Advances in Clinical Medicine 临床医学进展, 2026, 16(3), 2617-2634
Published Online March 2026 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2026.1631062

Hans汉斯

益生菌细胞外囊泡在糖尿病创面中的研究进展

陈子杰，杨　忠，杨小凡，陈振兵*

华中科技大学同济医学院附属协和医院手外科，湖北　武汉

收稿日期：2026年2月11日；录用日期：2026年3月4日；发布日期：2026年3月17日

摘　要

益生菌细胞外囊泡(PEVs)作为新兴的无细胞治疗平台，凭借其天然的生物相容性、低免疫原性、跨屏障递送能力及固有的生物活性，已在糖尿病创面等多种疾病的干预中展现出广泛而独特的应用潜力。糖尿病创面往往同时存在代谢紊乱、氧化应激损伤、慢性炎症、血管新生受损和微生物感染等多种微环境特征，PEVs可作为一种多功能“纳米药物”，通过递送其携带的多种活性成分，协同应对上述多重病理环节。这种一体化的功能特性，使其相较于单一功效的传统疗法更具优势，有望成为糖尿病创面崭新的、极具潜力的治疗手段。未来，通过工程化改造优化其靶向创面部位的能力，并系统评估其临床安全性及疗效，PEVs有望推动糖尿病创面治疗迈向纳米治疗的新阶段。

关键词

益生菌，细胞外囊泡，无细胞疗法，糖尿病创面

Research Progress of Probiotic Extracellular Vesicles in Diabetic Wounds

Zijie Chen, Zhong Yang, Xiaofan Yang, Zhenbing Chen*

Department of Hand Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan Hubei

Received: February 11, 2026; accepted: March 4, 2026; published: March 17, 2026

Abstract

Probiotic extracellular vesicles (PEVs), as an emerging cell-free therapeutic platform, have demonstrated extensive and unique application potential in the intervention of various diseases, including diabetic wounds, due to their natural biocompatibility, low immunogenicity, cross-barrier delivery ability and inherent biological activity. Diabetic wounds often have multiple microenvironmental characteristics such as metabolic disorders, oxidative stress damage, chronic inflammation, impaired

*通讯作者。

文章引用: 陈子杰, 杨忠, 杨小凡, 陈振兵. 益生菌细胞外囊泡在糖尿病创面中的研究进展[J]. 临床医学进展, 2026, 16(3): 2617-2634. DOI: 10.12677/acm.2026.1631062

angiogenesis and microbial infections simultaneously. PEVs can be used as a multifunctional "nano-medicine" to synergistically address the above multiple pathological links by delivering the various active components they carry. This integrated functional feature gives it an edge over traditional single-effect therapies and is expected to become a novel and highly promising treatment method for diabetic wounds. In the future, through engineering modification to optimize its ability to target wound sites and systematically evaluate its clinical safety and efficacy, PEVs is expected to drive the treatment of diabetic wounds towards a new stage of nanotherapy.

Keywords

Probiotics, Extracellular Vesicles, Cell-Free Therapy, Diabetic Wound

1. 引言

微生物在自然界中广泛存在，人类自出生后就被各种微生物所定植[1] [2]。近年来，随着对人体肠道微生物群探索的不断深入，研究者们发现益生菌和肠道微生物群相关疾病(如炎症性肠病、2 型糖尿病和肥胖症等)的联系十分紧密[2]，因此，越来越多的研究者开始关注益生菌对人类健康的影响。尽管人们对“益生菌”的概念并不陌生，但其直到本世纪初才被定义，根据 2002 年联合国粮农组织(FAO)/世界卫生组织(WHO)联合专家委员会的定义，益生菌(Probiotics)是一类当摄入量足够时，能够对宿主的健康产生益处的活的微生物[3]，主要来源于人和动物的肠道、母乳及发酵的食物[4]。常见的益生菌包括乳酸菌、双歧杆菌、链球菌、芽孢杆菌和某些特殊的大肠杆菌菌株[5]-[7]；此外，嗜粘蛋白阿克曼菌被认为是有前途的新一代益生菌[8]。

尽管大多数益生菌已被证明对人体健康有益，但活菌的使用可能存在潜在的感染风险，尤其是对免疫功能低下的婴幼儿和老年人而言[9] [10]。因此，探究益生菌发挥作用的安全途径成为了研究者们关注的重点。最近的研究发现，益生菌可以通过其自身的生物活性物质和代谢产物对多种疾病产生积极的治疗作用[11]，例如，*L. delbrueckii subsp. bulgaricus 1.0207* 产生的胞外多糖(EPS)能够减轻过氧化氢引起的 IPEC-J2 细胞氧化应激损伤[12]，*L.acidophilus* 分泌的戊酸能够抑制非酒精性脂肪肝病相关肝细胞癌的发展等[13]；此外，由益生菌分泌的细胞外囊泡也已经被证明在调节人体健康方面扮演着重要的角色，且其与活菌产生的生物学效应非常相似[14] [15]。

益生菌细胞外囊泡(Probiotic Extracellular Vesicles, PEVs)是益生菌在生长过程中自然释放的一种具有脂质双分子层结构的纳米级别的膜囊泡[7] [16]，直径大多在 20~400 nm 之间[17]。PEVs 内部包含着多种生物活性物质，例如核酸、蛋白质、脂质和代谢产物等[18]，从而可以携带相应的生物信息，发挥不同的生物学功能，是一种能够对宿主的健康产生有益作用的无细胞物质，具有很强的可控性和很高的生物安全性[18]-[20]。PEVs 不仅可以避免直接应用活菌给患者带来的潜在危害，而且还保留了亲本细菌的多种特性，具有与亲本细菌几乎相同的功能[21]。目前，PEVs 已经被证明在炎症相关性疾病[22] [23]、感染性疾病[24]、肿瘤[25]和伤口愈合[26] [27]等方面发挥着积极作用[28]。此外，相较于目前广泛应用的干细胞来源的细胞外囊泡，PEVs 具有增殖速度快、易于工程化改造、培养技术成熟和高载药量等优势[20] [29] [30]，为未来的疾病治疗和健康促进提供了新的方向。

众所周知，糖尿病创面(Diabetic Wound, DW)是糖尿病患者一种常见且严重的并发症，其延迟愈合或无法愈合可导致严重感染、截肢甚至死亡，这不仅严重影响了患者的身体健康和生活质量，还给社会造成了巨大的医疗和经济负担[31]。与普通创面相比，DW 微环境具有高糖、血管新生障碍、氧化应激损伤、慢性持续性炎症、缺氧和微生物感染等特点[31] [32]。传统的治疗方法(如清创、抗感染、敷料应用和创面减压等)往往无法取得令人满意的疗效，因此，寻找更为高效且经济的治疗方式是当前亟待解决的问题[33]。PEVs 因其多方面的治疗作用在 DW 中展现出独特优势，本文对其在 DW 中的应用进行了综述，以期为未来 DW 的治疗提供新的思路。

2. 细菌细胞外囊泡的生物发生途径

细菌细胞外囊泡(Bacterial Extracellular Vesicles, BEVs)因其不同的类型而具有不同的生物发生途径和内容物，通常，研究者们将革兰氏阴性菌产生的 BEVs 称为外膜囊泡(OMVs)，而将革兰氏阳性菌产生的 BEVs 称为细胞质膜囊泡(CMVs) [34] [35]。

2.1. 革兰氏阴性菌

最初的研究表明，OMVs 是在自然条件下产生的与细菌细胞壁更新相关的副产物，此后，OMVs 的产生机制逐渐被研究者们发现并阐明[5]。目前，比较公认的革兰氏阴性菌产生 OMVs 的方式有两种，即外膜起泡和爆炸性细胞裂解[17] [28] [36]。在外膜起泡机制中，聚糖生物合成不平衡、疏水性分子嵌入外膜或变性蛋白质积累均可能会引起物理应力，这种应力会造成膨胀压力增加，进而导致细菌细胞包膜紊乱和外膜膨出[17] [34] [36] [37]，从而通过外膜起泡机制产生 OMVs，此时，由于细菌细胞的内膜依然保持完整，细胞质成分无法随着起泡的过程进入 OMVs，故 OMVs 中不含有细胞质成分，但富含外膜成分和周质蛋白[17] [36] (见图 1)。除了上述典型的 OMVs，起泡机制还可产生另一类囊泡——外－内膜囊泡(OIMVs)。OIMVs 的产生始于自溶素对细菌肽聚糖层的削弱，当肽聚糖层被削弱之后，细菌细胞的内膜突入到周质中，使细胞质内容物进入囊泡，最后，囊泡连同周围的外膜一起从细菌细胞表面夹断并释放，形成 OIMVs [36]。与 OMVs 不同的是，尽管 OIMVs 也是由起泡机制产生，但其内部含有细胞质成分[34] [36] (见图 1)。爆炸性细胞裂解是产生爆炸性外膜囊泡(EOMVs)和爆炸性外－内膜囊泡(EOIMVs)的主要方式，此过程由噬菌体衍生的内溶素介导，该内溶素能降解细菌细胞壁的肽聚糖部分。一旦肽聚糖被降解，细胞就会因为失去了完整的结构而变得不稳定，从而聚集并发生爆炸，破碎的膜片段通过卷曲和自退火形成含有细胞质成分的 EOMVs 和 EOIMVs [36] [38] (见图 1)。

2.2. 革兰氏阳性菌

起初，由于革兰氏阳性菌细胞壁的肽聚糖层比较厚，且其缺乏外膜结构，研究者们普遍认为其不能产生 EVs [39] [40]。直到 20 世纪 90 年代，人们才在革兰氏阳性菌中发现了 EVs 的存在[40]。与革兰氏阴性菌中的爆炸性细胞裂解类似，缺陷原噬菌体编码的内溶素会破坏肽聚糖，从而使细菌的细胞质膜物质通过肽聚糖上的孔突出，随后这些物质以爆炸性 CMVs 的形式释放。然而，不同于爆炸性细胞裂解的是，在此过程中细菌的细胞壁并没有被完全水解，但大多数细菌细胞由于细胞质膜的完整性被破坏而死亡，这种产生 CMVs 的方式被命名为“冒泡细胞死亡”[39]。此外，与子细胞分离、细胞形状决定和细胞壁更新相关的自溶素也可以在诸如温度变化、缺氧和饥饿等应激条件下引起革兰氏阳性菌的冒泡细胞死亡[41]。肽聚糖水解酶和 β 内酰胺类抗生素通过削弱细菌细胞壁也可以刺激 CMVs 的释放[18] [36] [42]。尽管革兰氏阳性菌缺乏外膜结构，但其仍然可以通过膜起泡机制产生 EVs [18] [43]。研究表明，具有表面活性剂样活性和两亲性螺旋结构的 α 型酚溶性调节素可在细胞质膨胀压力下增强膜曲率，从而导致细胞质膜的破裂和 EVs 的生物发生[43]。由冒泡细胞死亡和膜起泡方式产生的 CMVs 中都富含细胞质成分和细

胞质膜蛋白，两者不同的是，通过前者产生的 CMVs 中含有内溶素或自溶素，而后者形成的 CMVs 中则不含这两种物质[36] (见图 1)。

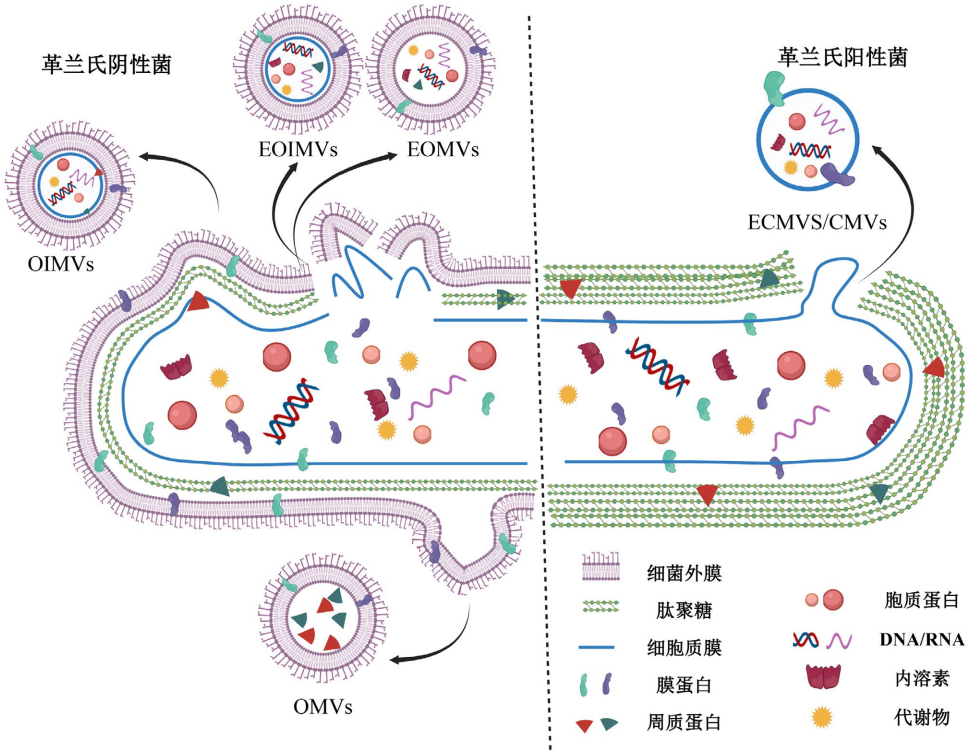

Figure 1. The biological occurrence pathway of extracellular vesicles in bacterial cells
图 1. 细菌细胞外囊泡的生物发生途径

3. PEVs 的分离纯化和表征方法

3.1. PEVs 的分离纯化

作为新兴的疾病治疗方式之一，PEVs 的富集和分离是临床转化和应用的前提。目前对 PEVs 的研究主要集中在对单一菌株进行培养和分离[44]。本文总结了几种常见的 PEVs 的富集和分离方法，并对其优缺点进行了分析(见表 1)。

Table 1. Separation and purification of PEVs
表 1. PEVs 的分离纯化

方法	原理	优点	不足	引文
超速离心	大小和密度	提取过程简单，成本低，EVs 均匀性好，适合大规模提取 EVs	效率有限，纯度有限，耗时长	[29] [45]
超滤	大小和形态	提取过程简单，产量高，EVs 均匀性好，对 EVs 的生物活性影响小	效率有限，纯度有限，过滤器易堵塞，对 EVs 的潜在损伤造成产品损失	[29] [35] [45] [46]
密度梯度离心	密度	纯度高	成本高，耗时长	[18] [23] [29] [46]-[48]

续表

体积排阻色谱	大小	纯度高，能够保持 EVs 的完整性和生物活性	耗时长，不适用于大规模提取	[29] [35] [44] [49] [50]
免疫亲和层析	受体－配体特异性结合	纯度高	成本高，仅适用于特定样品，不适用于大规模提取	[20] [44] [51]
沉淀法	溶解度	提取过程简单，成本低，适用于大规模提取	效率有限，纯度有限，耗时长	[35] [44] [52] [53]

3.2. PEVs 的表征

PEVs 作为益生菌分泌的纳米级颗粒，其组成、大小、数量和形态等特性直接影响其在环境适应、物种间通讯和疾病治疗中的效能[18] [54]。通过多维度的表征技术，研究者能够更加深入地了解 PEVs 的生物学特征，并为其在医学领域的应用提供理论支撑和技术保障。因此，对所获 PEVs 进行多角度的表征是进一步进行体内外研究的基础[18] [44] [53]。本文总结了几种常见的表征 PEVs 的方式，并对其进行了简单的介绍(见表 2)。

Table 2. Characterization of PEVs
表 2. PEVs 的表征

方法	检测内容	优点	不足	引用
DLS	大小	对单纯 EVs 测量速度快，能够测量 1 nm~6 μm 的颗粒，灵敏度高	对多分散悬浮液的精度较低，分辨率有限	[55] [56]
NTA	大小和颗粒数	快速简单，无需样品制备，样品量低，能够分析直径低至 30 nm 的 EVs，能够实时观察 EVs 的聚集	对多分散悬浮液的分辨率有限，不是特定于 EVs 的，无法分析非球形颗粒	[45] [57]
TRPS	大小和 zeta 电位	灵敏度高，无需样品制备，分辨率高，能够同时测量粒径和 zeta 电位	体积大的 EVs 易阻塞孔隙，不是特定于 EVs 的，设备昂贵，维护复杂	[58] [61]
TEM	形态、大小和结构	分辨率高，可用于直接成像，能够分析 EVs 的大小、形状和结构	电子束可能会损伤样品，低通量，样品制备过程复杂且可能改变样品的形态结构	[46] [47] [62]
Cryo-EM	形态和大小	分辨率高，可用于直接成像，液氮速冻减少结构损伤	技术门槛高，成本高	[50] [63] [64]
SEM	表面结构	能够保持样品形态，分辨率高，样品量低，适合大范围形貌分析	样品污染影响测量结果，无法分析内部结构	[50] [65] [66]
AFM	表面形态和成分变化	灵敏度高，分辨率高，生理条件下的成像	尖锐的探头尖端可能导致样品变形，测量仅限于表面，耗时长	[53] [67] [68]
BCA	总蛋白质浓度	灵敏度高，操作简单，成本低	无法区分 EVs 和其他蛋白	[45] [46] [53]

续表

SDS-PAGE	蛋白质分子量分布	复杂样品的可视化，快速分离，成本低	无法区分分子量相似的蛋白，可能失去灵敏度	[64] [69] [70]
考马斯亮蓝	总蛋白质浓度	快速，在室温下进行，成本低	灵敏度低	[53] [69]
WB	蛋白质的定性和半定量	特异性高，能够对 EVs 进行定性和半定量分析	效率低，耗时长，灵敏度低，需要大量的 EVs 蛋白	[71] [72]
MS	蛋白质组	灵敏度高，准确性高，高通量，能够进行全面的蛋白质鉴定，适合与其他方法联合应用	成本高，数据分析复杂，检测低丰度蛋白质的能力有限	[71] [73]
FTIR	EVs 的成分	能够揭示 EVs 的化学成分，样品量低，无损	特异性有限，灵敏度低，干扰多	[74] [75]

4. 糖尿病创面难愈合的机制

4.1. 高血糖

高血糖是 DW 的核心微环境特征，由胰岛素分泌不足或抵抗引起，长期高血糖通过激活多元醇通路、己糖胺通路及蛋白激酶 C (PKC)通路，导致抗氧化物质表达下降、晚期糖基化终末产物(AGEs)积累和氧化应激增强，进而加剧炎症反应[76] [77]。同时，高血糖会导致内皮细胞功能障碍，抑制成纤维细胞和角质形成细胞的迁移能力，并促进基质金属蛋白酶(MMPs)高表达，最终阻碍创面的增殖与重塑过程[78] [79] (见图 2)。

4.2. 氧化应激损伤

氧化应激在 DW 愈合中扮演着核心破坏性角色，其影响源于高血糖诱导的活性氧(ROS)过度积累和抗氧化防御系统失衡。具体而言，持续高血糖通过激活多种通路及 AGEs 形成，抑制超氧化物歧化酶(SOD)、过氧化氢酶(CAT)等关键抗氧化酶活性，打破氧化还原稳态，引发过度氧化应激[80]。这种状态通过多种机制干扰伤口愈合的各个阶段：在炎症期，ROS 过量导致中性粒细胞和巨噬细胞浸润，促进 M1 型巨噬细胞极化并释放 TNF-α、IL-1β、IL-6 等促炎因子，导致慢性炎症无法缓解；同时，氧化应激诱导造血干细胞功能异常，减少单核/巨噬细胞募集，进一步加剧免疫失调[81]。在增殖期，ROS 直接损伤内皮细胞功能，阻碍血管生成；此外，高 ROS 环境破坏角质形成细胞的迁移与增殖，延缓上皮化过程，并通过诱导成纤维细胞衰老和凋亡，削弱胶原合成与细胞外基质(ECM)沉积[82]。在重塑期，氧化应激上调 MMPs 的表达，同时下调组织抑制剂(TIMPs)的表达，导致 ECM 过度降解、胶原纤维结构紊乱，并抑制 TGF-β 信号通路，使伤口无法完成成熟修复[83] [84] (见图 2)。

4.3. 持续慢性炎症

持续的慢性炎症是导致 DW 难以愈合的另一关键机制。在正常的伤口愈合过程中，巨噬细胞会从促炎 M1 型向抗炎修复 M2 型动态转变，从而协调炎症消退和组织修复；然而，糖尿病环境下巨噬细胞的这一动态过程被破坏[85]。具体而言，持续高血糖导致 AGEs 过度积累，后者通过激活 AGE 受体(RAGE)上调 NF-κB 通路，促进 TNF-α 等炎症因子过度表达，使巨噬细胞停滞在 M1 状态，无法正常向 M2 表型转变；同时，组蛋白修饰酶的异常调控加剧了巨噬细胞的这种极化失调[86] [87]。此外，糖尿病环境下巨

噬细胞吞噬和清除凋亡细胞的能力被削弱，导致胞葬作用受损，使凋亡细胞累积并进一步放大炎症反应[88] [89] (见图 2)。

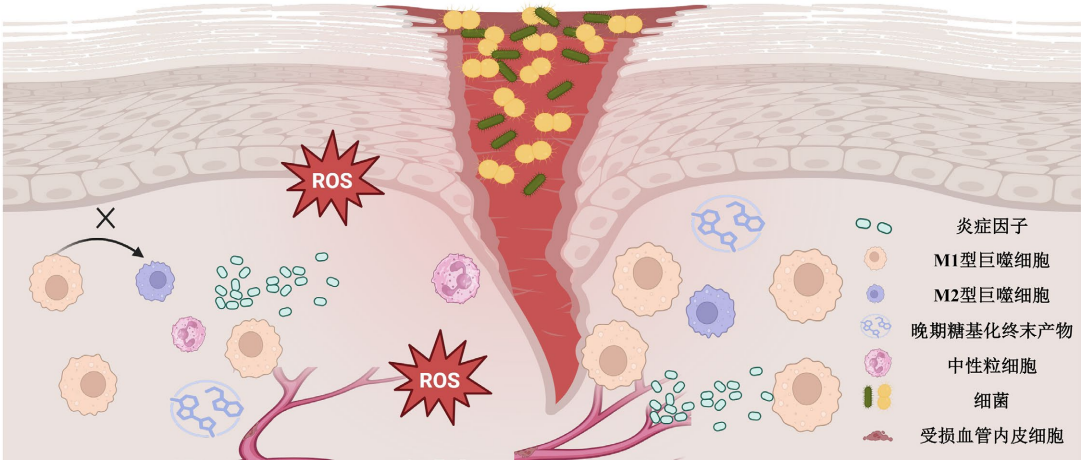

Figure 2. The mechanism of difficult wound healing in diabetes patients
图 2. 糖尿病创面难愈合的机制

4.4. 血管新生受损与缺血缺氧

DW 中的血管新生受损是一个复杂的多因素过程，核心源于持续高血糖引发的代谢紊乱，最终导致伤口内新生血管密度降低。首先，糖脂代谢紊乱会降低内皮 NO 合酶(eNOS)的表达和内皮细胞膜中 L-精氨酸的运输能力，从而导致 eNOS 产生的 NO 减少；在伤口的氧化应激环境下，超氧阴离子(O_2^-)产生增加，并与 NO 结合形成过氧亚硝酸盐(ONOO−)，不仅降低了 NO 的生物活性，还导致 eNOS 解耦联，进一步加剧氧化损伤；同时，AGEs 的积累降低了 NO 的活性并增加了血管通透性，使内皮功能障碍加重并导致微血管血栓形成、血管基底膜增厚[90] [91]。其次，炎症信号通路失调加剧了血管新生障碍，DW 中巨噬细胞极化失衡(M1 促炎表型过度而 M2 抗炎表型不足)阻碍了血管的新生[92] [93]。此外，血管生成相关因子失衡也是导致血管新生受损的又一关键因素。在 DW 中，促血管生成因子如血管内皮生长因子(VEGF)和血小板衍生生长因子(PDGF)表达减少，而抗血管生成因子如色素上皮衍生因子(PEDF)表达增加，PEDF 通过抑制 Wnt/β-catenin 通路阻碍内皮祖细胞(EPCs)活化，同时高血糖下调 HIF-1α，减少其下游 VEGF 等因子产生，破坏新血管形成的动态平衡[94]-[96]。此外，高血糖、氧化应激和慢性炎症使 EPCs 的动员、存活和功能受损，最终导致血管新生不足，愈合进程延迟[97]。大血管粥样硬化、微血管病变以及血管新生障碍直接导致组织灌注不足，造成了组织的缺血缺氧状态。创面的缺氧环境直接损害了成纤维细胞的增殖与胶原合成能力，并抑制角质形成细胞的迁移与上皮化过程[98] [99]。这些因素相互叠加，形成一个恶性循环，最终导致 DW 难以愈合(见图 2)。

4.5. 微生物感染

在 DW 的愈合过程中，感染是一个由多重病理生理机制协同驱动的严重并发症，它不仅直接表现为病原体(如金黄色葡萄球菌、大肠杆菌)定植及生物膜形成，更通过引发持续而失调的宿主反应，显著恶化伤口的病理环境，导致愈合延迟，甚至引发全身感染[100]-[102]。首先，糖尿病高血糖与氧化应激的微环境通过多重机制削弱宿主防御：中性粒细胞的趋化、吞噬及杀菌功能受损，其异常形成的中性粒细胞胞外陷阱(NETs)在清除病原体的同时反而加剧组织损伤[100] [103]；巨噬细胞则难以从 M1 表型向 M2 表型转换，导致创面陷入以 TNF-α、IL-6 等促炎因子持续高表达为特征的慢性炎症状态[100]；同时，糖尿病

固有的血管病变与血管新生不足造成微循环障碍，导致组织缺血缺氧，削弱了局部免疫防御及药物输送[101]；感觉神经病变则导致保护性痛觉丧失，使得创伤与感染早期难以被察觉[100] [101]。在此基础上形成的细菌生物膜，构成一道物理与生理屏障，不仅增强细菌本身的耐药性，亦严重阻碍抗生素渗透及修复细胞迁移，临床上常表现为渗出增多、蜂窝织炎、深部脓肿乃至骨髓炎，极大增加了治疗复杂性与死亡率[100]-[102]。此外，细菌感染不仅能够导致 ROS 生成增加，进一步加重伤口部位的氧化应激和炎症反应，还能抑制 VEGF、PDGF 等关键生长因子的生物活性，并破坏 MMPs 与 TIMPs 之间的平衡，导致细胞外基质降解与沉积紊乱，胶原结构异常，上皮化进程受阻，使创面长期处于难愈状态[100] [101] [104] (见图 2)。

5. PEVs 在糖尿病创面中的应用

作为一种新兴的生物疗法，PEVs 已在多种疾病的治疗中展现出卓越的应用潜力，通过探索其携带的关键活性成分，能够进一步了解其不同的生物学效应。鉴于此，下表系统梳理了 PEVs 在不同疾病模型中发挥的核心功能及其分子机制，旨在为糖尿病创面的治疗中提供有价值的借鉴(见表 3)。

Table 3. The mechanism of action of PEVs in different diseases
表 3. PEVs 在不同疾病中的作用机制

菌株	活性成分	受体/通路	生物学效应	引用
L. plantarum APsul-loc 331261			诱导抗炎因子 IL-10 的分泌，促进巨噬细胞向 M2 型转化	[23]
L. rhamnosus GG	miR-21-5p	PI3K/AKT/HIF1α 信号通路	促进细胞增殖、迁移及血管生成	[27]
L. reuteri	miR-21a-5p	PI3K/AKT 信号通路	促进细胞增殖、迁移及血管生成；减轻糖尿病伤口炎症	[105]
L. animalis			促进血管生成，增强成骨，减少细胞凋亡	[46]
L. plantarum	cbn-let-7	Nrf2/HO-1 信号通路	抑制铁死亡，促进巨噬细胞向 M2 型转化	[45]
L. reuteri		TLR2，MAPK 和 NF-κB 信号通路	清除细胞内 ROS，减轻氧化应激损伤、恢复线粒体功能，促进小胶质细胞向 M2 型转化	[106]
L. rhamnosus		脂质和动脉粥样硬化通路	促进脂质外流，促进泡沫状巨噬细胞向 M2 型转化	[107]
L. johnsonii		NLRP3 和 MAPK 信号通路	促进巨噬细胞向 M2 型转化，修复肠道屏障	[22]
L. druckerii			促进细胞增值迁移，血管生成，调节胶原沉积	[108]
L. plantarum			抑制金黄色葡萄球菌和痤疮丙酸杆菌具有最高的活性	[109]
Ligilactobacillus salivarius *Ligilactobacillus saerimneri*	肽聚糖水解酶、肽聚糖识别蛋白和金属肽酶		抑制沙门氏菌和空肠弯曲菌的活性	[110]

续表

L. rhamnosus GG	FPR1/2，PI3K/Akt 信号通路	增强巨噬细胞的吞噬作用和大肠杆菌清除能力，降低炎症因子水平	[111]
A. muciniphila	TLR-2 和 TLR-4	改善脂质和能量代谢，减少炎症因子	[112]
A. muciniphila	AMPK 信号通路	改善葡萄糖耐量	[113]
L. salivarius	Beclin-1 和 PPAR 相关通路	增强肝细胞线粒体自噬，改善脂质代谢	[114]

5.1. 调节巨噬细胞极化状态和抗炎作用

DW 的特征之一是持续的慢性炎症损伤，其中 M1 型巨噬细胞过度活化导致促炎细胞因子大量释放，阻碍愈合进程。PEVs 作为益生菌代谢产物的重要载体，近年来在免疫调节和抗炎治疗中展现出巨大潜力。多项研究表明，源自乳酸杆菌属(如 *L. plantarum* 和 *L. rhamnosus* 等)的 EVs 能够通过调控巨噬细胞极化状态，显著抑制炎症反应并促进组织修复[115]。其抗炎作用主要体现在下调促炎因子(如 TNF-α、IL-6、IL-1β 和 iNOS 等)的表达，同时上调抗炎介质(如 IL-10、Arg-1 和 TGF-β 等)的水平，从而重塑免疫微环境[23] [116]。PEVs 能够调节关键通路的活化，例如，*L. plantarum* EVs 通过激活 NRF2/HO-1 通路增强细胞抗氧化能力，并抑制 LPS 诱导的巨噬细胞铁死亡，减少 ROS 积累和脂质过氧化，进而缓解氧化应激和炎症损伤[45]；*L. reuteri* EVs 则能通过调控 TLR2 依赖的胞吞作用穿越血脑屏障，靶向缺血脑区，同时通过清除过量 ROS 和抑制 MAPK 及 NF-κB 通路抑制小胶质细胞向 M1 型极化[106]。体内研究进一步证实，PEVs 在急性肺损伤、肠道炎症、动脉粥样硬化和缺血性中风等疾病模型中能有效减少炎症细胞浸润、增强上皮屏障完整性并促进病灶修复。其中，*L. rhamnosus* EVs 通过增强转录因子 NR1H3 的活性上调 ABCA1 介导的脂质外流，同时促进泡沫状巨噬细胞分化为 M2 型，从而缓解动脉粥样硬化的进程[107]；*L. johnsonii* EVs 则通过抑制 MAPK 信号通路来增强巨噬细胞的 M2 型转化，进而阻断 NLRP3 炎症小体活化，减轻肠道炎症损伤[22] (图 3)。这些研究结果不仅揭示了 PEVs 作为一种天然纳米药物在免疫代谢调控中的多效性，还为其作为新型抗炎制剂在慢性炎症性疾病中的临床应用提供了理论依据。

5.2. 促进细胞增殖、迁移和血管新生

PEVs 在组织修复和再生中展现出显著的促进细胞增殖、迁移和血管新生的作用，其机制主要涉及囊泡内携带的生物活性分子(如 miRNAs 等)通过调控关键信号通路(如 PI3K/AKT 和 HIF-1α 等)来调节细胞功能[27] [105]。在体外研究中，PEVs 能够被角质形成细胞、成纤维细胞和血管内皮细胞有效内化，进而显著促进细胞增殖，如用 *L. reuteri EVs*、*L. rhamnosus GG* EVs 或 *L. druckerii* EVs 处理后角质形成细胞、成纤维细胞和血管内皮细胞的存活率显著提高，且 Ki67 阳性细胞比例增加；同时，划痕实验和 Transwell 迁移实验表明 PEVs 处理能够促进细胞迁移[26] [27] [105] [108]。在血管生成方面，PEVs 通过调控 VEGF 等血管生成因子表达促进内皮细胞小管形成。最近的研究表明，*L. reuteri* EVs 或 *L. rhamnosus GG* EVs 处理后血管内皮细胞的分支点和总管长显著增加，进一步探究发现，这些 PEVs 的生物学功能与其携带的特异性 miRNA 密切相关，当 PEVs 被细胞内化后，其携带的 miRNA 被释放到胞质中，通过激活 PI3K/AKT 和 HIF-1α 信号通路，上调促血管生成相关因子的表达以刺激血管新生，体内研究进一步验证了 PEVs 的

这些作用[27] [105]；此外，*L. animalis* EVs 能够进入内皮细胞和骨细胞直接促进血管生成、增强成骨并减少细胞凋亡[46] (图 3)。总之，PEVs 作为一种新型纳米药物，通过多靶点调控细胞增殖、迁移和血管新生，为慢性伤口和糖尿病溃疡等疾病提供了潜在的治疗策略。

5.3. 调节微生物群

PEVs 作为益生菌代谢产物的重要载体，在抗菌治疗中展现出巨大的潜力，其作用机制涉及直接抗菌活性和间接免疫调节双重途径[54] [117]。研究表明，源自乳酸杆菌属的 EVs 能通过携带多种生物活性分子(如细菌素、肽聚糖水解酶和模式识别蛋白)直接抑制病原体生长：例如，*L. plantarum* EVs 对金黄色葡萄球菌和痤疮丙酸杆菌产生显著的抑制效应，并通过水解肽聚糖破坏病原体细胞壁[109]。类似地，*Ligilactobacillus* 来源的 EVs 富含溶菌酶和肽聚糖识别蛋白，能水解沙门氏菌和空肠弯曲菌的肽聚糖层，使病原体裂解[110]。同时，PEVs 能间接增强宿主免疫防御：*L. rhamnosus GG* EVs 在脓毒症模型中激活巨噬细胞表面的 FPR1/2 受体，促进巨噬细胞中 ROS 生成和 PI3K/Akt 通路活化，从而提升巨噬细胞对大肠杆菌的吞噬活性和杀伤效率，降低炎症因子(如 IL-6、TNF-α)水平并减轻多器官损伤[111]。此外，PEVs 还能间接削弱病原体致病性，例如，*Ligilactobacillus* EVs 可下调沙门氏菌和空肠弯曲菌的侵袭基因和黏附基因表达，从而降低病原体对宿主细胞的入侵能力[110]。在特应性皮炎模型中，*L. plantarum* EVs 虽然主要针对免疫调节，但其能拮抗金黄色葡萄球菌 EVs 诱导的炎症，间接抑制细菌定植[118]。这些发现共同表明，PEVs 通过多靶点作用为应对抗生素耐药问题提供了新型解决方案，其纳米尺寸和天然来源特性使其在安全性上优于传统抗生素(图 3)。

5.4. 调节代谢状态

PEVs 作为微生物－宿主相互作用的关键媒介，在代谢调节中发挥着不可忽视的作用，主要通过调控炎症反应改善糖尿病等代谢紊乱[119]。研究表明，诸如 *Akkermia muciniphila*、*L. plantarum* 和 *L. salivarius* 等益生菌衍生的 EVs 能够调节 Toll 样受体(TLR2 和 TLR4)信号通路，降低促炎细胞因子(如 TNF-α、IL-6)水平，并增加抗炎因子(如 IL-10)分泌，间接改善胰岛素抵抗[112] [113] [120]。此外，通过肠－肝轴，PEVs 可以增强肝细胞线粒体自噬(如通过 Beclin-1 和 PINK1/Parkin 通路)，优化能量稳态，并调节糖代谢关键酶(如 G6PASE)以维持血糖平衡[113] [114] [121] (图 3)。

5.5. 工程化修饰和作为载体递送药物

PEVs 作为一种新兴的天然纳米载体，具有生物相容性高、免疫原性可控、易于大规模生产等优势。尤其通过工程化修饰，PEVs 可实现靶向递送、智能释药及多功能协同治疗[122]。一方面，通过合成生物学技术，利用表面蛋白(如 ClyA、Lpp-OmpA 等融合蛋白系统)将靶向分子(如 CXCR4 用于骨靶向)或治疗性蛋白(如 BMP-2 用于成骨)锚定于 PEVs 膜表面，从而可以靶向病变细胞，提高药物的局部浓度并减少全身副作用[123]-[126]。另一方面，通过电穿孔、膜融合等方法向 PEVs 内加载多种治疗药物，可以在创面局部实现可控释放，避免因药物穿透性能低下而导致利用效率降低[122] [127] [128]。同时，针对糖尿病创面独特的微环境特征可设计智能响应型 PEVs，实现药物在病变局部的可控释放，例如，通过 ROS 响应型硫缩酮连接子或 PD-L1 阻断适配体，能够实现 PEVs 在高 ROS 环境中的响应性释放；基于 pH 响应性纳米酶的设计理念，可将葡萄糖氧化酶或聚肽类似物锚定于 PEVs 表面，使其能够在酸性微环境中更好地发挥作用[129]-[131]。此外，通过与脂质体杂交或在 PEVs 膜表面进行改造可以增强 PEVs 的穿透能力，使其能够更好地穿透创面组织屏障并发挥作用[102] [132] [133]。在未来，工程化 PEVs 可与智能水凝胶或 3D 支架结合，构建局部缓释系统，从而实现按需释放[108] [134] (图 3)。

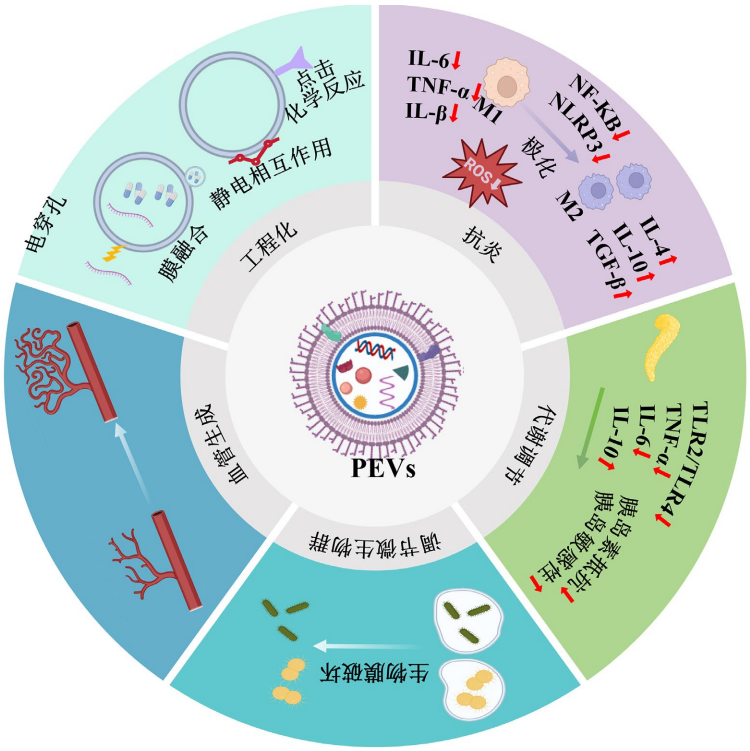

Figure 3. The application of PEVs in diabetic wounds
图 3. PEVs 在糖尿病创面中的应用

6. 总结与展望

PEVs 作为由益生菌在生长代谢过程中自然释放的纳米颗粒，正迅速成为生物医学领域的前沿焦点。它们携带源自本体细菌的蛋白质、核酸、脂质及代谢产物等功能性“货物”，不仅继承了母体菌株良好的生物相容性和低免疫原性，更具备了跨越生物学屏障(如肠上皮屏障、血脑屏障)的卓越能力与潜在的细胞靶向性，这使 PEVs 超越了传统“活菌治疗”的局限，成为益生菌发挥健康益处的关键效应物质和信号载体，展现出作为新型无细胞治疗剂和智能药物递送载体的巨大潜能，充当着超越种属界限的精密生物信使。现有的研究已经证明了 PEVs 在 DW 等疾病中发挥着积极的治疗作用，其强大的抗炎、抗氧化、代谢调节和微生物调节能力为糖尿病难愈创面的治疗提供了新的思路和策略。然而，尽管前景广阔，PEVs 从基础研究走向临床应用仍面临一系列核心挑战，包括其长期安全性(如革兰氏阴性菌 LPS 的毒性需通过基因敲除降低)、标准化生产(如不同的分离方法可能导致产物异质性和功能差异)、质量控制(不同菌株之间的疗效差异)以及个体化差异带来的疗效波动[29] [135]。未来，随着对 PEVs 研究的不断深入，我们有望逐步攻克上述挑战。一方面，通过基因编辑技术等手段，能够更精准地调控 PEVs 的成分，降低其潜在毒性，提高长期安全性，为临床应用扫除障碍[29]。另一方面，建立标准化的生产纯化与质量控制体系，制定统一规范的操作流程，将有效减少产物异质性和功能差异，确保 PEVs 的质量稳定可靠。同时，深入探究不同菌株来源 EVs 的作用机制和疗效差异，结合个体基因组、代谢组等特征，实现个性化精准治疗，将极大提升 PEVs 的治疗效果。总之，PEVs 作为一种新型无细胞生物治疗手段，将在疾病治疗和组织再生领域发挥重要作用，为人类健康事业带来新的突破和希望。

基金项目

本研究得到国家自然科学基金面上项目资助(No.82472566)。

参考文献

[1] Silva, D.R., Sardi, J.D.C.O., Pitangui, N.D.S., Roque, S.M., Silva, A.C.B.D. and Rosalen, P.L. (2020) Probiotics as an Alternative Antimicrobial Therapy: Current Reality and Future Directions. *Journal of Functional Foods*, **73**, Article ID: 104080. https://doi.org/10.1016/j.jff.2020.104080

[2] de Vos, W.M., Tilg, H., Van Hul, M. and Cani, P.D. (2022) Gut Microbiome and Health: Mechanistic Insights. *Gut*, **71**, 1020-1032. https://doi.org/10.1136/gutjnl-2021-326789

[3] Hill, C., Guarner, F., Reid, G., Gibson, G.R., Merenstein, D.J., Pot, B., *et al.* (2014) The International Scientific Association for Probiotics and Prebiotics Consensus Statement on the Scope and Appropriate Use of the Term Probiotic. *Nature Reviews Gastroenterology & Hepatology*, **11**, 506-514. https://doi.org/10.1038/nrgastro.2014.66

[4] Fentie, E.G., Lim, K., Jeong, M. and Shin, J. (2024) A Comprehensive Review of the Characterization, Host Interactions, and Stabilization Advancements on Probiotics: Addressing the Challenges in Functional Food Diversification. *Comprehensive Reviews in Food Science and Food Safety*, **23**, e13424. https://doi.org/10.1111/1541-4337.13424

[5] Chen, X., Li, Q., Xie, J. and Nie, S. (2024) Immunomodulatory Effects of Probiotic-Derived Extracellular Vesicles: Opportunities and Challenges. *Journal of Agricultural and Food Chemistry*, **72**, 19259-19273. https://doi.org/10.1021/acs.jafc.4c04223

[6] Abdelhamid, A.G., El-Masry, S.S. and El-Dougdoug, N.K. (2019) Probiotic Lactobacillus and Bifidobacterium Strains Possess Safety Characteristics, Antiviral Activities and Host Adherence Factors Revealed by Genome Mining. *EPMA Journal*, **10**, 337-350. https://doi.org/10.1007/s13167-019-00184-z

[7] Zhang, Y., Song, M., Fan, J., Guo, X. and Tao, S. (2024) Impact of Probiotics-Derived Extracellular Vesicles on Livestock Gut Barrier Function. *Journal of Animal Science and Biotechnology*, **15**, Article No. 149. https://doi.org/10.1186/s40104-024-01102-8

[8] Menjivar, C., Pagella, E. and Biswas, I. (2024) *Akkermansia muciniphila*. *Trends in Microbiology*, **32**, 1143-1144. https://doi.org/10.1016/j.tim.2024.08.010

[9] Li, Z., Li, M., Fang, X., Yu, D. and Hu, X. (2024) Dietary *Lactobacillus johnsonii*-Derived Extracellular Vesicles Ameliorate Acute Colitis by Regulating Gut Microbiota and Maintaining Intestinal Barrier Homeostasis. *Food & Function*, **15**, 11757-11779. https://doi.org/10.1039/d4fo04194a

[10] Shah, A.B., Baiseitova, A., Zahoor, M., Ahmad, I., Ikram, M., Bakhsh, A., *et al.* (2024) Probiotic Significance of *Lactobacillus* Strains: A Comprehensive Review on Health Impacts, Research Gaps, and Future Prospects. *Gut Microbes*, **16**, Article ID: 2431643. https://doi.org/10.1080/19490976.2024.2431643

[11] Lee, W. and Hase, K. (2014) Gut Microbiota-Generated Metabolites in Animal Health and Disease. *Nature Chemical Biology*, **10**, 416-424. https://doi.org/10.1038/nchembio.1535

[12] Liu, D., Yue, Y., Ping, L., Sun, C., Zheng, T., Cheng, Y., *et al.* (2024) *Lactobacillus delbrueckii* Subsp. *Bulgaricus* 1.0207 Exopolysaccharides Attenuate Hydrogen Peroxide-Induced Oxidative Stress Damage in IPEC-J2 Cells through the Keap1/Nrf2 Pathway. *Antioxidants*, **13**, Article 1150. https://doi.org/10.3390/antiox13091150

[13] Lau, H.C., Zhang, X., Ji, F., Lin, Y., Liang, W., Li, Q., *et al.* (2024) *Lactobacillus acidophilus* Suppresses Non-Alcoholic Fatty Liver Disease-Associated Hepatocellular Carcinoma through Producing Valeric Acid. *eBioMedicine*, **100**, Article ID: 104952. https://doi.org/10.1016/j.ebiom.2023.104952

[14] Krzyżek, P., Marinacci, B., Vitale, I. and Grande, R. (2023) Extracellular Vesicles of Probiotics: Shedding Light on the Biological Activity and Future Applications. *Pharmaceutics*, **15**, Article 522. https://doi.org/10.3390/pharmaceutics15020522

[15] Bleibel, L., Dziomba, S., Waleron, K.F., Kowalczyk, E. and Karbownik, M.S. (2023) Deciphering Psychobiotics' Mechanism of Action: Bacterial Extracellular Vesicles in the Spotlight. *Frontiers in Microbiology*, **14**, Article 1211447. https://doi.org/10.3389/fmicb.2023.1211447

[16] Kim, J.H., Lee, J., Park, J. and Gho, Y.S. (2015) Gram-Negative and Gram-Positive Bacterial Extracellular Vesicles. *Seminars in Cell & Developmental Biology*, **40**, 97-104. https://doi.org/10.1016/j.semcdb.2015.02.006

[17] Toyofuku, M., Nomura, N. and Eberl, L. (2018) Types and Origins of Bacterial Membrane Vesicles. *Nature Reviews Microbiology*, **17**, 13-24. https://doi.org/10.1038/s41579-018-0112-2

[18] Li, M., Mao, B., Tang, X., Zhang, Q., Zhao, J., Chen, W., *et al.* (2024) Lactic Acid Bacteria Derived Extracellular Vesicles: Emerging Bioactive Nanoparticles in Modulating Host Health. *Gut Microbes*, **16**, Article ID: 2427311. https://doi.org/10.1080/19490976.2024.2427311

[19] Kaparakis-Liaskos, M. and Ferrero, R.L. (2015) Immune Modulation by Bacterial Outer Membrane Vesicles. *Nature Reviews Immunology*, **15**, 375-387. https://doi.org/10.1038/nri3837

[20] Niu, L., Chen, W., Yin, Z., Tan, H., Cui, J. and Su, J. (2025) Bacterial Extracellular Vesicles in Osteoarthritis: A New

Bridge of the Gut-Joint Axis. *Gut Microbes*, **17**, Article ID: 2489069. https://doi.org/10.1080/19490976.2025.2489069

[21] Zhang, X., Wang, Y., E, Q., Naveed, M., Wang, X., Liu, Y., *et al.* (2025) The Biological Activity and Potential of Probiotics-Derived Extracellular Vesicles as Postbiotics in Modulating Microbiota-Host Communication. *Journal of Nanobiotechnology*, **23**, Article No. 349. https://doi.org/10.1186/s12951-025-03435-6

[22] Tao, S., Fan, J., Li, J., Wu, Z., Yao, Y., Wang, Z., *et al.* (2025) Extracellular Vesicles Derived from *Lactobacillus johnsonii* Promote Gut Barrier Homeostasis by Enhancing M2 Macrophage Polarization. *Journal of Advanced Research*, **69**, 545-563. https://doi.org/10.1016/j.jare.2024.03.011

[23] Kim, W., Lee, E.J., Bae, I., Myoung, K., Kim, S.T., Park, P.J., *et al.* (2020) *Lactobacillus plantarum*-Derived Extracellular Vesicles Induce Anti-Inflammatory M2 Macrophage Polarization *in Vitro*. *Journal of Extracellular Vesicles*, **9**, Article ID: 1793514. https://doi.org/10.1080/20013078.2020.1793514

[24] Zhou, H., Huang, W., Li, J., Chen, P., Shen, L., Huang, W., *et al.* (2025) Oral Probiotic Extracellular Vesicle Therapy Mitigates Influenza a Virus Infection via Blunting IL-17 Signaling. *Bioactive Materials*, **45**, 401-416. https://doi.org/10.1016/j.bioactmat.2024.11.016

[25] Yi, S., Jung, E., Kim, H., Choi, J., Kim, S., Lim, E., *et al.* (2024) Harnessing *Lactobacillus reuteri*-Derived Extracellular Vesicles for Multifaceted Cancer Treatment. *Small*, **21**, e2406094. https://doi.org/10.1002/smll.202406094

[26] Zhou, C., Cao, H., Wang, Y., Yao, C., Zou, Y., Liu, J., *et al.* (2025) Anchoring of Probiotic-Membrane Vesicles in Hydrogels Facilitates Wound Vascularization. *ACS Nano*, **19**, 3325-3338. https://doi.org/10.1021/acsnano.4c11986

[27] Wang, J., Li, X., Zhao, X., Yuan, S., Dou, H., Cheng, T., *et al.* (2024) Lactobacillus Rhamnosus GG-Derived Extracellular Vesicles Promote Wound Healing via miR-21-5p-Mediated Re-Epithelization and Angiogenesis. *Journal of Nanobiotechnology*, **22**, Article No. 644. https://doi.org/10.1186/s12951-024-02893-8

[28] 乔郁. 产胞外囊泡益生菌的筛选及其成分组学的解析[D]: [硕士学位论文]. 沈阳: 沈阳农业大学, 2025.

[29] Guo, J., Huang, Z., Wang, Q., Wang, M., Ming, Y., Chen, W., *et al.* (2025) Opportunities and Challenges of Bacterial Extracellular Vesicles in Regenerative Medicine. *Journal of Nanobiotechnology*, **23**, Article No. 4. https://doi.org/10.1186/s12951-024-02935-1

[30] Liu, H., Zhang, Q., Wang, S., Weng, W., Jing, Y. and Su, J. (2022) Bacterial Extracellular Vesicles as Bioactive Nanocarriers for Drug Delivery: Advances and Perspectives. *Bioactive Materials*, **14**, 169-181. https://doi.org/10.1016/j.bioactmat.2021.12.006

[31] Burgess, J.L., Wyant, W.A., Abdo Abujamra, B., Kirsner, R.S. and Jozic, I. (2021) Diabetic Wound-Healing Science. *Medicina*, **57**, Article 1072. https://doi.org/10.3390/medicina57101072

[32] Huang, K., Mi, B., Xiong, Y., Fu, Z., Zhou, W., Liu, W., *et al.* (2025) Angiogenesis during Diabetic Wound Repair: From Mechanism to Therapy Opportunity. *Burns & Trauma*, **13**, tkae052. https://doi.org/10.1093/burnst/tkae052

[33] Yang, J., Chen, Z., Pan, D., Li, H. and Shen, J. (2020) Umbilical Cord-Derived Mesenchymal Stem Cell-Derived Exosomes Combined Pluronic F127 Hydrogel Promote Chronic Diabetic Wound Healing and Complete Skin Regeneration. *International Journal of Nanomedicine*, **15**, 5911-5926. https://doi.org/10.2147/ijn.s249129

[34] Xie, J., Haesebrouck, F., Van Hoecke, L. and Vandenbroucke, R.E. (2023) Bacterial Extracellular Vesicles: An Emerging Avenue to Tackle Diseases. *Trends in Microbiology*, **31**, 1206-1224. https://doi.org/10.1016/j.tim.2023.05.010

[35] Xie, J., Li, Q., Haesebrouck, F., Van Hoecke, L. and Vandenbroucke, R.E. (2022) The Tremendous Biomedical Potential of Bacterial Extracellular Vesicles. *Trends in Biotechnology*, **40**, 1173-1194. https://doi.org/10.1016/j.tibtech.2022.03.005

[36] Toyofuku, M., Schild, S., Kaparakis-Liaskos, M. and Eberl, L. (2023) Composition and Functions of Bacterial Membrane Vesicles. *Nature Reviews Microbiology*, **21**, 415-430. https://doi.org/10.1038/s41579-023-00875-5

[37] Díaz-Garrido, N., Badia, J. and Baldomà, L. (2021) Microbiota-Derived Extracellular Vesicles in Interkingdom Communication in the Gut. *Journal of Extracellular Vesicles*, **10**, e12161. https://doi.org/10.1002/jev2.12161

[38] Turnbull, L., Toyofuku, M., Hynen, A.L., Kurosawa, M., Pessi, G., Petty, N.K., *et al.* (2016) Explosive Cell Lysis as a Mechanism for the Biogenesis of Bacterial Membrane Vesicles and Biofilms. *Nature Communications*, **7**, Article No. 11220. https://doi.org/10.1038/ncomms11220

[39] Toyofuku, M., Cárcamo-Oyarce, G., Yamamoto, T., Eisenstein, F., Hsiao, C., Kurosawa, M., *et al.* (2017) Prophage-triggered Membrane Vesicle Formation through Peptidoglycan Damage in *Bacillus subtilis*. *Nature Communications*, **8**, Article No. 481. https://doi.org/10.1038/s41467-017-00492-w

[40] Brown, L., Wolf, J.M., Prados-Rosales, R. and Casadevall, A. (2015) Through the Wall: Extracellular Vesicles in Gram-Positive Bacteria, Mycobacteria and Fungi. *Nature Reviews Microbiology*, **13**, 620-630. https://doi.org/10.1038/nrmicro3480

[41] Abe, K., Toyofuku, M., Nomura, N. and Obana, N. (2021) Autolysis-Mediated Membrane Vesicle Formation in *Bacillus subtilis*. *Environmental Microbiology*, **23**, 2632-2647. https://doi.org/10.1111/1462-2920.15502

[42] Andreoni, F., Toyofuku, M., Menzi, C., Kalawong, R., Mairpady Shambat, S., François, P., *et al.* (2019) Antibiotics Stimulate Formation of Vesicles in *Staphylococcus aureus* in Both Phage-Dependent and -Independent Fashions and via Different Routes. *Antimicrobial Agents and Chemotherapy*, **63**. https://doi.org/10.1128/aac.01439-18

[43] Wang, X., Thompson, C.D., Weidenmaier, C. and Lee, J.C. (2018) Release of *Staphylococcus aureus* Extracellular Vesicles and Their Application as a Vaccine Platform. *Nature Communications*, **9**, Article No. 1379. https://doi.org/10.1038/s41467-018-03847-z

[44] Liu, C., Yazdani, N., Moran, C.S., Salomon, C., Seneviratne, C.J., Ivanovski, S., *et al.* (2024) Unveiling Clinical Applications of Bacterial Extracellular Vesicles as Natural Nanomaterials in Disease Diagnosis and Therapeutics. *Acta Biomaterialia*, **180**, 18-45. https://doi.org/10.1016/j.actbio.2024.04.022

[45] Zhao, Q., Lai, J., Jiang, Y., Cui, E., Chang, H., Pan, R., *et al.* (2025) *Lactiplantibacillus plantarum*-Derived Extracellular Vesicles Alleviate Acute Lung Injury by Inhibiting Ferroptosis of Macrophages. *Journal of Nanobiotechnology*, **23**, Article No. 307. https://doi.org/10.1186/s12951-025-03405-y

[46] Chen, C., Rao, S., Yue, T., Tan, Y., Yin, H., Chen, L., *et al.* (2022) Glucocorticoid-Induced Loss of Beneficial Gut Bacterial Extracellular Vesicles Is Associated with the Pathogenesis of Osteonecrosis. *Science Advances*, **8**, eabg8335. https://doi.org/10.1126/sciadv.abg8335

[47] Gujrati, V., Kim, S., Kim, S., Min, J.J., Choy, H.E., Kim, S.C., *et al.* (2014) Bioengineered Bacterial Outer Membrane Vesicles as Cell-Specific Drug-Delivery Vehicles for Cancer Therapy. *ACS Nano*, **8**, 1525-1537. https://doi.org/10.1021/nn405724x

[48] Hu, R., Lin, H., Li, J., Zhao, Y., Wang, M., Sun, X., *et al.* (2020) Probiotic *Escherichia coli* Nissle 1917-Derived Outer Membrane Vesicles Enhance Immunomodulation and Antimicrobial Activity in RAW264.7 Macrophages. *BMC Microbiology*, **20**, Article No. 268. https://doi.org/10.1186/s12866-020-01953-x

[49] Rodovalho, V.D.R., Luz, B.S.R.D., Rabah, H., do Carmo, F.L.R., Folador, E.L., Nicolas, A., *et al.* (2020) Extracellular Vesicles Produced by the Probiotic *Propionibacterium freudenreichii* CIRM-BIA 129 Mitigate Inflammation by Modulating the NF-*κ*B Pathway. *Frontiers in Microbiology*, **11**, Article 1544. https://doi.org/10.3389/fmicb.2020.01544

[50] Mehanny, M., Koch, M., Lehr, C. and Fuhrmann, G. (2020) Streptococcal Extracellular Membrane Vesicles Are Rapidly Internalized by Immune Cells and Alter Their Cytokine Release. *Frontiers in Immunology*, **11**, Article 80. https://doi.org/10.3389/fimmu.2020.00080

[51] Alves, N.J., Turner, K.B., DiVito, K.A., Daniele, M.A. and Walper, S.A. (2017) Affinity Purification of Bacterial Outer Membrane Vesicles (OMVs) Utilizing a His-Tag Mutant. *Research in Microbiology*, **168**, 139-146. https://doi.org/10.1016/j.resmic.2016.10.001

[52] Li, M., Zhou, H., Yang, C., Wu, Y., Zhou, X., Liu, H., *et al.* (2020) Bacterial Outer Membrane Vesicles as a Platform for Biomedical Applications: An Update. *Journal of Controlled Release*, **323**, 253-268. https://doi.org/10.1016/j.jconrel.2020.04.031

[53] Aytar Çelik, P., Derkuş, B., Erdoğan, K., Barut, D., Blaise Manga, E., Yıldırım, Y., *et al.* (2022) Bacterial Membrane Vesicle Functions, Laboratory Methods, and Applications. *Biotechnology Advances*, **54**, Article ID: 107869. https://doi.org/10.1016/j.biotechadv.2021.107869

[54] Domínguez Rubio, A.P., D'Antoni, C.L., Piuri, M. and Pérez, O.E. (2022) Probiotics, Their Extracellular Vesicles and Infectious Diseases. *Frontiers in Microbiology*, **13**, Article 864720. https://doi.org/10.3389/fmicb.2022.864720

[55] Gao, W., Fang, R.H., Thamphiwatana, S., Luk, B.T., Li, J., Angsantikul, P., *et al.* (2015) Modulating Antibacterial Immunity via Bacterial Membrane-Coated Nanoparticles. *Nano Letters*, **15**, 1403-1409. https://doi.org/10.1021/nl504798g

[56] Piotrowska, M., Ciura, K., Zalewska, M., Dawid, M., Correia, B., Sawicka, P., *et al.* (2020) Capillary Zone Electrophoresis of Bacterial Extracellular Vesicles: A Proof of Concept. *Journal of Chromatography A*, **1621**, Article ID: 461047. https://doi.org/10.1016/j.chroma.2020.461047

[57] Gerritzen, M.J.H., Martens, D.E., Wijffels, R.H. and Stork, M. (2017) High Throughput Nanoparticle Tracking Analysis for Monitoring Outer Membrane Vesicle Production. *Journal of Extracellular Vesicles*, **6**, Article ID: 1333883. https://doi.org/10.1080/20013078.2017.1333883

[58] Vogel, R., Pal, A.K., Jambhrunkar, S., Patel, P., Thakur, S.S., Reátegui, E., *et al.* (2017) High-Resolution Single Particle Zeta Potential Characterisation of Biological Nanoparticles Using Tunable Resistive Pulse Sensing. *Scientific Reports*, **7**, Article No. 17479. https://doi.org/10.1038/s41598-017-14981-x

[59] Coumans, F.A.W., van der Pol, E., Böing, A.N., Hajji, N., Sturk, G., van Leeuwen, T.G., *et al.* (2014) Reproducible Extracellular Vesicle Size and Concentration Determination with Tunable Resistive Pulse Sensing. *Journal of Extracellular Vesicles*, **3**, Article ID: 25922. https://doi.org/10.3402/jev.v3.25922

[60] Tartaglia, N.R., Breyne, K., Meyer, E., Cauty, C., Jardin, J., Chrétien, D., *et al.* (2018) *Staphylococcus aureus* Extracellular Vesicles Elicit an Immunostimulatory Response *in Vivo* on the Murine Mammary Gland. *Frontiers in Cellular and Infection Microbiology*, **8**, Article 277. https://doi.org/10.3389/fcimb.2018.00277

[61] Anderson, W., Kozak, D., Coleman, V.A., Jämting, Å.K. and Trau, M. (2013) A Comparative Study of Submicron

Particle Sizing Platforms: Accuracy, Precision and Resolution Analysis of Polydisperse Particle Size Distributions. *Journal of Colloid and Interface Science*, **405**, 322-330. https://doi.org/10.1016/j.jcis.2013.02.030

[62] Kim, O.Y., Park, H.T., Dinh, N.T.H., Choi, S.J., Lee, J., Kim, J.H., *et al.* (2017) Bacterial Outer Membrane Vesicles Suppress Tumor by Interferon-*γ*-Mediated Antitumor Response. *Nature Communications*, **8**, Article No. 626. https://doi.org/10.1038/s41467-017-00729-8

[63] Camacho, A.I., Irache, J.M., de Souza, J., Sánchez-Gómez, S. and Gamazo, C. (2013) Nanoparticle-Based Vaccine for Mucosal Protection against Shigella Flexneri in Mice. *Vaccine*, **31**, 3288-3294. https://doi.org/10.1016/j.vaccine.2013.05.020

[64] Thoma, J., Manioglu, S., Kalbermatter, D., Bosshart, P.D., Fotiadis, D. and Müller, D.J. (2018) Protein-Enriched Outer Membrane Vesicles as a Native Platform for Outer Membrane Protein Studies. *Communications Biology*, **1**, Article No. 23. https://doi.org/10.1038/s42003-018-0027-5

[65] Harrison, N.A., Gardner, C.L., da Silva, D.R., Gonzalez, C.F. and Lorca, G.L. (2021) Identification of Biomarkers for Systemic Distribution of Nanovesicles from *Lactobacillus johnsonii* N6.2. *Frontiers in Immunology*, **12**, Article 723433. https://doi.org/10.3389/fimmu.2021.723433

[66] Grande, R., Celia, C., Mincione, G., Stringaro, A., Di Marzio, L., Colone, M., *et al.* (2017) Detection and Physicochemical Characterization of Membrane Vesicles (MVs) of *Lactobacillus reuteri* DSM 17938. *Frontiers in Microbiology*, **8**, Article 1040. https://doi.org/10.3389/fmicb.2017.01040

[67] Kikuchi, Y., Obana, N., Toyofuku, M., Kodera, N., Soma, T., Ando, T., *et al.* (2020) Diversity of Physical Properties of Bacterial Extracellular Membrane Vesicles Revealed through Atomic Force Microscopy Phase Imaging. *Nanoscale*, **12**, 7950-7959. https://doi.org/10.1039/c9nr10850e

[68] Potter, M., Hanson, C., Anderson, A.J., Vargis, E. and Britt, D.W. (2020) Abiotic Stressors Impact Outer Membrane Vesicle Composition in a Beneficial Rhizobacterium: Raman Spectroscopy Characterization. *Scientific Reports*, **10**, Article No. 21289. https://doi.org/10.1038/s41598-020-78357-4

[69] Stevenson, T.C., Cywes-Bentley, C., Moeller, T.D., Weyant, K.B., Putnam, D., Chang, Y., *et al.* (2018) Immunization with Outer Membrane Vesicles Displaying Conserved Surface Polysaccharide Antigen Elicits Broadly Antimicrobial Antibodies. *Proceedings of the National Academy of Sciences of the United States of America*, **115**, E3106-E3115. https://doi.org/10.1073/pnas.1718341115

[70] Martora, F., Pinto, F., Folliero, V., Cammarota, M., Dell'Annunziata, F., Squillaci, G., *et al.* (2019) Isolation, Characterization and Analysis of Pro-Inflammatory Potential of *Klebsiella pneumoniae* Outer Membrane Vesicles. *Microbial Pathogenesis*, **136**, Article ID: 103719. https://doi.org/10.1016/j.micpath.2019.103719

[71] Kim, H.Y., Song, M., Gho, Y.S., Kim, H. and Choi, B. (2021) Extracellular Vesicles Derived from the Periodontal Pathogen *Filifactor alocis* Induce Systemic Bone Loss through Toll-Like Receptor 2. *Journal of Extracellular Vesicles*, **10**, e12157. https://doi.org/10.1002/jev2.12157

[72] Chen, D.J., Osterrieder, N., Metzger, S.M., Buckles, E., Doody, A.M., DeLisa, M.P., *et al.* (2010) Delivery of Foreign Antigens by Engineered Outer Membrane Vesicle Vaccines. *Proceedings of the National Academy of Sciences of the United States of America*, **107**, 3099-3104. https://doi.org/10.1073/pnas.0805532107

[73] Kim, D.J., Yang, J., Seo, H., Lee, W.H., Ho Lee, D., Kym, S., *et al.* (2020) Colorectal Cancer Diagnostic Model Utilizing Metagenomic and Metabolomic Data of Stool Microbial Extracellular Vesicles. *Scientific Reports*, **10**, Article No. 2860. https://doi.org/10.1038/s41598-020-59529-8

[74] Huang, B., Liu, C., Yang, J., Xiang, E., Ivanovski, S. and Han, P. (2024) Saliva Biofilm-Derived Outer Membrane Vesicles Regulate Biofilm Formation and Immune Response of Oral Epithelial Cells on Titanium Surfaces. *Clinical Oral Investigations*, **28**, Article No. 75. https://doi.org/10.1007/s00784-023-05454-9

[75] Szöllősi, D., Hajdrik, P., Tordai, H., Horváth, I., Veres, D.S., Gillich, B., *et al.* (2023) Molecular Imaging of Bacterial Outer Membrane Vesicles Based on Bacterial Surface Display. *Scientific Reports*, **13**, Article No. 18752. https://doi.org/10.1038/s41598-023-45628-9

[76] Patel, S., Srivastava, S., Singh, M.R. and Singh, D. (2019) Mechanistic Insight into Diabetic Wounds: Pathogenesis, Molecular Targets and Treatment Strategies to Pace Wound Healing. *Biomedicine & Pharmacotherapy*, **112**, Article ID: 108615. https://doi.org/10.1016/j.biopha.2019.108615

[77] Tang, W.H., Martin, K.A. and Hwa, J. (2012) Aldose Reductase, Oxidative Stress, and Diabetic Mellitus. *Frontiers in Pharmacology*, **3**, Article 87. https://doi.org/10.3389/fphar.2012.00087

[78] Dong, Z., Liu, X., Li, S. and Fu, X. (2025) Inhibition and Rescue of Hyperglycemia-Induced Cellular Senescence by Mitochondrial Transfer from Enucleated Mesenchymal Stem Cell-Derived Microvesicles for Chronic Wound Healing. *Advanced Science*, **12**, e01612. https://doi.org/10.1002/advs.202501612

[79] Kruse, C.R., Singh, M., Sørensen, J.A., Eriksson, E. and Nuutila, K. (2016) The Effect of Local Hyperglycemia on Skin Cells *in Vitro* and on Wound Healing in Euglycemic Rats. *Journal of Surgical Research*, **206**, 418-426. https://doi.org/10.1016/j.jss.2016.08.060

[80] Evans, J.L., Goldfine, I.D., Maddux, B.A. and Grodsky, G.M. (2002) Oxidative Stress and Stress-Activated Signaling Pathways: A Unifying Hypothesis of Type 2 Diabetes. *Endocrine Reviews*, **23**, 599-622. https://doi.org/10.1210/er.2001-0039

[81] Yan, J., Tie, G., Wang, S., Tutto, A., DeMarco, N., Khair, L., *et al.* (2018) Diabetes Impairs Wound Healing by Dnmt1-Dependent Dysregulation of Hematopoietic Stem Cells Differentiation Towards Macrophages. *Nature Communications*, **9**, Article No. 33. https://doi.org/10.1038/s41467-017-02425-z

[82] Zhang, W., Chen, L., Xiong, Y., Panayi, A.C., Abududilibaier, A., Hu, Y., *et al.* (2021) Antioxidant Therapy and Antioxidant-Related Bionanomaterials in Diabetic Wound Healing. *Frontiers in Bioengineering and Biotechnology*, **9**, Article 707479. https://doi.org/10.3389/fbioe.2021.707479

[83] Xu, Z., Yang, W., Zhang, R., Zhang, G., Liang, X., Zhao, N., *et al.* (2025) Microenvironment-Programmed siRNA-Based Hydrogel for Spatiotemporal Gene Silencing in Wound Healing. *Advanced Materials*, **37**, e09558. https://doi.org/10.1002/adma.202509558

[84] Zheng, X., Deng, S., Li, Y., Luo, Z., Gan, Z., Zheng, Z., *et al.* (2025) Targeting m^{6}A Demethylase FTO to Heal Diabetic Wounds with Ros-Scavenging Nanocolloidal Hydrogels. *Biomaterials*, **317**, Article ID: 123065. https://doi.org/10.1016/j.biomaterials.2024.123065

[85] Huang, F., Lu, X., Yang, Y., Yang, Y., Li, Y., Kuai, L., *et al.* (2022) Microenvironment-Based Diabetic Foot Ulcer Nanomedicine. *Advanced Science*, **10**, Article ID: 2203308. https://doi.org/10.1002/advs.202203308

[86] Wang, J., Feng, J., Ni, Y., Wang, Y., Zhang, T., Cao, Y., *et al.* (2024) Histone Modifications and Their Roles in Macrophage-Mediated Inflammation: A New Target for Diabetic Wound Healing. *Frontiers in Immunology*, **15**, Article 1450440. https://doi.org/10.3389/fimmu.2024.1450440

[87] Davis, F.M., denDekker, A., Kimball, A., Joshi, A.D., El Azzouny, M., Wolf, S.J., *et al.* (2020) Epigenetic Regulation of TLR4 in Diabetic Macrophages Modulates Immunometabolism and Wound Repair. *The Journal of Immunology*, **204**, 2503-2513. https://doi.org/10.4049/jimmunol.1901263

[88] Huang, J., Zhang, S., Ding, X., Li, S., Luo, X., Cao, Y., *et al.* (2022) Research Progress on the Mechanism by Which Skin Macrophage Dysfunction Mediates Chronic Inflammatory Injury in Diabetic Skin. *Frontiers in Endocrinology*, **13**, Article 960551. https://doi.org/10.3389/fendo.2022.960551

[89] Bannon, P., Wood, S., Restivo, T., Campbell, L., Hardman, M.J. and Mace, K.A. (2013) Diabetes Induces Stable Intrinsic Changes to Myeloid Cells That Contribute to Chronic Inflammation during Wound Healing in Mice. *Disease Models & Mechanisms*, **6**, 1434-1447. https://doi.org/10.1242/dmm.012237

[90] Wan, L., Bai, X., Zhou, Q., Chen, C., Wang, H., Liu, T., *et al.* (2022) The Advanced Glycation End-Products (AGEs)/ROS/NLRP3 Inflammasome Axis Contributes to Delayed Diabetic Corneal Wound Healing and Nerve Regeneration. *International Journal of Biological Sciences*, **18**, 809-825. https://doi.org/10.7150/ijbs.63219

[91] Soro-Paavonen, A., Zhang, W., Venardos, K., Coughlan, M.T., Harris, E., Tong, D.C., *et al.* (2010) Advanced Glycation End-Products Induce Vascular Dysfunction via Resistance to Nitric Oxide and Suppression of Endothelial Nitric Oxide Synthase. *Journal of Hypertension*, **28**, 780-788. https://doi.org/10.1097/hjh.0b013e328335043e

[92] Guo, L., Zhu, Z., Shi, C., Jia, Y., Nurzat, Y., Su, W., *et al.* (2023) Drug Suspending during Wound Healing Effectively Weakens Immunosuppression-Related Complications by Preserving CD8$^+$ T Cell Function. *Wound Repair and Regeneration*, **31**, 489-499. https://doi.org/10.1111/wrr.13086

[93] Yang, P., Li, S., Zhang, H., Ding, X. and Tan, Q. (2022) LRG1 Accelerates Wound Healing in Diabetic Rats by Promoting Angiogenesis via the Wnt/β-Catenin Signaling Pathway. *The International Journal of Lower Extremity Wounds*, **23**, 568-576. https://doi.org/10.1177/15347346221081610

[94] Lin, C.J., Lan, Y.M., Ou, M.Q., Ji, L.Q. and Lin, S.D. (2019) Expression of miR-217 and HIF-1α/VEGF Pathway in Patients with Diabetic Foot Ulcer and Its Effect on Angiogenesis of Diabetic Foot Ulcer Rats. *Journal of Endocrinological Investigation*, **42**, 1307-1317. https://doi.org/10.1007/s40618-019-01053-2

[95] Qi, W., Yang, C., Dai, Z., Che, D., Feng, J., Mao, Y., *et al.* (2014) High Levels of Pigment Epithelium-Derived Factor in Diabetes Impair Wound Healing through Suppression of Wnt Signaling. *Diabetes*, **64**, 1407-1419. https://doi.org/10.2337/db14-1111

[96] Catrina, S. and Zheng, X. (2021) Hypoxia and Hypoxia-Inducible Factors in Diabetes and Its Complications. *Diabetologia*, **64**, 709-716. https://doi.org/10.1007/s00125-021-05380-z

[97] Short, W.D., Steen, E., Kaul, A., Wang, X., Olutoye, O.O., Vangapandu, H.V., *et al.* (2022) IL-10 Promotes Endothelial Progenitor Cell Infiltration and Wound Healing via STAT3. *The FASEB Journal*, **36**, e22298. https://doi.org/10.1096/fj.201901024rr

[98] Semenza, G.L. (2010) Vascular Responses to Hypoxia and Ischemia. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **30**, 648-652. https://doi.org/10.1161/atvbaha.108.181644

[99] Chen, X., Zhang, L., Chai, W., Tian, P., Kim, J., Ding, J., *et al.* (2023) Hypoxic Microenvironment Reconstruction with Synergistic Biofunctional Ions Promotes Diabetic Wound Healing. *Advanced Healthcare Materials*, **12**, Article ID:

2301984. https://doi.org/10.1002/adhm.202301984

[100] Deng, H., Li, B., Shen, Q., Zhang, C., Kuang, L., Chen, R., *et al.* (2023) Mechanisms of Diabetic Foot Ulceration: A Review. *Journal of Diabetes*, **15**, 299-312. https://doi.org/10.1111/1753-0407.13372

[101] Falanga, V. (2005) Wound Healing and Its Impairment in the Diabetic Foot. *The Lancet*, **366**, 1736-1743. https://doi.org/10.1016/s0140-6736(05)67700-8

[102] Jiang, G., Guo, J., Yan, C., He, Y., Chen, J., Zhang, M., *et al.* (2024) Biomimetic Hybrid Nanovesicles Improve Infected Diabetic Wound via Enhanced Targeted Delivery. *Journal of Controlled Release*, **365**, 193-207. https://doi.org/10.1016/j.jconrel.2023.11.019

[103] Zhang, H., Liang, Q., Ji, Y., Chen, Q., Jiang, W., Zhang, D., *et al.* (2025) Facile Fabrication of Antioxidative and Antibacterial Hydrogel Films to Accelerate Infected Diabetic Wound Healing. *Bioactive Materials*, **53**, 386-403. https://doi.org/10.1016/j.bioactmat.2025.07.026

[104] Chen, J., Liu, Y., Cheng, G., Guo, J., Du, S., Qiu, J., *et al.* (2022) Tailored Hydrogel Delivering Niobium Carbide Boosts Ros-Scavenging and Antimicrobial Activities for Diabetic Wound Healing. *Small*, **18**, Article ID: 2201300. https://doi.org/10.1002/smll.202201300

[105] Li, Y., Zheng, Z., Kong, X., Wang, Y., Liu, Z., Wang, W., *et al.* (2025) Bacteria Extracellular Vesicles Derived from *Lactobacillus reuteri* Delivering Intrinsic miR-21a-5p to Accelerate Diabetic Wound Healing. *Nano Research*, **18**, Article ID: 94908083. https://doi.org/10.26599/nr.2025.94908083

[106] Sun, M., Ma, J., Zhang, G., Song, M., Lv, R., Liang, J., *et al.* (2025) Brain Targeting Bacterial Extracellular Vesicles Enhance Ischemic Stroke Therapy via Efficient ROS Elimination and Suppression of Immune Infiltration. *ACS Nano*, **19**, 15491-15508. https://doi.org/10.1021/acsnano.4c16161

[107] Jing, B., Gao, Y., Wang, L., Guo, F., Jiang, D., Qin, S., *et al.* (2025) Probiotic Membrane Vesicles Ameliorate Atherosclerotic Plaques by Promoting Lipid Efflux and Polarization of Foamy Macrophages. *Journal of Nanobiotechnology*, **23**, Article No. 296. https://doi.org/10.1186/s12951-025-03360-8

[108] Qi, F., Xu, Y., Zheng, B., Li, Y., Zhang, J., Liu, Z., *et al.* (2024) The Core-shell Microneedle with Probiotic Extracellular Vesicles for Infected Wound Healing and Microbial Homeostasis Restoration. *Small*, **20**, Article ID: 2401551. https://doi.org/10.1002/smll.202401551

[109] Yadav, P., Debnath, N., Mehta, P.K., Kumar, A. and Yadav, A.K. (2025) Assessment of Antimicrobial Potential of *Lactiplantibacillus plantarum* and Their Derived Extracellular Vesicles. *Molecular Nutrition & Food Research*, **69**, e70035. https://doi.org/10.1002/mnfr.70035

[110] Miri, S., Mottawea, W., Leao, L., Chiba, M., Li, Y., Minic, Z., *et al.* (2024) *Ligilactobacillus*-Derived Extracellular Vesicles Inhibit Growth and Virulence of Enteric Pathogens. *Probiotics and Antimicrobial Proteins*, **17**, 2244-2261. https://doi.org/10.1007/s12602-024-10423-z

[111] Zhu, R., Zhang, Y., Wang, X., Liu, B.D., Chowdhury, D., Li, Z., *et al.* (2024) Probiotic Bacteria-Released Extracellular Vesicles Enhance Macrophage Phagocytosis in Polymicrobial Sepsis by Activating the FPR1/2 Pathway. *Molecular Medicine*, **30**, Article No. 216. https://doi.org/10.1186/s10020-024-00959-9

[112] Ashrafian, F., Shahriary, A., Behrouzi, A., Moradi, H.R., Keshavarz Azizi Raftar, S., Lari, A., *et al.* (2019) *Akkermansia muciniphila*-Derived Extracellular Vesicles as a Mucosal Delivery Vector for Amelioration of Obesity in Mice. *Frontiers in Microbiology*, **10**, Article 2155. https://doi.org/10.3389/fmicb.2019.02155

[113] Chelakkot, C., Choi, Y., Kim, D., Park, H.T., Ghim, J., Kwon, Y., *et al.* (2018) *Akkermansia muciniphila*-Derived Extracellular Vesicles Influence Gut Permeability through the Regulation of Tight Junctions. *Experimental & Molecular Medicine*, **50**, e450. https://doi.org/10.1038/emm.2017.282

[114] Zhu, L., Huang, J., Luo, Z., Yan, H., Wu, X. and Liao, R. (2025) *Lactobacillus salivarius* Extracellular Vesicles Enhance Gut and Liver Function in MAFLD. *Frontiers in Immunology*, **16**, Article 1660131. https://doi.org/10.3389/fimmu.2025.1660131

[115] 马东雪. 益生菌 E.coli 衍生的外膜囊泡调控 RAW264.7 巨噬细胞 M1 极化及代谢机制研究[D]: [硕士学位论文]. 重庆: 重庆医科大学, 2023.

[116] Chen, Q., Fang, Z., Yang, Z., Xv, X., Yang, M., Hou, H., *et al.* (2024) *Lactobacillus plantarum*-Derived Extracellular Vesicles Modulate Macrophage Polarization and Gut Homeostasis for Alleviating Ulcerative Colitis. *Journal of Agricultural and Food Chemistry*, **72**, 14713-14726. https://doi.org/10.1021/acs.jafc.4c01758

[117] González-Lozano, E., García-García, J., Gálvez, J., Hidalgo-García, L., Rodríguez-Nogales, A., Rodríguez-Cabezas, M.E., *et al.* (2022) Novel Horizons in Postbiotics: *Lactobacillaceae* Extracellular Vesicles and Their Applications in Health and Disease. *Nutrients*, **14**, Article 5296. https://doi.org/10.3390/nu14245296

[118] Kim, M., Choi, S.J., Choi, H., Choi, J., Park, H., Kim, E.K., *et al.* (2018) *Lactobacillus plantarum*-Derived Extracellular Vesicles Protect Atopic Dermatitis Induced by *Staphylococcus aureus*-Derived Extracellular Vesicles. *Allergy, Asthma & Immunology Research*, **10**, 516-532. https://doi.org/10.4168/aair.2018.10.5.516

[119] Díez-Sainz, E., Milagro, F.I., Riezu-Boj, J.I. and Lorente-Cebrián, S. (2021) Effects of Gut Microbiota-Derived Extracellular Vesicles on Obesity and Diabetes and Their Potential Modulation through Diet. *Journal of Physiology and Biochemistry*, **78**, 485-499. https://doi.org/10.1007/s13105-021-00837-6

[120] Ashrafian, F., Keshavarz Azizi Raftar, S., Lari, A., Shahryari, A., Abdollahiyan, S., Moradi, H.R., *et al.* (2021) Extracellular Vesicles and Pasteurized Cells Derived from *Akkermansia muciniphila* Protect against High-Fat Induced Obesity in Mice. *Microbial Cell Factories*, **20**, Article No. 219. https://doi.org/10.1186/s12934-021-01709-w

[121] Martínez-Ruiz, S., Badia, J. and Baldoma, L. (2025) Extracellular Vesicles from *Escherichia coli* Strains of the Gut Microbiota Trigger Hepatic Antioxidant and Anti-Lipogenic Effects via the Gut-Liver Axis in Healthy Neonatal Rats. *Nutrients*, **17**, Article 3066. https://doi.org/10.3390/nu17193066

[122] Wei, J., Ding, W., Song, K., Zhang, Y., Luo, Q. and Qi, C. (2025) Next-Generation Probiotics and Engineered Bevs for Precision Therapeutics in Osteoporosis. *Frontiers in Nutrition*, **12**, Article 1581971. https://doi.org/10.3389/fnut.2025.1581971

[123] Cheng, L., Peng, D., Liu, Z., Tang, J., Zhang, P., Li, M., *et al.* (2026) Engineered Bacterial Outer Membrane Vesicles Enhanced Tumor Immunotherapy through Remodeling Tumor Stroma and Targeted Delivery of CD73 siRNA. *Biomaterials*, **327**, Article ID: 123725. https://doi.org/10.1016/j.biomaterials.2025.123725

[124] Garling, A., Auvray, F., Epardaud, M., Oswald, É. and Branchu, P. (2025) Outer Membrane Vesicles as a Versatile Platform for Vaccine Development: Engineering Strategies, Applications and Challenges. *Journal of Extracellular Vesicles*, **14**, e70150. https://doi.org/10.1002/jev2.70150

[125] Liu, H., Song, P., Zhang, H., Zhou, F., Ji, N., Wang, M., *et al.* (2024) Synthetic Biology-Based Bacterial Extracellular Vesicles Displaying BMP-2 and CXCR4 to Ameliorate Osteoporosis. *Journal of Extracellular Vesicles*, **13**, e12429. https://doi.org/10.1002/jev2.12429

[126] Wang, Y., Hu, L., Wang, L., Zhang, C., Shen, W., Yang, H., *et al.* (2025) Engineered *Escherichia coli* Nissle 1917 Targeted Delivery of Extracellular PD-L1-Mfc Fragment for Treating Inflammatory Bowel Disease. *Acta Pharmaceutica Sinica B*, **15**, 6019-6033. https://doi.org/10.1016/j.apsb.2025.08.002

[127] Kong, X., Liu, H., Chen, S., Liu, Z., Chen, Q., Li, X., *et al.* (2025) Bioengineered Bacterial Extracellular Vesicles for Targeted Delivery of an Osteoclastogenesis-Inhibitory Peptide to Alleviate Osteoporosis. *Journal of Controlled Release*, **382**, Article ID: 113751. https://doi.org/10.1016/j.jconrel.2025.113751

[128] Yang, Y., Xu, L., Li, Y., Sun, Y., Tang, Y., Xiao, Z., *et al.* (2025) High-Yield Outer Membrane Vesicles Derived from Probiotics as a Nanoplatform for Precise Treatment and Prophylaxis of *Pseudomonas aeruginosa* Infection. *Journal of Extracellular Vesicles*, **14**, e70194. https://doi.org/10.1002/jev2.70194

[129] Kang, Y., Han, X., Zhou, S., Wang, X., Wang, Y., Song, P., *et al.* (2025) Engineered Apoptotic Extracellular Vesicles for Programmable Regulation of Neutrophil-Macrophage-ROS Pathogenic Axis to Reconstruct Rheumatoid Arthritis Microenvironment. *Advanced Materials*, **38**, e08072. https://doi.org/10.1002/adma.202508072

[130] Xu, J., An, Y., Sun, J., Xiong, Y., Liu, C., Zhang, S., *et al.* (2026) Oncolytic Virus OH2 Induces PD-L1 Upregulation via NF-κB Signaling and Synergizes with Anti-PD-L1 Therapy in Prostate Cancer through a Targeted Extracellular Vesicle Delivery System. *Journal for ImmunoTherapy of Cancer*, **14**, e013818. https://doi.org/10.1136/jitc-2025-013818

[131] Gong, Y., Lin, M., Li, D., Yao, R., Zhang, G., Sun, J., *et al.* (2025) Targeted Cascade Therapy with Multifunctional Nanovesicles Engineered from Synergistic Antibacterial Agents for Precision Treatment of Multidrug-resistant Infections and Biofilms. *Advanced Materials*, **38**, e11037. https://doi.org/10.1002/adma.202511037

[132] Shimoda, A., Miura, R., Tateno, H., Seo, N., Shiku, H., Sawada, S., *et al.* (2021) Assessment of Surface Glycan Diversity on Extracellular Vesicles by Lectin Microarray and Glycoengineering Strategies for Drug Delivery Applications. *Small Methods*, **6**, Article ID: 2100785. https://doi.org/10.1002/smtd.202100785

[133] Yan, C., Feng, K., Bao, B., Chen, J., Xu, X., Jiang, G., *et al.* (2024) Biohybrid Nanorobots Carrying Glycoengineered Extracellular Vesicles Promote Diabetic Wound Repair through Dual-enhanced Cell and Tissue Penetration. *Advanced Science*, **11**, Article ID: 2404456. https://doi.org/10.1002/advs.202404456

[134] Kuhn, T., Aljohmani, A., Frank, N., Zielke, L., Mehanny, M., Laschke, M.W., *et al.* (2024) A Cell-Free, Biomimetic Hydrogel Based on Probiotic Membrane Vesicles Ameliorates Wound Healing. *Journal of Controlled Release*, **365**, 969-980. https://doi.org/10.1016/j.jconrel.2023.12.011

[135] 罗晓霞, 覃思华, 王晖迪, 等. 细菌外囊泡在疾病发生发展中的作用机制及应用前景[J]. 协和医学杂志, 2023, 14(5): 915-924.