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益生菌-水凝胶递送系统的研究进展及应用潜力

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摘　要：益生菌是能够改善人体胃肠道、皮肤、阴道和口腔四大微生态系统的微生物群，常借由递送系统到达靶点以用于预防和治疗目的。水凝胶是最常见的递送系统载体，最近的研究针对水凝胶材料的改良主要可分为基质结构、填充物和外部涂层 3 个方面，新型水凝胶能够更好地帮助益生菌适应加工、储存环境及人体内微环境。人体不同微环境下益生菌对递送载体具有不同需求。口腔微环境的独特特性会成为益生菌定殖的新挑战，而水凝胶恰好能解决这些问题。水凝胶的应用必将加速口腔益生菌在临床研究和药物研发上的进程。

关键词：益生菌；水凝胶；递送系统；口腔益生菌

Research progress and potential application in oral cavity of hydrogel-based probiotic delivery systems

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Abstract: Probiotics can improve the microbiota of human oral cavity, gastrointestinal tract, skin, and vagina and reach the targets via delivery systems for preventive and therapeutic purposes. Hydrogel is currently accepted as the most common carrier of delivery systems. The recent studies aiming at improving hydrogel materials mainly focus on matrix structure, bulking agents, and external coating.

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The novel hydrogel contributes to the adaptation of probiotics to the processing and storage environment, as well as human body microenvironment. Probiotics have varying requirements for delivery carriers in different human microenvironments. The specific characteristics of the oral microenvironment pose a new challenge to the colonization of probiotics, to which hydrogel may be a solution. The application of hydrogel will expedite the course of clinical research and pharmaceutical development of oral probiotics.

Keywords: probiotics; hydrogel; delivery systems; oral probiotics

益生菌被定义为活的微生物，当以足够的量服用时，能够为个体的健康带来益处[1]。大量证据表明，益生菌是能够改善人体胃肠道、皮肤、阴道和口腔四大微生态系统的微生物群，常通过递送系统进入人体以用于预防和治疗目的[2–3]。其抗菌原理主要是与同一部位的病原体竞争，阻止其粘附和定殖[4]。由此可见，防止病原体生长的益生菌必须与病原体占据相同的生态位[5]，这对递送系统的靶向定位能力提出了要求。

益生菌常见的保护技术有冷冻干燥技术、低水活度保护技术和微囊包埋技术[6–8]。其中微囊包埋是递送系统中最主要应用到的技术。目前常用的微囊形式有固液两类，固体微囊以片剂为主，液体微囊以水凝胶为主[9–10]。水凝胶是一种常见的生物材料，具有独特的三维交联网状结构，能够吸收大量水和体液而不溶解[11]。水凝胶由一种或多种天然或合成聚合物组成，通过化学共价键结合或借由非共价键(如静电相互作用、疏水相互作用和氢键)进行物理交联，可用于递送系统[10]。在递送过程中，水凝胶可能直接对人体或病原体产生作用[12–13]，可能通过促进益生菌的生长和代谢帮助人体[14–16]，也可能单纯充当了递送介质[17]。现有口服水凝胶常利用胃部与肠道 pH、化学成分或酶(如胃酸、胆汁盐或消化酶)的差异，预设益生菌-水凝胶成分的相互作用断裂的时机，使水凝胶得以顺利通过胃部，将益生菌递送入肠道[18–20]。已有大量研究证实了水凝胶能保护益生菌免受胃肠道的损伤[21–23]，使用水凝胶负载益生菌用于生物治疗具有极可观的前景[24–25]。然而，释放益生菌的时机会影响其能力的发挥[26]。水凝胶在应用中的核心问题在于在递送过程中保护益生菌不受机体清除，并在治疗靶点释放益生菌[27–28]。

此外，除了胃肠微生态系统，针对人体其他部位的益生菌疗法也在逐渐受到关注，口腔是其中一个重要的新兴领域。口腔菌群对人体健康至关重要，不仅参与了致病环境的形成过程，还可用于口腔及全身疾病的诊断和治疗[29–30]。人体内诸如口腔的微生态环境受定殖于其中的菌群影响，各有其不同的特点，进而对于相应益生菌及其载体的选择产生了不同的需求，也为水凝胶材料的改良指明了新的方向。

之前的综述更多关注的是水凝胶材料的性能优化，而少有整合其在人体不同部位的差异化应用提出建议的。本文先分类介绍了益生菌-水凝胶材料改良的研究进展，然后阐述了新型水凝胶在益生菌产品加工、储存以及向人体各部位递送益生菌中的应用，并着重强调了改良水凝胶材料的口腔应用面临的挑战及未来的潜力。

1 改良的水凝胶材料

最近研究针对水凝胶材料的改良主要可分为基质结构、填充物和外部涂层 3 个方面(图 1)。

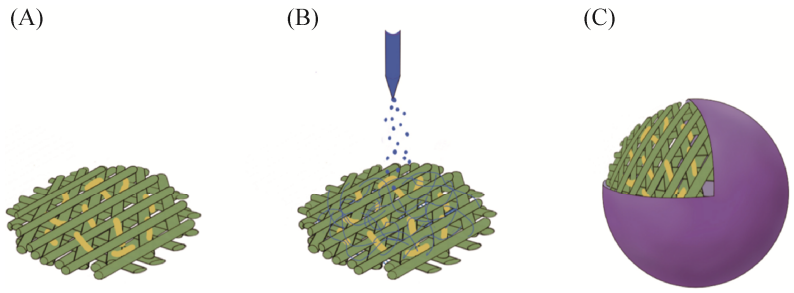

图 1　水凝胶的改良

Figure 1　Improvement of hydrogel. A: matrix structure. The cross-linking of polymer chains limits the internal probiotics, but the hydrogel made up by single matrix material is generally lack of compactness. B: bulking agents. Adding specific substances to the original matrix may be a helpful way of filling the natural pores created by the cross-linking, increasing the compactness of the hydrogel. C: external coating. Microencapsulation with coating materials can effectively protect probiotics, and usually have more advantages.

1.1　基质结构

在水凝胶的基质结构中，聚合物通过氢键、范德华力和疏水力等交联形成网状结构。常见的基质成分有多糖(如壳聚糖、果胶和藻酸盐)和蛋白质(明胶和乳清蛋白)[31–34]，一般具有较好的相容性[35]。在功能上，蛋白质能充当缓冲剂的作用，多糖则能提供物理屏障，保护被包裹的细胞免受胃酸和胆汁酸的影响[10]。

海藻酸盐(alginate)是最常见的水凝胶基质成分，也是水凝胶中被广泛研究改良的热点。以海藻酸盐作为基质的水凝胶具有良好的渗透性，利于所包裹的益生菌与外界环境进行空气和营养物质的交换[36]，封装效率可高达 98%[37]。对海藻酸盐形成的凝胶进行化学改性后，能使其具有更好的理化性质，发挥更好的功效[38]。Chang 等使用琥珀酸酐(succinate)改性海藻酸钠，并向其中加入表没食子儿茶素-3-没食子酸酯(epigallocatechin-3-gallate，EGCC)用于固定嗜黏蛋白阿克曼菌(*Akkermansia muciniphila*)——一种新近发现的可能用于治疗肥胖的菌种[39]。

明胶(gelatin)是一种较为简单和廉价的原料[31]，然而，纯明胶在干燥后质地脆、成型能力弱、延展性低、潮湿环境中易受细菌侵蚀而变质。相比海藻酸盐，使用时更需要采用不同的改性方法，包括化学改性、物理共混和复合改性[40]。改性后的明胶基质在耐热性和保护递送的益生菌活性等方面取得优异的性状，是基质结构的优质材料[41]。

纤维素是目前最丰富的可再生天然聚合物，其衍生物因具有生物降解性广受青睐。但纤维素衍生物大多是水溶性的，无法实现向小肠的药物递送[42]。Luan 等使用 2,2,6,6-四甲基哌啶 -1- 氧基自由基(2,2,6,6-tetramethylpiperidine-1-oxyl radical，TEMPO)介导的氧化可以将纤维素纤维/纤维素纳米纤维基质表面的羟基转化为羧基，以改善纤维素基水凝胶对胃部环境的耐受[43]。Praveschotinunt 等利用三叶因子(trefoil factors，TFFs)创建纤维基质，证实其可促进肠道屏障功能和上皮的恢复，进一步开拓了纤维素在水凝胶基质中广泛应用的未来[44]。

为适应食品药品业的生产需求，低成本化是水凝胶基质材料的重要趋向。例如 Juodeikiene 等使用价格低廉的农副产品苹果渣作为基质材料，除了能使凝胶硬度增加 3-5 倍，由于其中

含有大量的糖类和丰富的多酚类物质，可以促进其固定的乳杆菌(*Lactobacillus*)的生长和存活[45]。此外，Manna 等从腐乳工业废水中提取出凝乳肽(curd-peptide)，构建出一种原料经济环保的新型水凝胶[46]。

近些年，研究者尝试了各种复合交联的基质，使水凝胶的性能得到大幅提升。一项以乳清蛋白浓缩物(whey protein concentrate，WPC)-多糖为原料的实验表明，向基质中加入壳聚糖能改善乳清蛋白纤维的疏水性，并能促进氢键的强度[35]。另外，还有一些新的具有交联性的复合水凝胶，例如乙醇诱导组装的丙二醇藻酸盐/β-乳糖蛋白复合水凝胶[22]、海藻酸钠-低甲氧基果胶(low methoxyl pectin，LMP)或海藻酸钠-κ-卡拉胶(κ-carrageenan，KC)混合水凝胶[47]以及一种基于与氧化石墨烯和戊二醛双交联的明胶水凝胶[41]。

水凝胶的一些共性是极为重要的，如生物相容性、耐受胃环境和在肠道下缓慢释放益生菌，但如果对比不同水凝胶材质，影响其差异化应用的往往是特质。近几年新研发的新型水凝胶均被归入表 1，表中涉及已经研究验证的和最有可能对水凝胶应用于递送系统产生影响的 28 个特质。

值得一提的是，最近新提出的连续混沌细菌生物打印(continuous chaotic bioprinting)技术能够制造具有插入层的细菌菌株的水凝胶结构，这使得同时递送多种益生菌成为可能[68]。从单一益生菌递送向逐渐复杂的细菌微生态的递送，可能成为实现健康菌落移植疗法的重要工具。

1.2 填充剂

水凝胶的多孔网状结构容易造成H^+以及其他损伤细菌的物质进出，显著降低内部益生菌的效能[10]。除了改良、替换基质材料，另一个思路是对益生菌-水凝胶交联结构的天然孔隙进行填充。经过大量试验，水凝胶能够接纳包括分子、胶束、液滴、固体颗粒、脂质体、生物聚合物和结构化颗粒在内的多种成分，从而显示出不同特性，以适应益生菌载体的不同需求[69]。

海藻酸钙凝珠是较为成熟的代表材料之一，通过在基础的益生菌-海藻酸盐混合物中滴入钙溶液形成，可以保护微生物免于干燥条件下遭受损伤[67]。Zheng 等将乙二胺四乙酸(ethylenediaminetetraacetic acid，EDTA)加入海藻酸钙中制备水凝胶材料可在 pH 2.0 的环境中分解产生 Ca^{2+}，将海藻酸盐溶液转化为具有致密结构的水凝胶，其弹性模量从 534 Pa 急剧增加到 17.8 kPa，机械强度显著增大。同时，由于 Ca^{2+}与水凝胶的强络合作用，进入肠道的中性环境后水凝胶塌陷，释放益生菌[70]。钙离子除了作为形成微球的凝结剂，还可以作为微球中的有效成分[16]。但也有研究指出，与钙离子交联降低了海藻酸盐水凝胶的粘附性能，缩短了在肠道中的滞留时间[50]。

一个可行改进策略是在海藻酸基质中加入海藻提取物的胶凝组分作为填充材料。研究表明，这可以在限制结构收缩的同时降低孔隙率[48]。玉米淀粉也可用作藻酸盐珠粒中的填充剂[71]。然而，过量添加抗性淀粉可能会导致藻酸盐凝胶基质的破坏，增大酸性环境下细菌死亡的风险[10]。此外，葫芦巴(fenugreek)作为一种有弹性的生物聚合物，也可与海藻酸钠合成共混物以提高强度[64]。

果胶作为一种有效、食品级、经济、无毒且易于使用的常用基质[26]，在酸性环境中表现为大分子的聚集体，为避免蛋白酶和淀粉酶的破坏提供了一种物理屏障。相比只有果胶的封装材料，含有适当浓度葡萄糖的果胶可能更具优势，其原因可能是小分子的葡萄糖相比果胶

表 1 新型复合水凝胶组成及其特性

Table 1 The composition and properties of novel hydrogel

Material properties	Material composition
pH sensitivity	Chitosan hydrochloride/sodium alginate[13] Graphene oxide/glutaraldehyde/gelatin[41] Calcium alginate/fucoidans[48] Sodium alginate/zein[49] Calcium alginate/whey protein concentrate (WPC)[7] WPC/pullulan[35] Thiolated chitosan/sodium alginate[50] Pectin/glucose[34] Gelatin/gum arabic[51] Gelatin/gum arabic/sucrose[52]
Temperature sensitivity	Sodium alginate/chitosan[53] Poloxamer407/sodium alginate[56] Apple pomace/pectin[45]
Bile salt tolerance	WPC/pullulan[35] Sodium alginate/zein[49] Pectin/starch[58] Sodium alginate/starch[20]
Biodegradability	Copaiba oil/carbomer[60] Chitosan hydrochloride/sodium alginate[13] Pectin/starch[58] (Modifeid)alginate[38] Chitosan/glucan[61]
Low cost Easy to prepare	Apple pomace/pectin[45] Sodium alginate/chitosan[53] DNA/gelatin/κ-carrageenan[62] Chitosan hydrochloride/sodium alginate[13] Gelatin[40] Sodium alginate/chitosan[53] Calcium alginate/fucoidans[48] Curd-peptide[46]
Gelling property	Sodium alginate/zein[49]
Oxidation resistance	Calcium alginate/fucoidans[48] Oil-in-water (O/W) emulsions[28] Kappa-carrageenan/locust bean gum/WPC[23]
Thermal stability	WPC/pullulan[35] Chitosan hydrochloride/sodium alginate[13] Fish gelatin/sodium alginate[59] Electrospun fiber/alginate[63] kappa-carrageenan/locust bean gum/WPC[23] Poloxamer407/sodium alginate[56]
Photostability	Propylene glycol alginate/β-lactoglobulin[22] Gelatin[40] Electrospun fiber/alginate[63]
Stability under refrigerated conditions (4 °C)	DNA/gelatin/κ-carrageenan[62] WPC/PUL/TRE[8] Thiolated hyaluronic acid[15] Calcium alginate/WPC[7] Pectin/glucose[34]
Low permeability	Sodium alginate/chitosan[53] Thiolated chitosan/sodium alginate[50] Chitosan hydrochloride/sodium alginate[13] Sodium alginate[54]
Ductility	Copaiba oil/carbomer[60] Low sodium alginate[23]
Moisture resistance	Chitosan hydrochloride/sodium alginate[13] Calcium alginate[67]
Collaborative delivery	Propylene glycol alginate/β-lactoglobulin[22] Sodium alginate[33]
Mechanical properties	Calcium alginate/fucoidans[48] Chitosan hydrochloride/sodium alginate[13] Thiolated hyaluronic acid[15] Sodium alginate/chitosan[53] Sodium alginate[54] Shellac[55] GO/glutaraldehyde/gelatin[41]
Film forming	Hydrogels of 2-hydroxyethyl methacrylate/polyethylene glycol diacrylate[57] Sodium alginate/zein[49]
Suitable water-content	Chitosan hydrochloride/sodium alginate[13] Fish gelatin/sodium alginate[59] WPC/pullulan(PUL)/trehalose(TRE) hydrogel[8] Collagen[12]
Rheology	WPC/PUL/TRE[8] Poloxamer407/sodium alginate[56] GO/glutaraldehyde/gelatin[41] Copaiba oil/carbomer[60]
Adhesion	Chitosan hydrochloride/sodium alginate[13] Thiolated chitosan/sodium alginate[50] Poloxamer407/sodium alginate[56]
Conducive to nutrition	Thiolated hyaluronic acid[15]
Conducive to probiotic growth	Apple pomace/pectin[45] Poly(ethylene glycol) dimethacrylate (PEG-DMA)[14] Thiolated hyaluronic acid[15]
Antibacterial ability	Chitosan hydrochloride/sodium alginate[13] GO/glutaraldehyde/gelatin[41] PEG-DMA[14] Poloxamer407/sodium alginate[56] Curd-peptide[46] Sodium alginate/fenugreek[64] Copaiba oil/carbomer[60]
Packaging efficiency	Sodium alginate/zein[49] Gelatin/gum arabic[51] (Modifeid)pectin[65] Fish gelatin/sodium alginate[59]
Applicable to dairy allergy	Sodium alginate/soy protein isolate[32] Thiolated hyaluronic acid[15] Sodium alginate/zein[49]
Sensory properties	Fish gelatin/sodium alginate[59] Sodium alginate/carrageenan[37] Calcium algifnate/WPC[7]
Low pH sensitivity	Gellan gum[66] Chitosan/glucan[61]
Lack of mechanical properties	Chitosan hydrochloride/sodium alginate[13] WPC/pullulan[8]
Toxicity	ZIF-8[33] GO/glutaraldehyde/gelatin[41]

更能被有效代谢，为益生菌提供能量来源[34]。另外，淀粉包裹的果胶水凝胶对胆盐溶液的破坏也有很好的保护作用，在1%胆盐溶液中培养1 h后仅从9.98 log CFU/g下降至8.18 log CFU/g，而游离细胞在相同条件下则完全失活[58]。类似地，透明质酸水凝胶具有高度不均匀的互连多孔结构对营养物具有高渗透性，可为鼠李糖乳杆菌(*Lactobacillus rhamnosus* GG)提供能量和营养供应，同时具有良好的物理屏障作用和热稳定性[15]。

随着新的基质材料被发现，可用填充物改良的水凝胶范围日益广泛。例如向以乳清蛋白浓缩物(WPC)普鲁兰糖(pulullan，PUL)为主体的水凝胶中加入海藻糖(TRE)，使水凝胶更具亲水特性，但在持水能力提高的同时，水凝胶的硬度和强度也有所降低，不利于WPC/PUL水凝胶网络结构的形成[8]。此外，Jonganurakkun等将DNA与阳离子聚合物结合制备水凝胶，可以用于包被口腔益生菌[62]，这可能作为一种新型载体，进一步拓宽益生菌-水凝胶递送系统的应用领域。

1.3 外部涂层

除了在海藻酸盐珠中加入填充剂外，使用包衣材料(如壳聚糖、乳清蛋白)构建外部涂层，是另一种提高微胶囊益生菌在胃肠消化过程中稳定性的方法[72]。

壳聚糖是外部涂层的常用材料之一。在交联剂的选择上，京尼平(genipin)可用于海藻酸盐-hylon 淀粉微胶囊壳聚糖外壳的构造[71]。但研究证明，单层壳聚糖形成的微囊不能很好地起到保护作用，反而降低了菌种的生存能力和耐酸性[73]。三层壳聚糖涂层具有良好的硬度，同时阻止了分子氧扩散到水凝胶颗粒中，但随着壳聚糖分子量的增加，粒子的硬度降低[53]。

此外，盐酸壳聚糖(chitosan hydrochloride)作为壳聚糖的一种水溶性衍生物，盐酸壳聚糖-海藻酸钠在微胶囊的边缘还有大量的Ca^{2+}交联，使聚合物基质更加致密，是一种肠道益生菌双重保护屏障载体[13]。壳聚糖和硫代壳聚糖(thiolated chitosan)的混合涂层则可提高体系的粘附性能，增加益生菌在肠壁的滞留时间[50]。

新的材料正逐渐应用于水凝胶的外部涂层。玉米醇溶蛋白(zein)包衣微胶囊明显提高了双歧杆菌(*Bifidobacterium*)对胆盐的耐受性，并降低了藻酸微球的孔隙率，减少了胃环境下内容物的释放[49]。虫胶(shellac)作为外壳可改善水凝胶微球体的疏水性和耐酸性[55]。最新研究运用自组装技术制备的丝素蛋白(silk fibroin)纳米涂层在小鼠肠粘膜炎模型中可以起到协同增强治疗效果[74]。

最近，一些新技术的应用为水凝胶的外层构建创造了新的可能。Grzywaczyk等利用电纺织技术将海藻酸钠-细菌混合层包裹两层N，N-二甲基-甲酰胺(N,N-dimethylformamide, DMF)混合层，既能提高稳定性、化学性和耐热性，又能减少细菌的浸出[63]。另一种多层藻酸盐水凝胶珠(multilayer alginate hydrogel beads，MAHBs)利用多层的外壳结构获得了细菌存活率、耐酸性、稳定性和缓释作用等多方面的提升，而且这些效果广泛适用于革兰氏阳性和阴性菌种[36]。但多层包衣的弊端也显而易见，高成本、高耗材以及对封装技术的要求限制了这一方法在实际应用中的普及。

此外，水包油(O/W)和油包水(W/O)体系的构建几乎革新了水凝胶的前沿研发，加入水、油乳化体系可以表现出较水凝胶更高的保护力，如添加乳清蛋白浓缩物微凝胶的稳定高内相乳液，可使植物乳杆菌(*Lactobacillus plantarum*)在巴氏杀菌后相对维持细胞活性[27]。酪蛋白包裹的益生菌与菜籽油混合后形成乳液，再与酪蛋白酸钠形成双乳液，提高了保护性和冻干状

态下的耐储存性[75]。W1/O/W2 双乳液还能够用于酸奶的益生菌强化，以在不干扰发酵剂培养和发酵的情况下增加功能[76]。此外，多层乳液相的水油复合凝胶也正在开发中，例如单酸甘油酯(monoglyceride)加入脱脂牛奶或水后，再加入菜籽油形成的三相乳液凝胶[77]。然而一项研究对比了 DNA/明胶/κ-卡拉胶交联成的水凝胶和一种固化乳液，发现传统水凝胶相比乳液可能更适合细菌在 4 °C 冷藏条件下生存，且更稳定、更容易制备[62]。油滴絮凝也是乳化体系面临的一个挑战，提示油相的稳定性可能是该载体改良的关键[27]。

2 新材料的应用前景

水凝胶作为最适合人体的一大类生物材料，应关注以人体不同部位为靶点的益生菌菌株差异，由此设计出能够递送不同益生菌的新型材料(表 2)。

表 2 常见益生菌适用的水凝胶材料

Table 2 Hydrogel material for common probiotics

Common probiotics	Corresponding material	Common probiotics	Corresponding material
Lactobacillus		Other Gram-positive bacteria	
Lactobacilluss rhamnosus	Sodium alginate hydrogel particles with chitosan coatings[53] Pectin hydrogel particles[26] Pectin-glucose hydrogel bead[34] Casein-based hydrogel gels[78] Thiolated hyaluronic acid-based hydrogel[15]	*Bifidobacterium*	Zein-sodium alginate hydrogel[49] DNA-based gels[62] Pectin-glucose hydrogel bead[34] Sodium alginate-carrageenan hydrogel[37] Chitosan-alginate hydrogel[79]
Lactobacillus acidophilus	Alginate-whey protein isolate biocomposite[80] Calcium alginate hydrogel beads[48]	*Streptococcus thermophilus*	Peptide hydrogel[46]
Lactobacillus plantarum	WPC/PUL/TRE[8] Whey protein concentrate hydrogel[81] Calcium alginate-cellulose hydrogel[72] Calcium alginate hydrogel beads[48]	*Enterococcus faecalis*	Sodium alginate-fenugreek hydrogel[64]
Lactobacillus Casei	Poloxamer 407-alginate hydrogel[56] Whey protein-calcium alginate Gel[7] Calcium alginate hydrogel beads[48] Pectin hydrogel particles[26]	*Bacillus licheniformis*	Chitosan hydrochloride-sodium alginate hydrogel[13]
Lactobacillus Paracasei	W1/O/W2 emulsion[76]		
Lactobacillus salivarius	Sodium alginate-pectin hydrogel[82]	Other Gram-negative bacteria	
Lactobacillus Reuteri	Chitosan nanohydrogel[83] Calcium alginate hydrogel beads[48]	*Escherichia coli*	Chitosan-alginate hydrogel[79]
Lactobacillus fermentum	Chitosan nanohydrogel [83] Calcium alginate hydrogel beads[48]	*Wilhelm ackermann*	Catechin-alginate hydrogel[39] W1/O/W2 emulsion[27]
Bacillus subtilis	Chitosan nanohydrogel[83]		
Lactobacillus bulgaricus	Chitosan-alginate hydrogel[79]	Fungus	
Others	Pectin-starch hydrogel[58]	Yeast	Collagen hydrogel[12] Gelatin hydrogel[31] Polyvinyl alcohol-gelatin hydrogel[40]

2.1 益生菌加工、储存

加工和储存是发生在益生菌递送过程之前的重要阶段，与递送行为本身同等重要。不同的食品中，不同加工和储存条件都会影响益生菌的存活。考虑到食品加工中需要进行的冷冻、高温、矿物质和抗氧化剂等处理[7-8]，对益生菌进行微封装可以提高益生菌在不同环境下的存活率和稳定性。

封装中常涉及的干燥方法包括低温干燥和高温干燥[10]。冷冻干燥是目前最受欢迎的保持活性的低温干燥方法，因为冷冻水是通过升华除去的，一定程度上减少了对生物结构的破坏[72]。Sun 等评估了一种电荷改性果胶水凝胶封装乳杆菌，发现水凝胶经过冷冻干燥处理后，乳杆菌在贮存和模拟胃肠环境中均表现出更高、更长期的稳定性[65]。然而，冷冻干燥仍然有可能导致细胞损伤和死亡，包括细胞质溶质的沉淀、细胞组分受到的机械压力和细胞膜的破裂[72]。水凝胶的交联结构可能在冷冻干燥过程中因扭曲而重回多孔结构。Sun 等用海藻糖(TRE)/乳清蛋白浓缩物(WPC)/普鲁兰糖(PUL)作为微囊壁，提高了植物乳杆菌在冷冻干燥和储存过程中的生存能力[8]。海藻酸钙/冷冻保护剂/纤维素复合物胶囊可在真空冷冻干燥过程中有效地保护细胞活性。

除了干燥步骤对细胞的损伤外，封装益生菌后对微胶囊的消毒也直接影响水凝胶的结构和益生菌的生存率。一些混合水凝胶可以增强益生菌对巴氏消毒法的耐受性，降低其对益生菌的损伤[32,84]。食品的加工和贮存过程也会给益生菌带来热损伤。果胶封存的微生物失活率受贮藏温度和时间影响较大，在 25–40 °C，果胶解聚率随温度的升高而增加[45]。很多研究证实了各种新型水凝胶抵抗热效应的能力，但仅仅停留在热对于凝胶形成的影响，应进一步评估热对于凝胶载体特性变化的影响[78]。

针对这些问题，微胶囊和其所装载的益生菌都在不断改良，以达到包封率、保护效果、产品多样性、经济和效益上的提升。用益生元进行处理也可以提高微生物在冷冻干燥过程中的存活率，例如含有玉米、菊粉和米糠的微粒比果胶微粒保持益生菌活力的时间更长[85]。丙二醇藻酸盐/β-乳糖蛋白复合水凝胶复合高内相乳液适用于共同递送姜黄素等疏水性功能成分[84]。海藻酸钠大豆蛋白分离基混合水凝胶则拥有更好的耐酸性，可应用于果汁的生产[32]。一项针对苹果益生菌零食的研究采用对流干燥法开发了含有双歧杆菌或植物乳杆菌的苹果干零食，前者联合海藻酸钠在食品加工和胃肠条件下的抗性和存活率已经得到证实[37]，但后者作为一种具有潜力的添加益生菌，由水凝胶承载的效果仍缺乏证实。

同时，要考虑到有些食品加入用水凝胶包被的益生菌后会影响其感官特性。添加胶囊形式的益生菌后，冰淇淋的质地和外观发生改变，如储存过程中粘度增加更显著(最高可达 3 倍)，冰淇淋样品中还观察到了沙粒状物质[7]。理想情况下，如果添加到食品中，颗粒直径控制在<100 μm 的范围内对口感的影响不大[86]。

另外，几乎所有研究都会评估益生菌在模拟胃酸环境下的存活率，以及在肠道中的溶胀和释放能力。但很多研究忽视了益生菌在食物、药物加工和长期储存过程中的活性变化，这对于益生菌产品生产是不可或缺的。

2.2 胃肠道微生态系统

肠道益生菌主要的种类有：鼠李糖乳杆菌、嗜酸乳杆菌(*Lactobacillus acidophilus*)、干酪乳杆菌(*Lactobacillus casei*)、植物乳杆菌、双歧杆菌和酵母菌(yeast)等[87]。水凝胶可以将这些益生菌递送到小肠或结肠，抵挡小肠环境中胰酶、

胆汁酸等成分对益生菌的影响[88]。透明质酸是一种有潜力的胃肠道靶向益生菌递送基质材料[15]。壳聚糖-硫酸葡聚糖和阿糖基木聚糖水凝胶均可用于胃肠道靶向的益生菌包埋[61,85]。

水凝胶良好的生物相容性也增加了胶囊化菌种的多样性，壳聚糖-藻酸钠水凝胶对保加利亚乳杆菌(*Lactobacillus bulgaricus*)、凝固芽孢杆菌(*Bacillus coagulans*)和双歧杆菌的胃肠道耐受性都有提升效果[79]。双歧杆菌对大肠杆菌的生物膜具有破坏作用，为验证其与四环素对胃肠道耐药性大肠杆菌的协同杀灭作用，Yuan等制备出海藻酸钠水凝胶，实现了在模拟胃酸和四环素环境下对双歧杆菌的保护作用[33]，这一突破性研究使益生菌与抗生素协同治疗耐药性大肠杆菌这一新治疗思路成为可能。

在水凝胶的封装系统评估中，研究者大多会测定其是否有良好的耐酸性和益生菌存活率[34]。然而，大部分研究仅使用活菌计数，这一方法只能证明细菌的生存率，仍需考虑在极端环境下细菌维持代谢的能力及与其益生菌作用相关的酶活性。目前有一些更能反映益生菌活性的检测方法被应用，如智能荧光探针标记法检测细菌活力[22]和动物实验测定抗菌活性[14,64]。Ta等通过协调信息素模型进行了复杂的消化酶活性、电解质成分和附加口服剂时细菌存活率的水凝胶评估实验，发现这些实验更接近于人体内消化过程的条件[19]，这提示现阶段的研究在实验条件的控制上还需要进一步的完善。

值得注意的是，在研发和评估过程中，还应考虑水凝胶对人体的毒性。例如，虽然氧化石墨烯(GO)的明胶水凝胶具备一定的性能优势，但考虑到人类细胞在长期暴露于GO后会诱导细胞凋亡和增殖抑制[41]，这一益生菌载体在癌症治疗中应慎用。

2.3 皮肤微生态系统

人的皮肤微环境中有复杂的理化因子[89]。当皮肤损伤时，环境变得利于病原菌定殖，延迟伤口愈合[90]。适宜的益生菌可占据烧伤皮肤表面，或酸化周围组织环境，抑制伤口床内病原菌的生长[12]。短乳杆菌(*Lactobacillus brevis*)、植物乳杆菌和发酵乳杆菌(*Lactobacillus fermentum*)都是已被证实的皮肤益生菌，一些皮肤共生菌也被认为是局部益生菌的候选，如无害产丙酸菌(*Propioniferax innocua*)，山羊葡萄球菌(*Staphylococcus caprae*)和痤疮丙酸杆菌(*Cutibacterium acnes*)[91]。

壳聚糖纳米凝胶递送罗伊氏乳杆菌(*Lactobacillus reuteri*)、发酵乳杆菌、枯草芽孢杆菌(*Bacillus subtilis*)相较单纯的壳多糖或者纱布具有更好的愈合效果[83]。多项研究均证实了植物乳杆菌对治疗复杂烧伤的价值，但使用水凝胶递送植物乳杆菌的潜力仍待开发[92–94]。以凝乳肽为基础的新型水凝胶具有作为伤口愈合剂的潜力，处理后的金黄色葡萄球菌死亡率可达62.54%[46]，目前仍缺乏关注。

水凝胶应用于伤口愈合的优势首先在于其暴露于外界环境条件下保护益生菌的能力。丙二醇藻酸盐/β-乳糖蛋白复合水凝胶和双层电纺织法制得的聚苯乙烯均具有较高的光稳定性，尤其是后者主要用于革兰氏阳性菌[22,63]，例如金黄色葡萄球菌(*Staphylococcus aureus*)[95]。一种聚乙二醇二甲基丙烯酸酯水凝胶可以诱导表皮葡萄球菌(*Staphylococcus epidermidis*)生长，与金黄色葡萄球菌竞争，从而降低皮肤伤口的感染风险[14]。

此外，一些新型水凝胶还可以发挥独特作用。酵母菌具有吸收紫外线的功能，是防晒功能的首选有效成分，酵母菌与明胶交联提高水凝胶防晒霜的紫外线阻隔能力，酵母浓度由

0 g/mL 增至 2 g/mL 时，防晒因子(SPF)可由 0.75 上升到 29.42，细胞生存率也由 46.6%上升到 99%[40]。当然，使用体验也需要纳入考量。水凝胶可以为创面提供足够的水分[40]。加入鱼明胶(fish gelatin，FG)的海藻酸钠双网络凝胶具有很好的透明性和保湿性，其再水化性能从 104.66%提高到 434.40%[59]，能够满足皮肤相关产品对感官特性的特殊要求。淀粉-海藻酸盐和乳糖蔗糖 LS55L-海藻酸盐珠在质地上均具有明显优势，而结冷胶-黄原胶和壳聚糖包被的海藻酸盐珠则具备柔软的特点[19]。

2.4 阴道微生态系统

阴道微生物菌群的平衡在维持阴道微生态的稳定中发挥重要作用，阴道正常 pH 值为 3.8–4.4[96]。在健康的阴道中，乳杆菌占主导地位，最常见的是惰性乳杆菌(*Lactobacillus iners*)，卷曲乳杆菌(*Lactobacillus crispatus*)，格氏乳杆菌 (*Lactobacillus gasseri*) 和詹氏乳杆菌(*Lactobacillus jensenii*)[97]。菌群失衡时，移植健康阴道的优势菌种可以与病原菌竞争，目前已有多种乳酸菌(Lactic acid bacteria)被证明可以减少阴道感染的症状[96]。

考虑到阴道液的稀释和清除作用，阴道益生菌药物对材料的粘附性能及流变性能要求较高，而流动性强的水凝胶往往缺乏硬度。例如泊洛沙姆 407 与海藻酸钠混合物凝胶虽然不能满足大部分细菌的培养要求，但特别适用于阴道递送干酪乳杆菌，可以实现较长的存活和停留时间[56]。天然黄连油制备的卡波姆-水凝胶对特定菌具有明显的杀菌活性，而不影响乳酸菌的生长，对 BALB/c 小鼠阴道黏膜的生物相容性良好，且释放动力学常数为 4.23/h，具有缓慢释放的特性[60]。

2.5 口腔微生态系统

四大微生态系统中的益生菌作用具有相似的机制，例如口腔(图 2)。

目前口腔治疗常用的抗生素和机械疗法往往会损伤共生菌群[101]，而共生菌群已被证明对于维护口腔健康十分重要[102–103]。益生菌疗法则可利用其靶向的优势杀死特定牙周病原体而不伤害共生菌群[101]。变形链球菌(*Streptococcus mutans*)的细胞外基质(EPS)包含参与牙齿表面

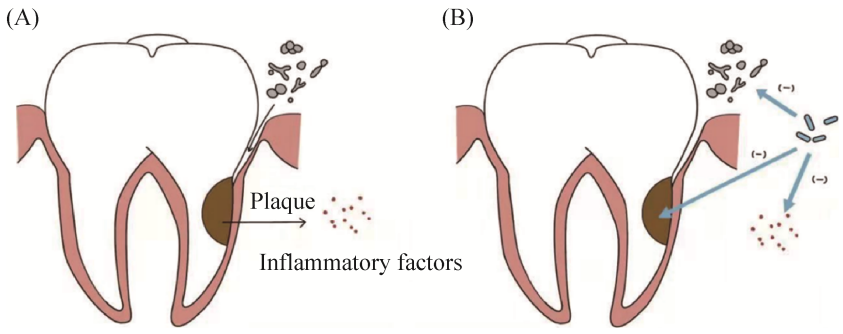

图 2 口腔细菌及益生菌作用机制

Figure 2 Mechanism of oral bacteria and probiotics. A: carbohydrates ferment in the oral cavity can form an acidic pH environment, where bacteria adheres and proliferates, forming plaque biofilm and promoting the development of inflammatory reaction. Inflammation activates the host immune response, releasing inflammatory factors which is further conducive to the growth of periodontal bacteria[98–99]. B: probiotics is a therapeutic method to prevent and treat oral diseases by inhibiting oral pathogenic microorganisms, reducing biofilm formation and regulating oral inflammation[98,100].

生物膜粘附和形成的重要毒力因子，白色念珠菌(*Candida albicans*)也是口腔疾病的常见致病菌。目前证实能抑制这些病原体的益生菌包括血链球菌(*Streptococcus sanguis*)、枯草芽孢杆菌、鼠李糖乳杆菌和双歧杆菌等[102,104–106]。副干酪乳杆菌(*Lactobacillus paracasei*)在基于结冷胶(gellan gum)的水凝胶中也能发挥抑制变形链球菌和白色念珠菌的益生菌作用，具有预防龋齿和口腔念珠菌病的潜力[107–108]。另一方面，益生菌也被证实在降低牙周探诊深度(PPD)和获得临床附着水平(CAL)方面有效[109]。

市场上常见的口腔益生菌载体有咀嚼片、锭剂和胶囊[110]，但因受材料所限，这些制剂往往是短效的。水凝胶吸收大量唾液而不溶解的特性可能更适合用于研发半永久制剂。同时，部分水凝胶材料具备很多更适应口腔微环境的独特特性，例如长期缓释作用、流变特性、粘附性能和胶凝特性等[36,49–50]。益生菌-水凝胶递送系统的应用或许可以拓展现有产品的形式，实现具有长期缓释作用的口腔贴剂和颊黏附凝胶等。天然黄连油制备的卡波姆水凝胶的杀菌作用不影响乳酸菌的生长，且具有缓慢释放的特性，其与阴道黏膜的生物相容性已经证实，在口腔中的应用潜力值得探究[60]。Yeung 等将海藻酸盐凝胶珠封装到单层壳聚糖中，发现其仅暴露在胃酸中几分钟细胞活力就下降了 6 log CFU/mL，却在接触唾液 30 min 后下降不到 1 log CFU/mL[73]。可见口腔相比胃肠道环境更温和，包括单层壳聚糖在内的很多不适应胃肠道极端微环境的水凝胶，或许不失为一种价廉、简易的口腔材料选择。

口腔是人体中较为复杂的微生物栖息地，呈现出一定程度的个体差异性[111]。由于其不同生态位分布的群落存在差异，不能将其视为整体进行益生菌定殖[112]，以水凝胶为代表的靶向递送系统的研发是十分必要的，例如置于颊粘膜上、牙龈沟或牙周袋内。然而目前针对口腔益生菌靶向递送的研究依然少见，这可能是由于口腔益生菌的临床证据尚不充分。水凝胶恰好是一种可以辅助益生菌临床试验的重要工具，能够加速人类不断深入对口腔益生菌新型菌株及其作用的探索。

此外，口腔菌群失衡与多种口腔疾病(如龋齿、牙周炎、口腔黏膜炎)和全身疾病(如胃肠道疾病、心血管系统疾病、神经系统疾病)有关联[29]，多种口腔益生菌被证明可改善全身疾病[113]。现有的益生菌-水凝胶的研发更关注口腔疾病而非全身疾病的治疗，但后者明显拥有更广阔的临床应用前景。总而言之，益生菌-水凝胶递送系统是一种极具潜力的全身疾病的口腔治疗途径。

3 结论及展望

之前的综述往往更关注某一种水凝胶材料(如壳聚糖、海藻酸盐)药物递送系统的潜力，以及如何通过改性进行性能优化。然而，并非所有材料的缺陷都能得到彻底优化，而如果放眼益生菌递送的差异化应用，有些缺陷变得不再是缺陷。随着新型材料的持续出现和益生菌靶点的逐渐多样化，水凝胶改良的关键反而转向了能否组合不同的材料，并且应用于适合的领域，以达到放大其优点、弥补其缺点的目的。本文全面地综述了目前新型水凝胶的改良思路，并在此基础上，结合临床应用分析了不同微生态靶点对水凝胶材料特性的需求。

体内应用要求水凝胶具有更高的安全性和使用体验。因此，除了应注意材料的选择外，在体外对制备的水凝胶进行评估时，也应加入更全面、严谨及对人体各微环境模拟程度更高

的实验。此外，受益于新型水凝胶载体的特性，一些具备充足潜力的益生菌生物治疗思路有了实现的可能，比如向微生物群失衡的部位移植健康菌落，以及耐药大肠杆菌的益生菌-抗生素协同疗法。

最重要的是，本文展望了益生菌-水凝胶递送系统应用于口腔治疗的前景。口腔益生菌领域的研究正在逐渐受到关注，开发出适合将益生菌递送至口腔生态位的载体变得愈加关键和紧迫。水凝胶的应用必将加速口腔益生菌在临床研究和药物研发上的进程。然而，从开发水凝胶更多的特性到足够严谨的体外评估，再到应用于临床，必然需要历经足够长的时间周期，这恰好也为尚不成熟的益生菌生物疗法提供了充足的成长时间，益生菌和水凝胶的发展无疑是双向驱动的。

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