复合材料学报
Acta Materiae Compositae Sinica
Engineering Village

生物质及生物质相关止血材料的研究进展

敖青 张戈 丁功涛 王子凡 TeowYeit Haan SajabMohd Shaiful 马忠仁 赵蕾

Research progress on biomass and biomass-related hemostatic materials

AO Qing, ZHANG Ge, DING Gongtao, WANG Zifan, TEOW Yeit Haan, SAJAB Mohd Shaiful, MA Zhongren, ZHAO Lei

在线阅读 View online: https://doi.org/10.13801/j.cnki.fhclxb.20240704.001

复合材料学报
Acta Materiae Compositae Sinica

第 42 卷 第 3 期 3 月 2025 年
Vol. 42 No. 3 Mar 2025

DOI：10.13801/j.cnki.fhclxb.20240704.001

生物质及生物质相关止血材料的研究进展

敖青[1]，张戈[1]，丁功涛[1]，王子凡[1]，Teow Yeit Haan[2]，Sajab Mohd Shaiful[2]，马忠仁[1]，赵蕾*[1]

（1. 西北民族大学 生物医学研究中心，兰州 730030；2. 马来西亚国立大学 工程与建筑环境学院，雪兰莪州，万宜镇 43600）

摘 要：伤口的快速止血和愈合对于解决意外事故造成的出血具有重要意义，相关止血材料的开发和应用一直备受关注。以角蛋白、丝素蛋白、胶原蛋白为代表的蛋白类和以纤维素、壳聚糖、海藻酸为代表的多糖类等生物质材料，因其无毒性、低抗原性、良好的生物相容性、生物可降解性等优点在止血领域展现了前所未有的应用价值。基于此，本文对生物质止血材料的设计、制备及止血应用的最新研究进展进行了全面综述，并对其发展前景做了展望，以期为新型高效止血材料的开发和实际应用提供思路。

关键词：生物质材料；蛋白质；多糖；止血性能；伤口止血

中图分类号：O636.9；TB332 **文献标志码**：A **文章编号**：1000-3851(2025)03-1240-15

Research progress on biomass and biomass-related hemostatic materials

AO Qing[1], ZHANG Ge[1], DING Gongtao[1], WANG Zifan[1], TEOW Yeit Haan[2], SAJAB Mohd Shaiful[2], MA Zhongren[1], ZHAO Lei*[1]

(1. Biomedical Research Center, Northwest Minzu University, Lanzhou 730030, China; 2. Faculty of Engineering and Built Environment, The National University of Malaysia, Bangi 43600, Selangor Darul Ehsan, Malaysia)

Abstract: The rapid hemostasis and healing of wounds after trauma hold great significance to solve the bleeding caused by accidents. Therefore, the development and application of related hemostatic materials have attracted much attention. Biomass-derived materials such as proteins including keratin, silk fibroin, collagen and polysaccharides including cellulose, chitosan, and alginic acid are favored by researchers because of their non-toxicity, low antigenicity, good biocompatibility, and biodegradability, and have shown unprecedented application value in the field of hemostasis. In this paper, the latest research results on the design, the preparation and the application of biomass hemostatic materials are comprehensively reviewed, and their development prospects are prospected, which will provide ideas for the development and practical application of new high-efficiency hemostatic materials.

Keywords: biomass materials; protein; polysaccharide; hemostasis properties; wound hemostasis

世界卫生组织 2020 年的统计结果显示，全世界每年约有 6 000 万人遭受严重创伤[1]，其中约 200 万人因受创后无法控制的出血而死亡[2]。意外创伤造成的严重出血的黄金急救时间只有几分钟[3]，因此快速、高效的止血材料在出血类伤者的救助中至关重要[4]。

为了实现伤口的快速、高效愈合，要求止血材料应满足以下条件：①通常能够在 2 min 内止血[5-6]；②能够很好地包覆不规则的创伤面[7]；③具备良好的稳定性，不与体内环境发生反应[8]；④无毒副作用[9]；⑤具备优良的生物相容性和可降解性[10]；⑥制备简便、来源广泛且价格低廉[11] 等。

现有的商用止血材料主要有无机止血材料 (战斗纱布、QuikClot、WoundStat 等)、聚合物止血材料 (Celox-D 、Homon 等) 和生物质止血材料 (HemCon、ChitoGauze PRO 等)。但是，以上止血

收稿日期：2024-05-10; 修回日期：2024-06-19；录用日期：2024-06-28；网络首发时间：2024-07-05 14:29:36
网络首发地址：https://doi.org/10.13801/j.cnki.fhclxb.20240704.001
基金项目：国家自然科学基金 (22104045); 甘肃省自然科学基金 (23JRRA1733; 23JRRA718)
National Natural Science Foundation of China (22104045); Natural Science Foundation of Gansu Province (23JRRA1733; 23JRRA718)
通信作者：赵蕾，博士，讲师，硕士生导师，主要研究方向为微流控技术辅助制备生物纳米材料 E-mail: zhaolei@xbmu.edu.cn
引用格式：敖青，张戈，丁功涛，等. 生物质及生物质相关止血材料的研究进展 [J]. 复合材料学报，2025，42(3)：1240-1254.
AO Qing, ZHANG Ge, DING Gongtao, et al. Research progress on biomass and biomass-related hemostatic materials[J]. Acta Materiae Compositae Sinica, 2025, 42(3): 1240-1254(in Chinese).

材料在使用过程中存在一些副作用，如战斗纱布对组织的粘附性较差，同时无机止血材料在作用过程中还会放出热量，进一步导致组织的继发性损伤和异常的异物反应[12]；而生物质止血材料 HemCon、ChitoGauze PRO 虽然都能够在 2 min 内完成止血，但其在长期使用时均存在导致使用部位微血管血栓的形成和软组织损伤等缺陷[13] (表 1)。综上，现有的商品化止血材料无法同时满足快速止血的目的[14]和良好的生物相容性[15]。因此，开发新型高效、生物相容性高的止血材料是目前该领域的研究重点。

表 1　现有商品化生物质止血材料

Table 1　Existing commercial biomass hemostatic materials

Hemostatic material	Product name	Manufacturer	Mechanism of hemostasis	Hemostatic effect	Limitations or deficiencies	Ref.
Fibrin sealant	Tisseel; Evicel; Beriplast P	Baxter; Ethicon; CSL; Behring	Simulates the coagulation process in the body and quickly forms blood clots	Complete hemostasis was achieved within 30 s (Arterial bypass) to 6 min (Carotid endarterectomy)	The price is expensive, and the cost of transportation and storage is high; It is contraindicated in patients with bovine allergies, who have adverse effects including rash, coagulation disorders, anaphylaxis, and death from premade antibodies	[16-17]
Oxidized cellulose	Surgicel; Cutanplast; Surgicel	Johnson; B. Braun; Ethicon	Immediately after the material encounters blood, the fluid in the blood is extracted and blood proteins, platelets, red blood cells and other active components are captured, resulting in an increased concentration of coagulation factors and an accelerated coagulation process	Hemostasis is usually successful within 5 min (Open surgery)	Foreign body reactions, minor postoperative complications, as foci of infection or anaphylaxis, manifested mainly by acute dermatitis, eczema, and serous tumors	[9, 18]
Gelatin sponges	Gelfoam; Gelfoam	Pfizer; Baxter	Attaches to the bleeding site, allowing platelets to stay in uniform pores, activating the coagulation cascade	Hemostasis was successfully achieved within 5 min (Reoperative cardiac surgery or emergency resternotomy)	Inability to pack bleeding, and the possibility of breaking the clot when the sponge is removed; It may cause thrombosis of small blood vessels or an inflammatory reaction	[17, 19]
Microporous polysaccharides	Arista AH	Starch Medical	It concentrates blood solids by absorbing water and low-molecular-weight compounds from the blood, thereby providing hemostasis and providing a scaffold for the formation of fibrin clots	Haemostasis was completed at 1 min 30 s (5 mm pork kidney incision) to 3 min 20 s (12 mm pork kidney incision)	There will be a slight inflammatory reaction at the beginning of use	[20-22]
Chitosan sponge	HemCon; ChitoGauze PRO; Celox	HemCon Medical Technologies; HemCon Medical Technologies; Z-Medica	Positively charged chitosan binds to negatively charged red blood cells. As a result, it leads to the formation of sticky clots to promote hemostasis	Complete hemostasis usually occurs within 2 min (Tooth extraction surgery)	For limb injuries, tourniquets are required	[23-24]

近年来，研究人员以生物质材料为主要原料，开发出了多种具有优异止血性能，且生物相容性好的止血材料。该类材料主要包括蛋白类和多糖类 (图 1)，本文将以蛋白类、多糖类这两个类型的生物质止血材料为主，对生物质止血材料的最新研究进行全面综述。

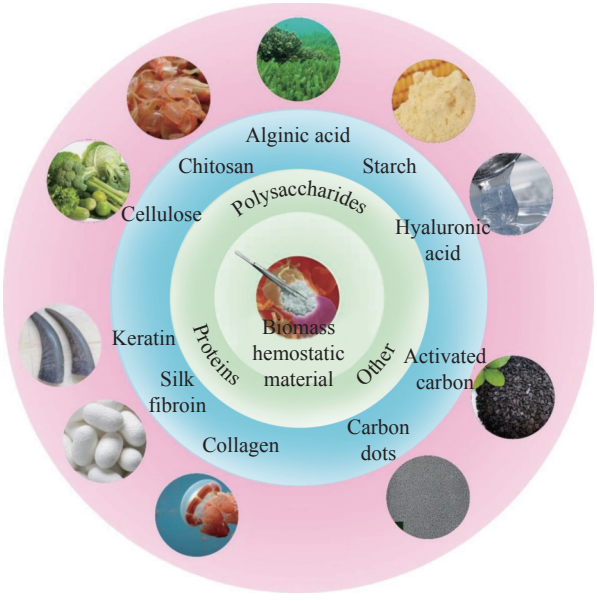


图 1　生物质止血材料

Fig. 1　Biomass hemostatic materials

1　蛋白类止血材料

蛋白类止血材料包括以角蛋白、丝素蛋白和胶原蛋白等蛋白为主要原料开发的止血材料(表 2)。蛋白类止血材料通常具有良好的生物相容性和可降解性等优点，近年来在止血领域备受关注。

1.1　角蛋白类止血材料

角蛋白是一种天然蛋白质，是牛毛、羊毛、毛发、指甲、蹄和角的主要成分[25-27]，具有良好的生物相容性和可降解性[28-29]。研究指出，角蛋白类生物材料不仅具有增加血小板、激活和促进纤维蛋白原聚合的功能[30]，同时可以产生易于细胞附着的底物[31]，是一种优良的生物类止血材料。

早在 2008 年，Aboushwareb 等[32] 就发现了人发角蛋白水凝胶在兔致死性肝损伤模型中的止血效果，通过使用角蛋白水凝胶进行伤口止血，兔子的存活率由原来的 0% 提高到 75%，显示出止血材料在疾病治疗中的重要意义。随后，2013 年 Rahmany 等[33] 的研究表明角蛋白能够显著缩短纤维蛋白原聚合成纤维蛋白的时间，从 60 min 缩短到 23 min，远高于正常生理条件下的聚合速度，证实角蛋白可以促使血液更快凝集，从而达到快速止血的效果。此外，这一作用机制不受温度和凝血因子浓度的影响，有力佐证了角蛋白在快速、有效止血方面的巨大应用潜力。Tang 等[34] 利用二硫键改组策略制备了一种可注射的角蛋白水凝胶，并将其应用于小鼠尾部截肢模型和急性出血肝损伤模型的止血中。结果表明，在尾部截肢模型中采用角蛋白水凝胶处理的小鼠完全止血的止血时间和出血量均优于普通止血材料；在肝损伤模型中可在 90 s 内实现闭塞凝血，远远优于普通止血材料的 200 多秒，显示出优异的创面愈合效果。2016 年 Luo 等[35] 通过改进乳化扩散法制备了一种角蛋白纳米颗粒，并将其用于大鼠出血肝脏组织的止血。这种角蛋白纳米颗粒能在创面形成高粘度角蛋白凝胶而加速止血作用，其止血效果强于单纯的角蛋白提取物。另外，与角蛋白水凝胶相比，角蛋白纳米颗粒更易储存和运输，具有更为广泛的应用前景。

1.2　丝素蛋白类止血材料

丝素蛋白是一种典型的天然蛋白质，是蚕丝的主要成分[36]，其 85% 的蛋白质由甘氨酸、丙氨酸和丝氨酸等组成[37]。丝素蛋白除具有良好的生物相容性和可降解性[38-39] 外，还具有优异的机械性能、良好的透气性[40-43]。

研究表明，丝素蛋白类材料能够通过促进成纤维细胞的增殖与再上皮化，以及胶原的合成，以此促进伤口的愈合，从而达到止血的效果[40]。

表 2　蛋白类止血材料的材料类型、体内模型和止血效果

Table 2　Material types, in vivo models, and hemostatic effects of protein-based hemostatic materials

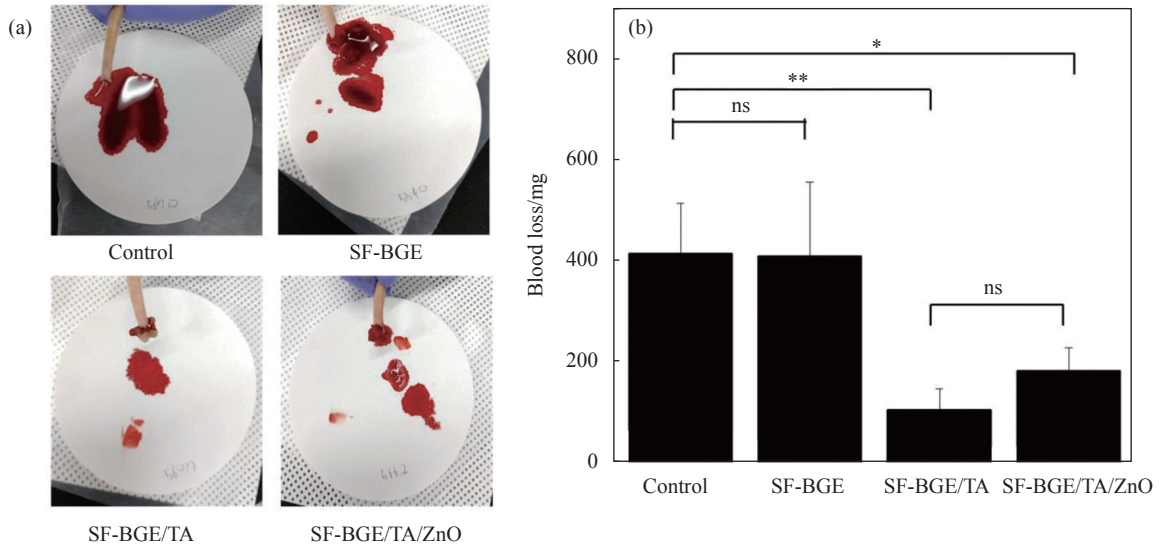
Hemostatic material	Type of material	Model of hemostasis	Hemostatic effect
Keratin	Injectable hydrogel[34]	Mouse model of liver injury	Occlusion hemostasis was achieved in 90 s
	Nanoparticles[35]	Rat model of liver injury and tail docking	The hemostasis time was 60 s and 90 s
Silk fibroin	Composite sponge[47]	Mouse model of liver injury	2 min 30 s to completely stop bleeding
	Nanocomposite hydrogels[48]	Rat tail docking model	The blood loss was only (183.4±50.1) mg
Collagen	Porous sponges[56]	Rat tail docking model	Complete hemostasis in 5 min 20 s
	Nanofiber membranes[57]	Rabbit ear artery, liver injury model	The hemostasis time was (95.34±10.05) s and (67.05±7.15) s
	Self-healing hydrogel[58]	Mouse hemorrhagic liver model	The blood loss was only (0.4±0.15) g

此外，还有研究发现丝素蛋白能够富集损伤部位血液中细胞和血浆，并加速凝血酶生成的凝血级联的周转，从而帮助在伤口形成血栓，起到促进凝血、减少出血的作用[44]。经过多年的发展，丝素蛋白止血材料的形态从一开始的粉末，到海绵、微球再到水凝胶，都展示出了优良的止血特性[45-46]，但丝素蛋白仍存在制备速度较慢的问题。为此，研究人员利用淀粉来提高丝素蛋白的凝固交联能力，淀粉的引入显著提高了丝素蛋白水凝胶的制备速率，所制备的淀粉-丝素蛋白海绵具有更好的膨胀率和吸水能力从而展现出更高的凝血率[47]。Yang 等[48] 将丁基缩水甘油醚引入到丝素蛋白的侧链中，制备了一种水溶性的改性丝素蛋白，进一步结合单宁酸和纳米氧化锌成功制备成了丝素蛋白基纳米复合水凝胶。这种水凝胶在大鼠的尾部切口模型中显示出良好的组织粘附性和止血性能，相对于普通丝素蛋白水凝胶，极大地减少了大鼠尾部的出血量 (图 2)。

1.3　胶原蛋白类止血材料

胶原蛋白是一直普遍存在于动物皮肤、肌腱等结缔组织中的蛋白质[49]，是细胞外基质最重要的组成成分[50]。胶原蛋白具有良好的生物相容性、低抗原性[51-52]、及优异的止血能力和促进伤口愈合性能[53-54]，但胶原蛋白的机械性能较差。因此，研究人员通常将其和其他材料混合，增强其机械性能。

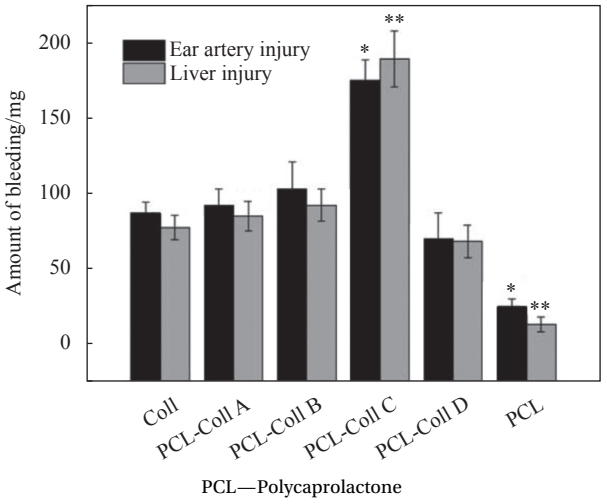
2015 年，Shi 等[55] 制备了一种羧甲基壳聚糖、海藻酸钠和胶原蛋白复合微球，能够促进血小板的黏附、聚集和活化，该材料具有很高的吸水性，对于受创面积较小的伤口具有良好的止血效果，但对于受创面较大的情况则并不理想且不适用于体内止血。面对这一问题，有研究人员通过冷冻干燥和化学交联的方式将海蜇中提取的胶原蛋白制备成多孔胶原蛋白海绵，有效减少了止血时间和失血量[56]。Cheng 等[57] 另辟蹊径，将 T4 噬菌体通过静电纺丝掺入聚己内酯/胶原蛋白纳米纤维膜中，T4 噬菌体能够提高纤维膜的抗菌效果，而聚己内酯则显著提高了纳米纤维膜的拉伸强度。这种纳米纤维膜还具有良好的生物相容性和生物降解性，能够支持小鼠内皮细胞的正常增殖，进一步用于小鼠的耳动脉和肝损伤模型，可显著缩短止血时间和减少出血量 (图 3)。为了应对复杂的受创伤口，Ding 等[58] 开发了一种用于伤口敷料的自愈型水凝胶，该水凝胶由胶原蛋白、壳聚糖和二醛封端聚乙二醇通过动态亚胺键组成。该水凝胶还具有自我修复、应变反应、抗菌和注射能力，适用面广，在小鼠表皮与肝损伤模型上都表现出了优异的止血效果。



SF—Silk fibroin; BGE—Butyl glycidyl ether; TA—Tannic acid; ns—No significance

图 2　(a) 截尾后给予 SF-BGE、SFBGE/TA 和 SF-BGE/TA/ZnO 水凝胶后失血的照片；(b) 对照组、SF-BGE、SF-BGE/TA、SF-BGE/TA、SF-BGE/TA/氧化锌水凝胶致伤大鼠的失血量 (结果报告为平均值±标准差 (n=3)；统计学处理采用单因素方差分析和 Tukey's 后置检验 (*p<0.05，**p<0.01))[48]

Fig. 2　(a) Photographs of blood loss after tail amputation and administration of SF-BGE, SFBGE/TA and SF-BGE/TA/ZnO hydrogel; (b) Blood loss from injury rat tail of control, SF-BGE, SF-BGE/TA, and SF-BGE/TA/ZnO hydrogel (The results are reported as the mean±standard deviation (n=3); Statistical significance was analyzed by one-way ANOVA and Tukey's post hoc test (*p<0.05, **p<0.01))[48]



PCL—Polycaprolactone

图 3 兔耳动脉和肝脏损伤模型中不同膜片的出血量 (PCL-Coll (A~D) 组与 Coll 组之间的统计学意义分别为*p<0.005，**p<0.05)[57]

Fig. 3 The amount of bleeding of different films in injury models of rabbit ear artery and liver (Statistical significances between PCL-Coll (A-D) groups and Coll are denoted as *p<0.05, **p<0.005)[57]

2 多糖类止血材料

多糖类化合物具有生物相容性好、可降解、来源广泛和无免疫反应等优点[11]，随着科学技术的发展和临床需求，纤维素、壳聚糖等越来越多的多糖材料被开发成止血剂 (表 3)。下面将具体阐述多糖类止血材料的最新研究进展。

2.1 纤维素类止血材料

纤维素是自然界中植物、微生物产生的最丰富的天然多糖，具有优异的拉伸性、可再生性、吸水性和廉价性[59-62]，在医用止血材料领域具有广阔的应用前景。早在 20 世纪 40 年代，纤维素就已经被制成止血纱布供外科手术使用[63]。但在实际运用中，纯纤维素材料的止血效果并不理想[64]。因此，现如今的纤维素止血材料更多的是指纤维素衍生物或纤维素复合材料。

氧化纤维素是纤维素衍生物中最常见的一种，因其具有良好的生物相容性、抗菌特性及可降解性而被广泛使用[65]。Velázquez-Aviña 等[66] 的研究证明氧化纤维素网在胃黏膜切除模型中具备良好的止血效果，氧化纤维素网能够激活血小板，并利用其高吸水特性实现机械止血。Bian 等[67] 利用氧化纳米纤维素与血管生成药物去铁胺 (DFO) 的制备了一种复合止血海绵。大鼠断尾模型和肝创伤模型的实验结果表明，该复合止血海绵的促凝作用优于临床上使用的胶原止血海绵，不仅所需全血凝固时间更短，失血量也变少，而且对内源性凝血途径的激活也更强效。

除氧化纤维素外，羧甲基纤维素也是纤维素的代表性衍生物[68]。Liu 等[69] 将胺化纳米银和明

表 3 多糖类止血材料的材料类型、体内模型和止血效果

Table 3 Material types, in vivo models, and hemostatic effects of polysaccharide hemostatic materials

Hemostatic material	Type of material	Model of hemostasis	Hemostatic effect
Cellulose	Composite sponge[67]	Rat tail docking and liver injury model	The blood loss was 159.46 mg and 80.44 mg
	Nanocomposite fibers[70]	Lemonified human plasma, lemonified bovine whole blood	The coagulation time was (143±19) s and (67±5) s
	Powder[83]	Mouse tail docking model	The hemostasis time was 158 s, and the blood loss was only 11.0 mg
Chitosan	Composite microspheres[85]	A model of tail docking and liver laceration in rats	The hemostasis time is 134 s and 99 s
	Composite hydrogel[86]	Rat model of liver injury and femoral artery injury	The hemostasis time was (53±3) s and (189±9) s
Alginic acid	Composite porous microspheres[91]	Rat model of liver laceration and tail breakage	The hemostasis time was (73±5) s and (134±5) s
	Foam[94]	Porcine liver injury model	The hemostasis time is 5 min
Starch	Superabsorbent hydrogel[101]	Rat model of femoral artery injury	The hemostasis time <10 s
	Powder[103]	Rabbit model of ear vein, dorsal, femoral artery, liver injury	The hemostasis time was 52 s, 46 s, 122 s and 102 s
Hyaluronic acid	Drug-loaded microporous powder[105]	Rabbit ear artery, liver injury model	The hemostasis time is (108±5) s and (120±6) s
	Sponge[113]	Mouse model of liver injury	The hemostasis time was <60 s, and the blood loss was only 23.2 mg
	Cryogel[114]	Rat model of liver injury	The hemostasis time is 72 s

胶引入羧甲基纤维素纳米纤维中，制成了一种纳米复合水凝胶。这种纳米复合水凝胶在小鼠的体内外止血实验中均显示出良好的止血效果，对伤口愈合有明显的促进作用。细胞毒性实验显示，在这种水凝胶的作用下，7 天内细胞存活率能达到 100%，说明其具有优异的生物相容性。

Udangawa 等[70] 通过湿法-电纺法制备了一种高性能纤维素-埃洛石止血纳米复合纤维，埃洛石能够促进血浆的凝结，而电纺纤维提供了更高的比表面积，二者结合赋予了复合纤维更好的凝血性能。这种复合纤维与现有的医用纱布相比，血液凝结速度提高了 2.4 倍，清洗过后凝血活性仅下降 24%，且可以重复利用。

2.2　壳聚糖类止血材料

壳聚糖是一种天然的生物质多糖[71]，是甲壳素脱乙酰基的产物[72]，其天然多糖含量仅次于纤维素[73]。壳聚糖来源广泛，在虾、蟹、昆虫和某些真菌中都含量颇丰[74-75]。壳聚糖是一种优良的创伤治疗材料，具有生物相容性、生物降解性、抗菌和内源性止血特性[76-78]，是近几十年来研究最多的生物多糖之一[79]。据报道，壳聚糖形成的阳离子簇可以与红细胞上的阴离子相互作用，诱导血小板聚集，实现止血[80-81]。这种机制不依赖于患者自身的凝血机制，因此即使在患有凝血障碍的患者中也是有效的[81-82]。

Wu 等[83] 以废弃的南极磷虾壳作为原料制备了脱乙酰度为 96% 的 A-壳聚糖粉末，其吸水率为 1 293%，能够促进血小板的黏附，而高脱乙酰度又使其具备聚集红细胞的能力。在小鼠断尾模型中，相较于其他两种商用壳聚糖，A-壳聚糖粉末使小鼠尾部止血加快了 55%，凝血时间缩短了 38%，其优异的水化性能可进一步改善止血效果。

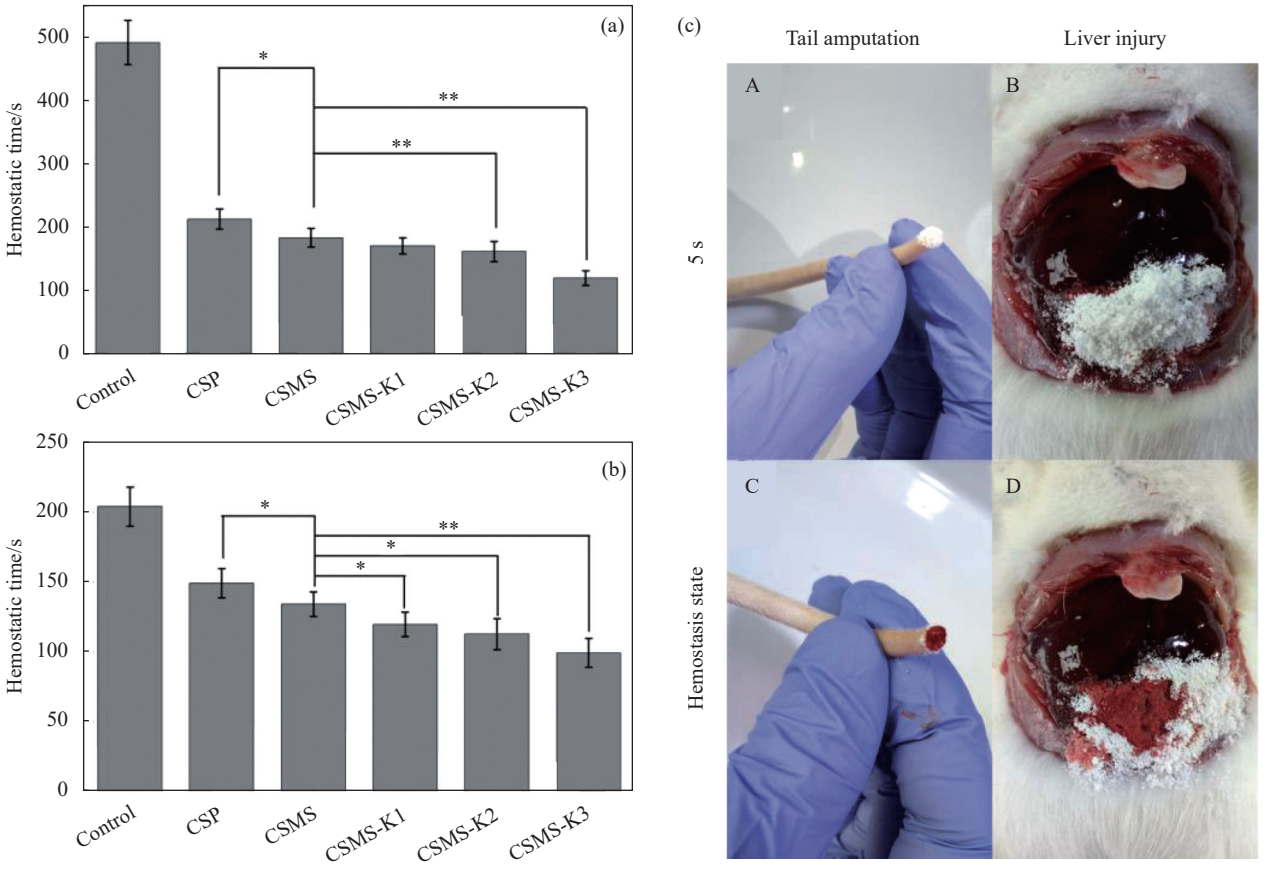
尽管壳聚糖具有良好的止血效果，但有研究发现，单纯的壳聚糖止血材料存在粘附力不足的问题[72, 84]，这使其止血性能在复杂创伤情况中的应用受到限制，难以满足临床需求。因此，止血用壳聚糖常常会复合其他材料或者进行改性。Sun 等[85] 利用反相微乳液结合、热诱导相分离的方法制备了壳聚糖-高岭土复合微球。在该复合微球在，壳聚糖能够借助自身所带的正电荷与带负电荷的红细胞膜发生静电相互作用，诱导红细胞在损伤部位黏附和聚集，形成血栓；而高岭土激活凝血因子，加速凝血酶的形成，以此加速凝血级联反应，导致纤维蛋白的快速生成，促进凝血。此外，这种复合微球还能够迅速吸收血液中的水分，促进红细胞浓缩。在这三种机制的相互作用下，复合微球的在大鼠断尾模型和肝撕裂伤模型中显示出优于纯壳聚糖微球的止血效果，随高岭土含量的增加，所需止血时间逐渐减少 (图 4)。

Sundaram 等[86] 制备了一种可注射、含有硅胶、钙离子和磷酸盐离子等多种止血因子共同作用的纳米生物玻璃-壳聚糖复合水凝胶，该复合水凝胶相较于普通壳聚糖水凝胶具有更好的止血效果。利用大鼠肝损伤模型和股动脉损伤模型进一步验证其止血效果，结果表明，所需的止血时间缩短，失血量减少。Zheng 等[87] 以 1,2-环氧基-4-乙烯基环己烷为交联剂，制备了一种低密度、高空隙率和高吸附能力的壳聚糖基结构，再用 N-卤胺-1 氯-2,2,5,5-四甲基-4-咪唑烷酮进行改性，制得 N-卤胺/多孔壳聚糖材料，N-卤胺的引入能够有效提高多孔壳聚糖材料的抗菌能力，N-卤胺/多孔壳聚糖材料对血细胞的凝集和血小板的吸附能力显著高于多孔壳聚糖材料。

2.3　海藻酸类止血材料

海藻酸是一种天然的阴离子线性多糖[88]，由线性、未支化的 α-1 古龙酸和 1,4-连接的 β-D-甘露糖酸残基组成[4]。海藻酸主要来源于藻类和微生物，具有高吸水率、低毒性、良好的生物相容性和生物降解性等特点[89]，是一种理想的止血材料[90]。海藻酸可以与钙、锌和钠等离子形成海藻酸盐。

Pan 等[91] 利用微乳液和热诱导相分离法制备了一种壳聚糖-海藻酸锌复合多孔微球，在大鼠肝撕裂伤模型中取得了良好的止血效果。壳聚糖通过静电相互作用凝聚红细胞形成软血块；而海藻酸锌组分中的锌离子参与凝固级联反应，加速纤维蛋白的生成，形成纤维增强的硬血块，二者的协同作用使得大鼠肝撕裂伤所需的止血时间 ((73±5) s) 比壳聚糖微球少了一半。海藻酸本身并不具备良好的抗菌性能[92]，限制了其在生物医学领域的应用。为此，Tong 等[93] 制备了一种聚谷氨酸/海藻酸盐/纳米银颗粒复合微球，纳米银的杀菌特性赋予该复合微球优良的抗菌性能。实验结果显示该复合微球不仅具有广谱抗菌活性，能够有效的抑制革兰氏阴性菌和革兰氏阳性菌，而且具有 pH 敏感的溶胀性能和良好的止血性能，能够促进严重出血时血液中的水吸收并促进凝血因



CSP—Chitosan particles; CSMS—Chitosan porous microspheres; * indicates difference between the two groups of data and $p<0.05$; ** indicates significant difference and $p<0.01$

图 4　(a) 大鼠断尾模型的止血时间；(b) 大鼠肝撕裂伤模型止血时间；(c) 大鼠断尾和肝撕裂模型的数字图像 (将 CSMS-K3 涂于 A 尾部切割处和 B 肝撕裂伤处；涂抹 CSMS-K3 5 min 后 C 大鼠尾部切割处和 D 肝撕裂伤处；伤处形成暗红色血块，出血停止)[85]

Fig. 4　(a) Hemostasis time in rat tail amputation model; (b) Hemostasis time in rat liver laceration model; (c) Digital images of rat tail amputation and liver laceration models (CSMS-K3 was applied onto A the tail cut and B on the liver injury; 5 min after application on the C rat tail cut and D the liver laceration; Dark-red blood clot was formed on the injured sites, bleeding stopped)[85]

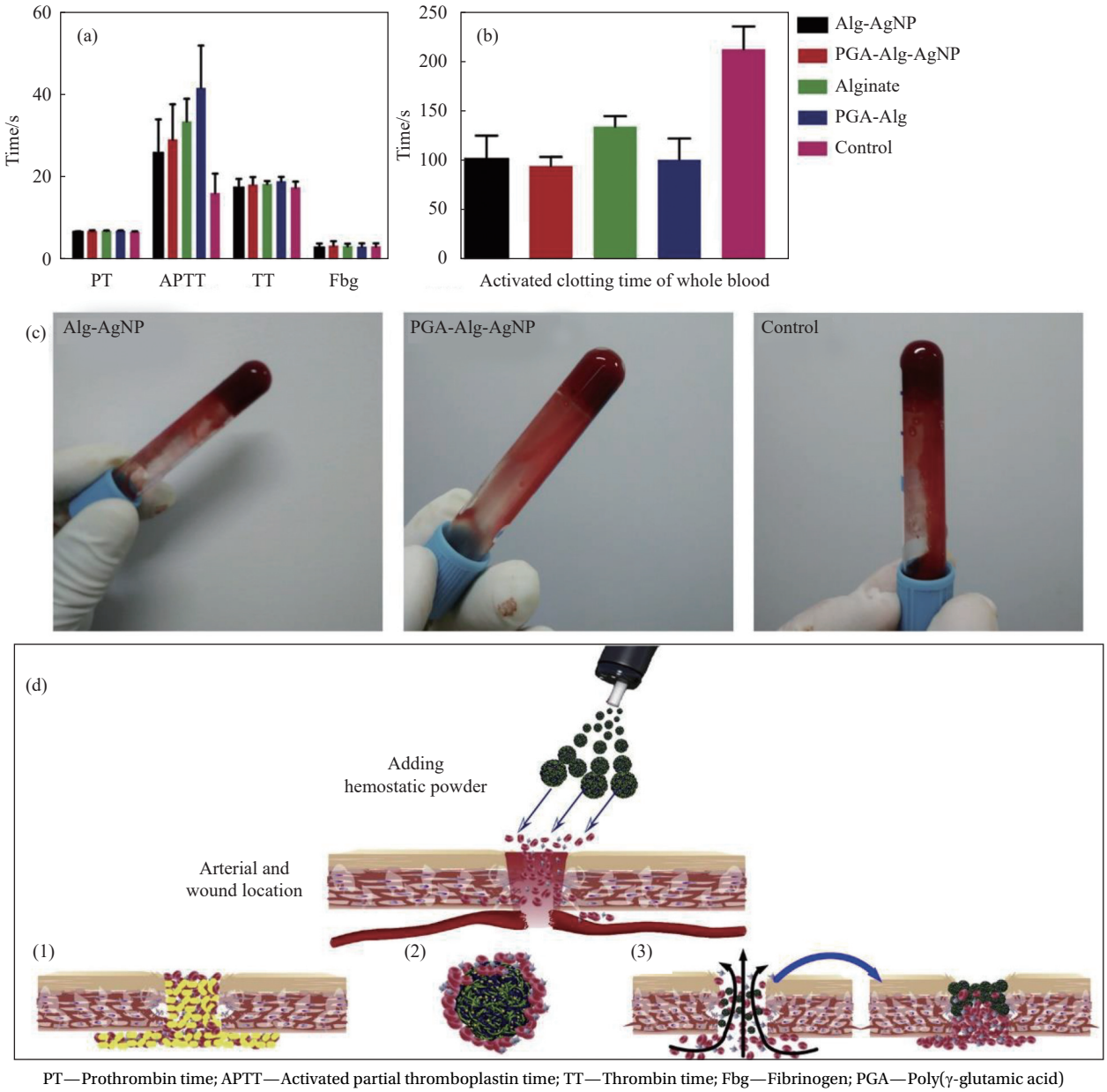
子的聚集 (图 5)。

为了解决海藻酸机械性能不足的问题，Choudhary 等[94] 另辟蹊径地开发了一种疏水改性壳聚糖/疏水改性海藻酸盐止血泡沫。这种泡沫具有增强的流变性，通过壳聚糖和海藻酸盐链的结合，在气泡周围形成凝聚态，从而形成更有效的止血屏障。Zheng 等[95] 开发了一种复合水凝胶，借助 N-羟基丁二酰亚胺、共轭海藻酸盐、聚乙二醇二丙烯酸酯、单宁酸和 Fe^{3+}离子一系列分子的相互作用和交联，形成了具有高弹性和韧性的止血水凝胶，单宁酸和 Fe^{3+}离子对血液的高亲和力进一步增强了止血作用。

2.4　淀粉类止血材料

淀粉是一种天然的可生物降解的材料[96]，由直链淀粉和支链淀粉两种多糖组成[97]。淀粉主要来源于玉米、水稻、小麦和土豆等植物[98]，价格低廉且具有良好的水溶性和无细胞毒性[89, 99]。在止血领域通常使用的是微孔淀粉 (又称多孔淀粉)，这是一种酶变性淀粉，由于其巨大的比表面积、高孔隙率和良好的吸水性[100]，以及其能够被人体自身的酶逐渐降解为低聚糖、麦芽糖和葡萄糖，最终被人体吸收的优势[97]，具有极大的应用潜力。

Mirzakhanian 等[101] 通过自由基聚合法制备了一种快速溶胀多孔高吸水性丙烯酰胺-淀粉水凝胶，其具备 4 000% 的吸水膨胀效能和低细胞毒性，能够迅速膨胀形成密封剂以促进凝血，在大鼠股动脉损伤模型中仅用不到 10 s 就取得了良好的止血效果。淀粉本身并不具备良好的抗菌效果[102]。为此，Hou 等[103] 制备了一种介孔硅酸锌钙-微孔淀粉止血粉末，锌离子能与细菌膜和膜蛋白结合，破坏细菌结构或破坏负责电子传递系统的酶；钙离子能够促进纤维蛋白的形成，锌钙结合赋予了



PT—Prothrombin time; APTT—Activated partial thromboplastin time; TT—Thrombin time; Fbg—Fibrinogen; PGA—Poly(γ-glutamic acid)

图 5　纯海藻酸微球、Alg/Ag NPs、PGA/Alg/Ag NPs 和 PGA/Alg 复合微球的止血分析：(a) 血浆凝血性能；(b) 凝血时间；(c) 凝血图像；(d) PGA/Alg/AgNPs 微球的止血示意图 ((1) 止血剂提供外源性凝血成分，加速伤口血液凝结；(2) 止血剂促进红细胞、凝血因子、血小板聚集，加速凝血；(3) 止血剂吸收血液中水分，增加血细胞、血小板、凝血因子浓度，阻断创面，促进聚集止血[93])

Fig. 5　Hemostasis assays of pure alginate microspheres, Alg/Ag NPs, PGA/Alg/Ag NPs, and PGA/Alg composite microspheres: (a) Blood plasma clotting performance; (b) Clotting blood time; (c) Coagulation images; (d) Schematic hemostasis of PGA/Alg/Ag NPs microspheres ((1) The hemostatic agent provides extrinsic coagulation components to accelerate blood clotting on the wound; (2) The hemostatic agent promotes the aggregation of red blood cells, coagulation factors and platelets, and accelerates the coagulation; (3) The hemostatic agent absorbs water in the blood, increases the concentration of blood cells, platelets, and coagulation factors, block the wound area and promotes the aggregation and hemostasis[93])

该止血粉末优良的抗菌性能和止血性能，在兔耳静脉、皮肤、动脉和肝脏损伤的动物模型中均取得了良好的止血效果，其中 15wt% 含量的介孔硅酸锌钙的止血效果最为显著，相较于普通微孔淀粉，其止血时间大大缩短。

但一般的淀粉止血粉末存在着易被血流冲走、自凝聚能力较弱等缺点[104]，为了解决这一问题，Su 等[105] 制备了一种负载氨甲环酸的载药交联微孔淀粉粉末，氨甲环酸能够抑制纤维蛋白的溶解、提高血栓强度从而促进血液凝结，并赋予了止血粉末更高的机械强度，在兔耳动脉损伤和肝损伤模型中均取得了良好的止血效果，甚至比商用止

血剂 Arista 具有更好的止血能力。Cui 等[106] 制备了一种由淀粉、琥珀酸酐和多巴胺组成的可注射性组织黏附水凝胶，以解决淀粉对组织粘附力不足的问题，这种水凝胶具备良好的组织粘附性并能促进红细胞的聚集，促进凝血。进一步，Su 等[107] 为了赋予淀粉止血材料抗菌能力制备了一种嵌入淀粉微球的温敏性凝胶，淀粉微球被阳离子单宁酸衍生物改性以获得抗菌能力，结果表明该水凝胶对金黄色葡萄球菌和大肠杆菌均具有良好的抑菌效果，而且该水凝胶对温度的敏感性使其能够作为纱布涂层使用协助止血，效果良好，应用前景广泛。

2.5 透明质酸类止血材料

透明质酸是成纤维细胞在创面过程中产生的一种天然阴离子多糖[108-109]，由 D-葡糖醛酸和 N-乙酰-D-氨基葡萄糖组成[110]。透明质酸具有良好的生物相容性、生物降解性、保湿性和胶凝性[89]，能够促进细胞增殖和促进伤口愈合[111-112]。

纯透明质酸材料的止血效果并不好，为此，Liu 等[113] 采用自发泡法制备了一种透明质酸和阳离子葡聚糖组成的交联多糖止血海绵，与未经交联的多糖止血海绵相比，其具备更高的孔隙率 (48.9%) 和膨胀率 (520%)，在小鼠肝出血模型中取得了良好的止血效果，在 1 min 中内成功止住了肝脏出血，失血量仅为 23.2 mg。Wang 等[114] 制备了一种透明质酸-水性聚氨酯杂化冷冻凝胶，具有较大的孔隙结构与溶胀率，能够浓缩血液从而促进血小板黏附与红细胞聚集，与商用止血纱布 213 s 的止血时间相比，其在大鼠肝损伤模型中的止血时间显著减少 (仅需 72 s)。

3 其他生物质止血材料

利用生物质材料制备的碳点和活性炭是近几年兴起的新型止血材料，该类止血材料主要是通过激活血浆凝血因子，裂解血小板，释放血小板因子的方式促进凝血[115]。这类材料还可以释放增强肌肉张力的物质，引起血管收缩，协助止血。现对中药制备的碳点和活性炭类止血材料的最新研究进展进行简要的概述。

3.1 中药类碳点

碳点是一种尺寸小于 10 nm 的新型零维碳基纳米材料[115]，具有易表面官能化、毒性低、机械强度好、亲水性好、生物相容性和抗菌活性优异等优点[116-119]。此外，碳点的来源广泛，价格低廉，制备方法简单、环保[120-121]。有研究表明，低浓度的碳点能够激活血小板[122]。原料不同，所合成碳点的止血效果也不同，因此有研究人员将目光转向具有止血效用的中药，以中药等生物质为原料合成碳点，并将其用于止血材料[123]。中药类碳点因其原材料本身就具有止血效果，在制备成碳点后具有便于不规则伤口止血和在保留其生物活性或减少毒副作用的同时具备良好的水溶性等优势[123-125]，其有效止血成分也因此增加，如黄芩中的黄芩苷和汉黄酮苷转化为易吸收、止血作用较强的黄芩素和汉黄藤素[115]。

相关研究中，Sun 等[126] 用改进的热解法制备了荆芥穗碳点，不需要进一步改性，也不需要外表面钝化剂，在尖吻鳗蛇毒模型和小鼠断尾、肝损伤模型中均取得了优异的止血效果 (止血时间分别为 4 min 和 (3.14±0.5) min)。尖吻鳗蛇毒能够破坏正常的凝血机制，导致凝血因子和血小板的大量消耗，而荆芥穗碳点能够抑制尖吻鳗蛇毒的出血活性，并提高伤口的血小板含量，加速凝血，具有作为新型止血材料的潜力。Liu 等[127] 采用热解法制备了一种黄柏皮源性碳点，能够明显缩短小鼠断尾和肝损伤处的出血时间 (分别为 2.95 min 和 1.74 min)，与市售的止血剂相比效果相近，但黄柏皮源性碳点对细胞的毒性极低，甚至对细胞活力具有增强作用。同样的，Zhang 等[128] 制备的黄芩碳点能够激活纤维蛋白系统和内源性凝血途径，抑制炎症细胞因子的释放，实现快速止血的目的。

3.2 中药类活性炭

活性炭是由果壳、中药材等含碳原料经热解、活化加工制备而成的碳基材料，具有较大的比表面积、发达的孔隙结构、较高的吸附能力和比表面活性[115, 129]。中草药活性炭用于止血已有 2 000 多年历史[130]，有研究证明，一些草药的止血功能可以在碳化后产生，如生茜草具有活血化瘀的作用，而炭化茜草主要有止血作用[115]。有研究人员通过液相氧化在活性炭表面引入含氧基团，发现含氧基团的增加可增强活性炭的止血作用，促进凝血和血小板的凝集[131]。

Wang 等[132] 将传统中草药大黄制备成了活性炭，显示出良好的止血、抗菌和抗炎作用。但这种材料粒径小，难以涂抹和固定，因此 Wang 通过冷冻干燥制备了含有大黄活性炭的丝素蛋白/壳

聚糖海绵支架，较高剂量下能够抑制大肠杆菌和金黄色葡萄球菌的生长。此支架在小鼠肝损伤模型中也取得了良好的止血效果(失血量仅为0.2 g)，还能促进组织愈合，满足了止血材料应具有良好的生物相容性、止血能力和抗菌性能的基本要求，作为止血材料具有极大的应用潜力。

4　总结与展望

无法控制的出血是许多创伤导致死亡的主要原因，开发既能够快速止血、满足不规则创口需求，又具有良好的生物相容性、低毒性和抗菌性的止血材料在生物医学领域中，尤其是在临床应用领域具有重要意义。生物质止血材料相比其他止血材料具有独特的天然优势，如角蛋白类止血材料能够促使纤维蛋白原聚合成纤维蛋白，加速凝血；丝素蛋白类止血材料能够促进成纤维细胞增殖、再上皮化和胶原合成，以此促进伤口的止血和愈合；胶原蛋白类止血材料的抗原性低；纤维素类止血材料具备优异的机械性能和可再生性；壳聚糖类止血材料表面的阳离子簇可以与红细胞上的阴离子相互作用，诱导血小板聚集，实现止血；海藻酸类止血材料具有优异的吸水性和生物降解性；淀粉类止血材料和透明质酸类止血材料具有优异的生物相容性和可降解性。相比之下，中药类碳点、活性炭等生物质止血材料的研究较少。目前来看，无论哪一类生物质止血材料都很难实现完美止血性、高抗菌性及低毒和低抗原性的并存，复合生物质止血材料必然是未来的发展趋势。此外，新型生物质止血材料的开发必需综合考虑各种生物质材料的物理性质、化学性质和生理学性质，以赋予其优异的止血性、低毒性、低抗原性、抗菌性和生物相容性等综合性能。

参考文献：

[1] VOS T, LIM S S, ABBAFATI C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019[J]. The Lancet, 2020, 396(10258): 1204-1222.

[2] BAYLIS J R, LEE M M, ST JOHN A E, et al. Topical tranexamic acid inhibits fibrinolysis more effectively when formulated with self-propelling particles[J]. Journal of Thrombosis and Haemostasis, 2019, 17(10): 1645-1654.

[3] LIU C, LIU X, LIU C, et al. A highly efficient, in situ wet-adhesive dextran derivative sponge for rapid hemostasis[J]. Biomaterials, 2019, 205: 23-37.

[4] HICKMAN D A, PAWLOWSKI C L, SEKHON U D S, et al. Biomaterials and advanced technologies for hemostatic management of bleeding[J]. Advanced Materials, 2018, 30(4): 1700859.

[5] HOLCOMB J B, STANSBURY L G, CHAMPION H R, et al. Understanding combat casualty care statistics[J]. The Journal of Trauma: Injury, Infection, and Critical Care, 2006, 60(2): 397-401.

[6] ZHONG Y, HU H, MIN N, et al. Application and outlook of topical hemostatic materials: A narrative review[J]. Annals of Translational Medicine, 2021, 9(7): 577.

[7] GIDAY S A, KIM Y, KRISHNAMURTY D M, et al. Long-term randomized controlled trial of a novel nanopowder hemostatic agent (TC-325) for control of severe arterial upper gastrointestinal bleeding in a porcine model[J]. Endoscopy, 2011, 43(4): 296-299.

[8] KATSUYAMA S, MIYAZAKI Y, KOBAYASHI S, et al. Novel, infection-free, advanced hemostatic material: Physical properties and preclinical efficacy[J]. Minimally Invasive Therapy & Allied Technologies, 2020, 29(5): 283-292.

[9] ZHANG S, LI J, CHEN S, et al. Oxidized cellulose-based hemostatic materials[J]. Carbohydrate Polymers, 2020, 230: 115585.

[10] MONTAZERIAN H, DAVOODI E, BAIDYA A, et al. Engineered hemostatic biomaterials for sealing wounds[J]. Chemical Reviews, 2022, 122(15): 12864-12903.

[11] YANG X, LIU W, LI N, et al. Design and development of polysaccharide hemostatic materials and their hemostatic mechanism[J]. Biomaterials Science, 2017, 5(12): 2357-2368.

[12] CHEN J, CHENG W, CHEN S, et al. Urushiol-functionalized mesoporous silica nanoparticles and their self-assembly into a Janus membrane as a highly efficient hemostatic material[J]. Nanoscale, 2018, 10(48): 22818-22829.

[13] OTROCKA-DOMAGALA I, JASTRZEBSKI P, ADAMIAK Z, et al. Safety of the long-term application of QuikClot Combat Gauze, ChitoGauze PRO and Celox Gauze in a femoral artery injury model in swine—A preliminary study[J]. Polish Journal of Veterinary Sciences, 2016, 19(2): 337-343.

[14] SUN X, LI J, SHAO K, et al. A composite sponge based on alkylated chitosan and diatom-biosilica for rapid hemostasis[J]. International Journal of Biological Macromolecules, 2021, 182: 2097-2107.

[15] YU L, ZHANG H, XIAO L, et al. A bio-inorganic hybrid hemostatic gauze for effective control of fatal emergency hemorrhage in "Platinum Ten Minutes"[J]. ACS Applied Materials & Interfaces, 2022, 14(19): 21814-21821.

[16] ALBALA D M. Fibrin sealants in clinical practice[J]. Cardiovascular Surgery, 2003, 11(Supplement 1): 5-11.

[17] HONG Y M, LOUGHLIN K R. The use of hemostatic agents and sealants in urology[J]. The Journal of Urology, 2006, 176(6): 2367-2374.

[18] AL-ATTAR N, DE JONGE E, KOCHARIAN R, et al. Safety and hemostatic effectiveness of SURGICEL® powder in mild and moderate intraoperative bleeding[J]. Clinical and Applied Thrombosis/Hemostasis, 2023, 29: 10760296231190376.

[19] KTARI O, FRASSANITO P, GESSI M, et al. Gelfoam Migration: A Potential Cause of Recurrent Hydrocephalus[J]. World Neurosurgery, 2020, 142: 212-217.

[20] HUMPHREYS M R, LINGEMAN J E, TERRY C, et al. Renal injury and the application of polysaccharide hemospheres: A laparoscopic experimental model[J]. Journal of Endourology, 2008, 22(6): 1375-1381.

[21] LYBARGER K S. Review of evidence supporting the Arista™ absorbable powder hemostat[J]. Medical Devices: Evidence and Research, 2024, 17: 173-188.

[22] ZHU J, WU Z, SUN W, et al. Hemostatic efficacy and biocompatibility evaluation of a novel absorbable porous starch hemostat[J]. Surgical Innovation, 2022, 29(3): 367-377.

[23] AZARGOON H, WILLIAMS B J, SOLOMON E S, et al. Assessment of hemostatic efficacy and osseous wound healing using HemCon dental dressing[J]. Journal of Endodontics, 2011, 37(6): 807-811.

[24] WEDMORE I, MCMANUS J G, PUSATERI A E, et al. A special report on the chitosan-based hemostatic dressing: Experience in current combat operations[J]. Journal of Trauma and Acute Care Surgery, 2006, 60(3): 655-658.

[25] BURNETT L R, RAHMANY M B, RICHTER J R, et al. Hemostatic properties and the role of cell receptor recognition in human hair keratin protein hydrogels[J]. Biomaterials, 2013, 34(11): 2632-2640.

[26] LUSIANA, REICHL S, MULLER-GOYMANN C C. Keratin film made of human hair as a nail plate model for studying drug permeation[J]. European Journal of Pharmaceutics and Biopharmaceutics, 2011, 78(3): 432-440.

[27] SHAVANDI A, SILVA T H, BEKHIT A A, et al. Keratin: Dissolution, extraction and biomedical application[J]. Biomaterials Science, 2017, 5(9): 1699-1735.

[28] YAN R R, XUE D, SU C, et al. A keratin/chitosan sponge with excellent hemostatic performance for uncontrolled bleeding[J]. Colloids and Surfaces B: Biointerfaces, 2022, 218: 112770.

[29] YE W, QIN M, QIU R, et al. Keratin-based wound dressings: From waste to wealth[J]. International Journal of Biological Macromolecules, 2022, 211: 183-197.

[30] FENG C C, LU W F, LIU Y C, et al. A hemostatic keratin/alginate hydrogel scaffold with methylene blue mediated antimicrobial photodynamic therapy[J]. Journal of Materials Chemistry B, 2022, 10(25): 4878-4888.

[31] VERMA V, VERMA P, RAY P, et al. Preparation of scaffolds from human hair proteins for tissue-engineering applications[J]. Biomedical Materials, 2008, 3(2): 025007.

[32] ABOUSHWAREB T, EBERLI D, WARD C, et al. A keratin biomaterial gel hemostat derived from human hair: Evaluation in a rabbit model of lethal liver injury[J]. Journal of Biomedical Materials Research Part B: Applied Biomaterials, 2009, 90(1): 45-54.

[33] RAHMANY M B, HANTGAN R R, VAN DYKE M. A mechanistic investigation of the effect of keratin-based hemostatic agents on coagulation[J]. Biomaterials, 2013, 34(10): 2492-2500.

[34] TANG A, LI Y, YAO Y, et al. Injectable keratin hydrogels as hemostatic and wound dressing materials[J]. Biomaterials Science, 2021, 9(11): 4169-4177.

[35] LUO T, HAO S, CHEN X, et al. Development and assessment of kerateine nanoparticles for use as a hemostatic agent[J]. Materials Science and Engineering: C, 2016, 63: 352-358.

[36] HAGHNIAZ R, GANGRADE A, MONTAZERIAN H, et al. An all-in-one transient theranostic platform for intelligent management of hemorrhage[J]. Advanced Science, 2023, 10(24): e2301406.

[37] ZHU H, WU B, FENG X, et al. Preparation and characterization of bioactive mesoporous calcium silicate-silk fibroin composite films[J]. Journal of Biomedical Materials Research Part B: Applied Biomaterials, 2011, 98(2): 330-341.

[38] SARAN K, SHI P, RANJAN S, et al. A moldable putty containing silk fibroin yolk shell particles for improved hemostasis and bone repair[J]. Advanced Healthcare Materials, 2015, 4(3): 432-445.

[39] WEI W, LIU J, PENG Z, et al. Gellable silk fibroin-polyethylene sponge for hemostasis[J]. Artificial Cells Nanomedicine and Biotechnology, 2020, 48(1): 28-36.

[40] GIL E S, PANILAITIS B, BELLAS E, et al. Functionalized silk biomaterials for wound healing[J]. Advanced Healthcare Materials, 2013, 2(1): 206-217.

[41] LI X, LI B, MA J, et al. Development of a silk fibroin/HTCC/PVA sponge for chronic wound dressing[J]. Journal of Bioactive and Compatible Polymers, 2014, 29(4): 398-411.

[42] QIAO Z, LYU X, HE S, et al. A mussel-inspired supramolecular hydrogel with robust tissue anchor for rapid

hemostasis of arterial and visceral bleedings[J]. Bioactive Materials, 2021, 6(9): 2829-2840.

[43] SHEFA A A, TAZ M, LEE S Y, et al. Enhancement of hemostatic property of plant derived oxidized nanocellulose-silk fibroin based scaffolds by thrombin loading[J]. Carbohydrate Polymers, 2019, 208: 168-179.

[44] LEI C, ZHU H, LI J, et al. Preparation and hemostatic property of low molecular weight silk fibroin[J]. Journal of Biomaterials Science, Polymer Edition, 2016, 27(5): 403-418.

[45] BARKUN A N, MOOSAVI S, MARTEL M. Topical hemostatic agents: A systematic review with particular emphasis on endoscopic application in GI bleeding[J]. Gastrointestinal Endoscopy, 2013, 77(5): 692-700.

[46] HUANG X, FU Q, DENG Y, et al. Surface roughness of silk fibroin/alginate microspheres for rapid hemostasis in vitro and in vivo[J]. Carbohydrate Polymers, 2021, 253: 117256.

[47] LEE J, CHOI H N, CHA H J, et al. Microporous hemostatic sponge based on silk fibroin and starch with increased structural retentivity for contact activation of the coagulation cascade[J]. Biomacromolecules, 2023, 24(4): 1763-1773.

[48] YANG C M, LEE J, LEE S Y, et al. Silk fibroin/tannin/ZnO nanocomposite hydrogel with hemostatic activities[J]. Gels, 2022, 8(10): 650.

[49] SUN L, LI B, SONG W, et al. Comprehensive assessment of Nile tilapia skin collagen sponges as hemostatic dressings[J]. Materials Science and Engineering: C, 2020, 109: 110532.

[50] LIU X, ZHENG M, WANG X, et al. Biofabrication and characterization of collagens with different hierarchical architectures[J]. ACS Biomaterials Science & Engineering, 2019, 6(1): 739-748.

[51] JIANG X, WANG Y, FAN D, et al. A novel human-like collagen hemostatic sponge with uniform morphology, good biodegradability and biocompatibility[J]. Journal of Biomaterials Applications, 2017, 31(8): 1099-1107.

[52] WANG Q, CHEN J, WANG D, et al. Rapid hemostatic biomaterial from a natural bath sponge skeleton[J]. Marine Drugs, 2021, 19(4): 220.

[53] BROEKEMA F I, VAN OEVEREN W, BOERENDONK A, et al. Hemostatic action of polyurethane foam with 55% polyethylene glycol compared to collagen and gelatin[J]. Bio-Medical Materials and Engineering, 2016, 27(2-3): 149-159.

[54] LUO J, MENG Y, ZHENG L, et al. Fabrication and characterization of Chinese giant salamander skin composite collagen sponge as a high-strength rapid hemostatic material[J]. Journal of Biomaterials Science, Polymer Edition, 2018, 30(4): 247-262.

[55] SHI X, FANG Q, DING M, et al. Microspheres of carboxymethyl chitosan, sodium alginate and collagen for a novel hemostatic in vitro study[J]. Journal of Biomaterials Applications, 2015, 30(7): 1092-1102.

[56] DAO M, CHENG X, SHAO Z, et al. Isolation, characterization and evaluation of collagen from jellyfish *Rhopilema esculentum* Kishinouye for use in hemostatic applications[J]. PLOS One, 2017, 12(1): e0169731.

[57] CHENG W, ZHANG Z, XU R, et al. Incorporation of bacteriophages in polycaprolactone/collagen fibers for antibacterial hemostatic dual-function[J]. Journal of Biomedical Materials Research Part B: Applied Biomaterials, 2018, 106(7): 2588-2595.

[58] DING C, TIAN M, FENG R, et al. Novel self-healing hydrogel with injectable, pH-responsive, strain-sensitive, promoting wound-healing, and hemostatic properties based on collagen and chitosan[J]. ACS Biomaterials Science & Engineering, 2020, 6(7): 3855-3867.

[59] CIDREIRA A C M, DE CASTRO K C, HATAMI T, et al. Cellulose nanocrystals-based materials as hemostatic agents for wound dressings: A review[J]. Biomedical Microdevices, 2021, 23(4): 43.

[60] FAN X, LI M, YANG Q, et al. Morphology-controllable cellulose/chitosan sponge for deep wound hemostasis with surfactant and pore-foaming agent[J]. Materials Science and Engineering: C, 2021, 118: 111408.

[61] FAN X, LI Y, LI N, et al. Rapid hemostatic chitosan/cellulose composite sponge by alkali/urea method for massive haemorrhage[J]. International Journal of Biological Macromolecules, 2020, 164: 2769-2778.

[62] LAURENCE S, BAREILLE R, BAQUEY C, et al. Development of a resorbable macroporous cellulosic material used as hemostatic in an osseous environment[J]. Journal of Biomedical Materials Research Part A, 2005, 73A(4): 422-429.

[63] LI B, PAN W, SUN X, et al. Hemostatic effect and safety evaluation of oxidized regenerated cellulose in total knee arthroplasty—A randomized controlledtrial[J]. BMC Musculoskeletal Disorders, 2023, 24(1): 797.

[64] AYDEMIR SEZER U, SAHIN İ, ARU B, et al. Cytotoxicity, bactericidal and hemostatic evaluation of oxidized cellulose microparticles: Structure and oxidation degree approach[J]. Carbohydrate Polymers, 2019, 219: 87-94.

[65] HERNáNDEZ-BONILLA S, RODRíGUEZ-GARCíA A M, JIMéNEZ-HEFFERNAN J A, et al. FNA cytology of postoperative pseudotumoral lesions induced by oxidized cellulose hemostatic agents[J]. Cancer Cytopathology, 2019,

127(12): 765-770.

[66] VELáZQUEZ-AVIñA J, MöNKEMüLLER K, SAKAI P, et al. Hemostatic effect of oxidized regenerated cellulose in an experimental gastric mucosal resection model[J]. Endoscopy, 2014, 46(10): 878-882.

[67] BIAN J, BAO L, GAO X, et al. Bacteria-engineered porous sponge for hemostasis and vascularization[J]. Journal of Nanobiotechnology, 2022, 20(1): 47.

[68] OHTA S, NISHIYAMA T, SAKODA M, et al. Development of carboxymethyl cellulose nonwoven sheet as a novel hemostatic agent[J]. Journal of Bioscience and Bioengineering, 2015, 119(6): 718-723.

[69] LIU R, DAI L, SI C, et al. Antibacterial and hemostatic hydrogel via nanocomposite from cellulose nanofibers[J]. Carbohydrate Polymers, 2018, 195: 63-70.

[70] UDANGAWA R N, MIKAEL P E, MANCINELLI C, et al. Novel cellulose—Halloysite hemostatic nanocomposite fibers with a dramatic reduction in human plasma coagulation time[J]. ACS Applied Materials & Interfaces, 2019, 11(17): 15447-15456.

[71] WU Z, ZHOU W, DENG W, et al. Antibacterial and hemostatic thiol-modified chitosan-immobilized AgNPs composite sponges[J]. ACS Applied Materials & Interfaces, 2020, 12(18): 20307-20320.

[72] RADWAN-PRAGŁOWSKA J, PIĄTKOWSKI M, DEINEKA V, et al. Chitosan-based bioactive hemostatic agents with antibacterial properties—Synthesis and characterization[J]. Molecules, 2019, 24(14): 2629.

[73] LAN G, LU B, WANG T, et al. Chitosan/gelatin composite sponge is an absorbable surgical hemostatic agent[J]. Colloids and Surfaces B: Biointerfaces, 2015, 136: 1026-1034.

[74] GHEORGHIȚĂ D, MOLDOVAN H, ROBU A, et al. Chitosan-based biomaterials for hemostatic applications: A review of recent advances[J]. International Journal of Molecular Sciences, 2023, 24(13): 10540.

[75] HU Z, ZHANG D-Y, LU S-T, et al. Chitosan-based composite materials for prospective hemostatic applications[J]. Marine Drugs, 2018, 16(8): 273.

[76] YAN T, CHENG F, WEI X, et al. Biodegradable collagen sponge reinforced with chitosan/calcium pyrophosphate nanoflowers for rapid hemostasis[J]. Carbohydrate Polymers, 2017, 170: 271-280.

[77] DOWLING M B, KUMAR R, KEIBLER M A, et al. A self-assembling hydrophobically modified chitosan capable of reversible hemostatic action[J]. Biomaterials, 2011, 32(13): 3351-3357.

[78] KUMAR A, VIMAL A, KUMAR A. Why chitosan? From properties to perspective of mucosal drug delivery[J]. International Journal of Biological Macromolecules, 2016, 91: 615-622.

[79] BELLICH B, D'AGOSTINO I, SEMERARO S, et al. "The Good, the Bad and the Ugly" of chitosans[J]. Marine Drugs, 2016, 14(5): 99.

[80] KHAN M A, MUJAHID M. A review on recent advances in chitosan based composite for hemostatic dressings[J]. International Journal of Biological Macromolecules, 2019, 124: 138-147.

[81] LORD M S, CHENG B, MCCARTHY S J, et al. The modulation of platelet adhesion and activation by chitosan through plasma and extracellular matrix proteins[J]. Biomaterials, 2011, 32(28): 6655-6662.

[82] FISCHER T, THATTE H, NICHOLS T, et al. Synergistic platelet integrin signaling and factor XII activation in poly-acetyl glucosamine fiber-mediated hemostasis[J]. Biomaterials, 2005, 26(27): 5433-5443.

[83] WU S, HUANG Z, YUE J, et al. The efficient hemostatic effect of Antarctic krill chitosan is related to its hydration property[J]. Carbohydrate Polymers, 2015, 132: 295-303.

[84] LI B, WANG J, GUI Q, et al. Continuous production of uniform chitosan beads as hemostatic dressings by a facile flow injection method[J]. Journal of Materials Chemistry B, 2020, 8(35): 7941-7946.

[85] SUN X, TANG Z, PAN M, et al. Chitosan/kaolin composite porous microspheres with high hemostatic efficacy[J]. Carbohydrate Polymers, 2017, 177: 135-143.

[86] SUNDARAM M N, AMIRTHALINGAM S, MONY U, et al. Injectable chitosan-nano bioglass composite hemostatic hydrogel for effective bleeding control[J]. International Journal of Biological Macromolecules, 2019, 129: 936-943.

[87] ZHENG Y, PAN N, LIU Y, et al. Novel porous chitosan/N-halamine structure with efficient antibacterial and hemostatic properties[J]. Carbohydrate Polymers, 2021, 253: 117205.

[88] LEE K Y, MOONEY D J. Alginate: Properties and biomedical applications[J]. Progress in Polymer Science, 2012, 37(1): 106-126.

[89] CHEN Y, WU L, LI P, et al. Polysaccharide based hemostatic strategy for ultrarapid hemostasis[J]. Macromolecular Bioscience, 2020, 20(4): e1900370.

[90] ALAVI M, RAI M. Recent progress in nanoformulations of silver nanoparticles with cellulose, chitosan, and alginic acid biopolymers for antibacterial applications[J]. Applied Microbiology and Biotechnology, 2019, 103(21-22): 8669-8676.

[91] PAN M, TANG Z, TU J, et al. Porous chitosan microspheres containing zinc ion for enhanced thrombosis and hemostasis[J]. Materials Science and Engineering: C,

2018, 85: 27-36.

[92] ZHONG W. Efficacy and toxicity of antibacterial agents used in wound dressings[J]. Cutaneous and Ocular Toxicology, 2015, 34(1): 61-67.

[93] TONG Z, YANG J, LIN L, et al. In situ synthesis of poly(γ-glutamic acid)/alginate/AgNP composite microspheres with antibacterial and hemostatic properties[J]. Carbohydrate Polymers, 2019, 221: 21-28.

[94] CHOUDHARY H, RUDY M B, DOWLING M B, et al. Foams with enhanced rheology for stopping bleeding[J]. ACS Applied Materials & Interfaces, 2021, 13(12): 13958-13967.

[95] ZHENG Y, SHARIATI K, GHOVVATI M, et al. Hemostatic patch with ultra-strengthened mechanical properties for efficient adhesion to wet surfaces[J]. Biomaterials, 2023, 301: 122240.

[96] YANG X, LIU W, XI G, et al. Fabricating antimicrobial peptide-immobilized starch sponges for hemorrhage control and antibacterial treatment[J]. Carbohydrate Polymers, 2019, 222: 115012.

[97] CHEN J, CHEN S, CHENG W, et al. Fabrication of porous starch microspheres by electrostatic spray and supercritical CO_2 and its hemostatic performance[J]. International Journal of Biological Macromolecules, 2019, 123: 1-9.

[98] PAVLOVIC S, BRANDAO P R G. Adsorption of starch, amylose, amylopectin and glucose monomer and their effect on the flotation of hematite and quartz[J]. Minerals Engineering, 2003, 16(11): 1117-1122.

[99] LIU G, GU Z, HONG Y, et al. Electrospun starch nanofibers: Recent advances, challenges, and strategies for potential pharmaceutical applications[J]. Journal of Controlled Release, 2017, 252: 95-107.

[100] CHEN F, CAO X, YU J, et al. Quaternary ammonium groups modified starch microspheres for instant hemorrhage control[J]. Colloids and Surfaces B: Biointerfaces, 2017, 159: 937-944.

[101] MIRZAKHANIAN Z, FAGHIHI K, BARATI A, et al. Synthesis and characterization of fast-swelling porous superabsorbent hydrogel based on starch as a hemostatic agent[J]. Journal of Biomaterials Science, Polymer Edition, 2015, 26(18): 1439-1451.

[102] AWASTHI G P, ADHIKARI S P, KO S, et al. Facile synthesis of ZnO flowers modified graphene like MoS_2 sheets for enhanced visible-light-driven photocatalytic activity and antibacterial properties[J]. Journal of Alloys and Compounds, 2016, 682: 208-215.

[103] HOU Y, XIA Y, PAN Y, et al. Influences of mesoporous zinc-calcium silicate on water absorption, degradability, antibacterial efficacy, hemostatic performances and cell viability to microporous starch based hemostat[J]. Materials Science and Engineering: C, 2017, 76: 340-349.

[104] QIAN J, CHEN Y, YANG H, et al. Preparation and characterization of crosslinked porous starch hemostatic[J]. International Journal of Biological Macromolecules, 2020, 160: 429-436.

[105] SU H, WEI S, CHEN F, et al. Tranexamic acid-loaded starch hemostatic microspheres[J]. RSC Advances, 2019, 9(11): 6245-6253.

[106] CUI R, CHEN F, ZHAO Y, et al. A novel injectable starch-based tissue adhesive for hemostasis[J]. Journal of Materials Chemistry B, 2020, 8(36): 8282-8293.

[107] SU Y, CHEN H, LIU Q, et al. Thermoresponsive gels with embedded starch microspheres for optimized antibacterial and hemostatic properties[J]. ACS Applied Materials & Interfaces, 2024, 16(10): 12321-12331.

[108] MASTERS K S, SHAH D N, LEINWAND L A, et al. Crosslinked hyaluronan scaffolds as a biologically active carrier for valvular interstitial cells[J]. Biomaterials, 2005, 26(15): 2517-2525.

[109] YAMANLAR S, SANT S, BOUDOU T, et al. Surface functionalization of hyaluronic acid hydrogels by polyelectrolyte multilayer films[J]. Biomaterials, 2011, 32(24): 5590-5599.

[110] WANG Y, LIU G, WU L, et al. Rational design of porous starch/hyaluronic acid composites for hemostasis[J]. International Journal of Biological Macromolecules, 2020, 158: 1319-1329.

[111] ABALLAY A, HERMANS M H E. Neodermis formation in full thickness wounds using an esterified hyaluronic acid matrix[J]. Journal of Burn Care & Research, 2019, 40(5): 585-589.

[112] ROEHRS H, STOCCO J G, POTT F, et al. Dressings and topical agents containing hyaluronic acid for chronic wound healing[J]. The Cochrane Database of Systematic Reviews, 2023, 7(7): Cd012215.

[113] LIU J-Y, LI Y, HU Y, et al. Hemostatic porous sponges of cross-linked hyaluronic acid/cationized dextran by one self-foaming process[J]. Materials Science and Engineering: C, 2018, 83: 160-168.

[114] WANG M, HU J, OU Y, et al. Shape-recoverable hyaluronic acid-waterborne polyurethane hybrid cryogel accelerates hemostasis and wound healing[J]. ACS Applied Materials & Interfaces, 2022, 14(15): 17093-17108.

[115] CHEN Z, YE S Y, YANG Y, et al. A review on charred traditional Chinese herbs: Carbonization to yield a haemostatic effect[J]. Pharmaceutical Biology, 2019, 57(1): 498-506.

[116] DONG X, LIANG W, MEZIANI M J, et al. Carbon dots as

potent antimicrobial agents[J]. Theranostics, 2020, 10(2): 671-686.

[117] LI D, XU K-Y, ZHAO W-P, et al. Chinese medicinal herb-derived carbon dots for common diseases: Efficacies and potential mechanisms[J]. Frontiers in Pharmacology, 2022, 13: 815479.

[118] SZCZEPANKOWSKA J, KHACHATRYAN G, KHACHATRYAN K, et al. Carbon dots—Types, obtaining and application in biotechnology and food technology[J]. International Journal of Molecular Sciences, 2023, 24(19): 14984.

[119] VILLALBA-RODRíGUEZ A M, GONZáLEZ-GONZáLEZ R B, MARTíNEZ-RUIZ M, et al. Chitosan-based carbon dots with applied aspects: New frontiers of international interest in a material of marine origin[J]. Marine Drugs, 2022, 20(12): 782.

[120] KRYSTYJAN M, KHACHATRYAN G, KHACHATRYAN K, et al. Polysaccharides composite materials as carbon nanoparticles carrier[J]. Polymers, 2022, 14(5): 948.

[121] YAN X, ZHAO Y, LUO J, et al. Hemostatic bioactivity of novel pollen typhae carbonisata-derived carbon quantum dots[J]. Journal of Nanobiotechnology, 2017, 15(1): 60.

[122] LI S, GUO Z, ZHANG Y, et al. Blood compatibility evaluations of fluorescent carbon dots[J]. ACS Applied Materials & Interfaces, 2015, 7(34): 19153-19162.

[123] HAN B, SHEN L, XIE H, et al. Synthesis of carbon dots with hemostatic effects using traditional Chinese medicine as a biomass carbon source[J]. ACS Omega, 2023, 8(3): 3176-3183.

[124] WU T, LI M, LI T, et al. Natural biomass-derived carbon dots as a potent solubilizer with high biocompatibility and enhanced antioxidant activity[J]. Frontiers in Molecular Biosciences, 2023, 10: 1284599.

[125] ZHANG J, ZOU L, LI Q, et al. Carbon dots derived from traditional Chinese medicines with bioactivities: A rising star in clinical treatment[J]. ACS Applied Bio Materials, 2023, 6(10): 3984-4001.

[126] SUN Z, LU F, CHENG J, et al. Haemostatic bioactivity of novel *Schizonepetae Spica Carbonisata*-derived carbon dots via platelet counts elevation[J]. Artificial Cells, Nanomedicine, and Biotechnology, 2018, 46(sup3): 308-317.

[127] LIU X, WANG Y, YAN X, et al. Novel *Phellodendri Cortex* (Huang Bo)-derived carbon dots and their hemostatic effect[J]. Nanomedicine: Nanotechnology, Biology, and Medicine, 2018, 13(4): 391-405.

[128] ZHANG M, CHENG J, LUO J, et al. Protective effects of *Scutellariae Radix Carbonisata*-derived carbon dots on blood-heat and hemorrhage rats[J]. Frontiers in Pharmacology, 2023, 14: 1118550.

[129] ALTINTIG E, SARICI B, KARATAŞ S. Prepared activated carbon from hazelnut shell where coated nanocomposite with Ag+ used for antibacterial and adsorption properties[J]. Environmental Science and Pollution Research, 2022, 30(5): 13671-13687.

[130] CHENG P, XUE X, SU J, et al. ^{1}H NMR-based metabonomic revealed protective effect of Moutan Cortex charcoal on blood-heat and hemorrhage rats[J]. Journal of Pharmaceutical and Biomedical Analysis, 2019, 169: 151-158.

[131] ZHANG Y, GE X L, ZHANG J, et al. Effect of the oxygenic groups on activated carbon on its hemocompatibility[J]. Colloids and Surfaces B: Biointerfaces, 2024, 233: 113655.

[132] WANG S, ZHANG Y, SHI Y, et al. Rhubarb charcoal-cross-linked chitosan/silk fibroin sponge scaffold with efficient hemostasis, inflammation, and angiogenesis for promoting diabetic wound healing[J]. International Journal of Biological Macromolecules, 2023, 253(Pt 2): 126796.