improve food texture. Hou et al. developed an age-friendly, loaded β -carotene high-internal-phase Pickering emulsion that exhibits a beautiful texture, excellent swallowability, and significantly improved β -carotene stability^[150]. Furthermore, considering the biological activities of MPs components, such as antioxidant, antimicrobial, and potential regulation of blood lipids, it can be explored for application as a coloring-functional dual-activity factor in specific dietary scenarios to enhance the product's added value. Although there are no relevant reports on MPs, if 3D-printed MPs delivery systems are developed in the future, further human experiments should be conducted to verify their food taste and biological effects realistically.

5.3 Synergizing with emerging technologies for precision application

MPs are a natural food pigment that is garnering increasing attention in the food industry due to their excellent functional properties. Currently, the application of MPs are advancing towards a new stage of enhanced efficiency, precision, and safety through integration with multiple frontier technologies. In the field of 3D-printed food, MPs not only impart a natural, appealing red hue to printed products but also serve as rheological modifiers to regulate ink flow properties, thereby enhancing printing precision and structural stability. Currently, many natural pigments, such as carotenoids, anthocyanins, betanin, and curcumin, are employed in 3D food printing^[151]. Future research may focus on incorporating MPs into delivery systems, such as emulsion gels, and adapting them for 3D printing to enable customized food manufacturing that integrates hue, nutrition, and texture. In the field of artificial intelligence, it offers a data-driven approach for optimizing the design of MPs applications. By employing machine learning algorithms, it is possible to simulate and predict the stability and release behavior of MPs within diverse food substrates (such as high-protein or high-fat environments)^[152]. This enables rational design of delivery systems and process adjustments, significantly reducing trial-and-error costs and time during product development. In addition, synthetic biology offers a fundamental solution for ensuring the safety of MPs production. Through genetic

editing tools such as CRISPR-Cas9, the gene cluster responsible for producing citrinin in *Monascus purpureus* can be precisely knocked out. This enables the construction of high-yield engineered strains free from toxin residues, thereby overcoming safety bottlenecks at source and facilitating broader application of MPs across the food sector.

6. Conclusions

This review critically underscores that the advanced valorization of MPs is no longer solely constrained by extraction efficiency or intrinsic functionality, but rather historical disconnect between upstream bioprocessing and downstream formulation. While the practical application of MPs has traditionally been hindered by three core challenges: poor environmental stability, citrinin contamination risk, and low bioaccessibility, recent technological leaps are overcoming these barriers. The advent of green extraction technologies has substantially elevated MP quality. Concurrently, breakthroughs in advanced delivery systems (e.g., emulsions, hydrogels, and microcapsules) have profoundly enhanced MP stability and bioaccessibility, circumventing citrinin-associated toxicity risks and expanding their viability in high-value food matrices. Furthermore, utilizing natural biopolymers (such as pectin, chitosan, or proteins) for encapsulation perfectly aligns with the industry's "clean label" trajectory, making these innovations highly applicable to modern functional foods.

Looking forward, the next generation of MP development will be driven by synthetic biology for safe and efficient production, coupled with intelligent delivery and 3D/4D printing technologies to achieve spatially and temporally controlled, personalized release. Additionally, there remains a pressing need for clinical trials to substantiate their *in vivo* efficacy in human health.

Crucially, the functional valorization of MPs must evolve from a passive additive approach into a proactive, feedback-driven technical ecosystem. Within this paradigm, the precise upstream modulation of fermentation, specifically, tailoring the ratios of red, orange, and yellow pigments (MRPs, MOPs, and MYPs), serves as a predictive blueprint for the rational design of downstream wall materials. By seamlessly bridging metabolic engineering with materials science, this integrated framework ensures that delivery systems are meticulously customized to the unique physicochemical signatures of the dominant pigment fractions, thereby maximizing both structural stability and biological efficacy. Ultimately, this comprehensive roadmap facilitates the transition of MPs from traditional colorants to next-generation personalized functional ingredients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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