The article summarizes the synthesis of MOFs and application of MOFs in Diabetes Diagnosis, regulating blood glucose, and wound healing. And the title of this paper is "Application of metal-organic framework in diagnosis and treatment of diabetes and its wound healing". The title and content are not appropriate enough and should be adjusted.

(1) In this review, the author only listed the synthesis methods of some MOFs, and listed some advantages and disadvantages of different synthesis methods. There have been many corresponding reviews. The author should review the recent development of some MOFs, and this part should not include the scope of the review topics.

Response 1: Through a review of recent synthetic developments in MOFs, we have added the content of "biomimetic mineralization" in Table 1 and adjusted the content of the manuscript accordingly. Red font is new content. **(Line 77, 126-138)**

Table 1. Comparison of advantages and disadvantages of MOFs synthesis methods.

Synthetic methods	Advantages	Disadvantages	Ref.
Hydrothermal/solvothermal synthesis	Generality, simplicity and low cost. Can large-scale preparation at mild temperatures.	Long reaction time, high temperature requirement	[22, 27,28]
Microwave-assisted synthesis	Shorten the reaction time to a few hours or even several minutes. No excessive by-products, and the high purity and small size of MOFs obtained.	Reaction solvent requirements are limited	[29-31]
Room temperature synthesis	Reaction conditions are simple and can be prepared on a large scale.	Limited range of adaptation	[32,33]
Ultrasonic-assisted synthesis	Quickly disperse solutes and speed up the reaction process, improve the reaction efficiency.	Hard to get a lot of product	[34,35]
Mechanochemical synthesis	Safety, environmental protection	Hard to get a lot of product	[36,37]
Microfluidic synthesis	The effective mixing of organic phase and inorganic phase is realized.	Limited range of adaptation	[38,39]
Biomimetic mineralization	Beneficial to enhance the robustness, biocompatibility and biocompatibility of biomacromolecules.	Only suitable for biomacromolecules that are similar in size to the pore size of MOFs and are solvent resistant in the	[25,26,40]

preparation of MOFs.

"2.7 Biomineralization synthesis"

Biomineralization refers to the process of generating inorganic minerals by organisms through the regulation of biological macromolecules. Under certain physical and chemical conditions, proteins, enzymes and DNA can rapidly induce the formation of protective metal organic framework coatings by converting ions in solution into solid minerals under the control or influence of biological organic substances[25,26]. Biomimetic mineralization provides unprecedented protection from biological, thermal, and chemical degradation while maintaining biological activity by encapsulating biological macromolecules in porous metal-organic frameworks[52]. He et al. combined a low-cytotoxic and pH-sensitive biodegradable MOF material (Zeolitic imidazole framework-8 (ZIF-8)) with insulin (INS), GOx and catalase (CAT) co-loaded to form glucose-responsive NPs as functional "cores", enabling long-term glucose-responsive insulin delivery[40].

(2) In the paper, the logic of many narratives is problematic, such as lines 131-132 the author describes a large number of MOFs based immunosensors however, there are only two references.

Response 2: We refer to more studies on MOFS-based immunosensors to make the relevant issues in the manuscript more fully elaborated. Red font is new content. (Line 149-165, Line 249-255, Line 266-272)

"3. Application of MOFs in diabetes diagnosis"

There are three main reference values for the diagnosis of diabetes, including: 1). Fasting plasma, glucose is greater than or equal to 7.0 mM. 2). Random plasma glucose greater than or equal to 11.1 mM. 3). OGTT test two-hour plasma glucose greater than or equal to 11.1 mM. In order to monitor the blood sugar status of patients in real time, sensors with high sensitivity and high selectivity are particularly important. Compare to traditional invasive blood sampling, breath analysis is a non-invasive method suitable for frequent blood glucose monitoring. Acetone (ACE), a ketone produced when the body is forced to use stored fat as its primary source of energy, is now a widely accepted biomarker of diabetes.[53-56] Similarly, other immunological indicators have also been used as indicators to detect blood glucose levels. For example, glycosylated hemoglobin (HbA1c)[57], INS[58], retinol-binding protein 4 (RBP4)[59], tumor necrosis factor-α (TNF-α)[60],and so on. HbA1c is the free amino group of the N-terminal valine of the hemoglobin beta chain of different carbohydrates formed by glycosylation, and is closely related to the fasting blood glucose level in the past 2 to 3 months. Insufficient insulin release or insulin loss in target tissues can also easily lead to the occurrence of diabetes[61,62]. Insulin is involved in regulating blood sugar balance in the body, facilitating the absorption of glucose from fats and proteins. Therefore, it is necessary to develop an efficient and sensitive method for detecting insulin in serum. Xiang et al. found that RBP4 levels are increased when insulin resistance and diabetes occur[63,64]. During diabetes, the level of the inflammatory factor TNF-α is also elevated[60]. In recent years, MOFs nanoparticles have been used to enhance the catalytic activity of immunosensors by

virtue of their open metal sites and tunable microporous structures[65,66]. Therefore, many MOFs-based electrochemiluminescence (ECL) biosensors have been developed for the detection of diabetes, including blood glucose sensors[67-69], acetone and isopropanol sensors[70-72], and other sensors[57-60].

"3.3. Other sensors"

Antibody-labeled zirconium-metal-organic framework/Fe3O4(trimethyl chitosan)/gold nanocluster (Zr-MOF/Fe3O4(TMC)/AuNCs) nanocomposite can selectively capture HbA1c and isolate it from non-glycosylated Hb species and other glycosylated proteins in human blood samples[57]. Disposable Au electrodes were modified with copper(II) benzene-1,3,5-tricarboxylate (Cu-BTC)/phyllomidazole molecular leaf-like framework (ZIF-L) for insulin detection[58]. The aptamer was easily immobilized on the Cu-BTC/ZIF-L composite by physical adsorption, which promoted the specific interaction between the aptamer and insulin. The linear detection range of insulin based on Cu-BTC/ZIF-L composite was wide (0.1 pM ~ 5 mu M), and the lower detection limit was 0.027 pM. RBP4 has been regarded as an important serological biomarker for type 2 diabetes mellitus (T2DM). Taking advantage of dual-signal quenching@CNTs composite between luminol@AuPt/ZIF-67 hybrid and MnO2, an ECL immunosensor for RBP4 detection is proposed, providing another detection strategy for early clinical diagnosis of T2DM. (Fig. 4). Specifically the multifunctional AuPt/ZIF-67 hybrid has high peroxidase-like nanase activity and loading capacity, which can improve the ECL performance of luminol-H2O2 system.[59] The MnO2@CNTs composite can effectively quench the amplified initial signal by inhibiting the peroxidase-like activity of luminol@AuPt/ZIF-67 and the ECL-RET strategy. We know that carbon nanotubes (CNTs) have been widely used in the modification of metal oxides and other materials due to their unique nano-size, high specific surface area, superior adsorption effect and multi-functional binding sites[59]. Yola et al. developed a sensor platform on the surface of glassy carbon electrodes (GCEs) using a mixture of thiol-functionalized multi-walled carbon nanotubes (S-MWCNTs) and gold nanoparticles. Then, the capture TNF-α antibody binds to the sensor platform via amino-gold affinity. After capturing TNF-α antibody immobilization, the immunoreaction between AuNPs/S-MWCNTs immobilized with TNF-α primers and TNF-α secondary antibody-conjugated bimetallic Ni/Cu-MOFs was used to prepare a novel voltammetric TNF-α immunosensor[60].

(3) For the abbreviations of metal-organic framework materials, there are many expressions such as MOF, MOFs and MOFs. Whether the author refers to the same substance or not puzzled me. The author has a big problem in writing the whole paper.

Response 3: Both MOF and MOFs refer to metal-organic frameworks. When referring to a class of materials, such as Cu-based-MOF, Fe-based-MOF, Au-based-MOF, the singular form (MOF) is used;(Line 38, 41, 50, 106....) when the expression is the overall meaning, the plural form is used (MOFs).(Line196, 224, 314...) There are also some special cases where we strictly refer to the papers of other scholars, who may have other ideas on this issue.(Line 545,) Finally, we have corrected the wrong use of singular and plural in the article, such as line 374, 441, 787, 801.

(4) The content of the author's review does not match the title. It is suggested that the author delete some contents and add corresponding relevant contents.

Response 4: After careful consideration of the entire manuscript, we have decided to remove "wound healing" from the title, as wound healing is already included in the management of diabetes. The title of the manuscript was changed from "Application of metal-organic framework in diagnosis and treatment of diabetes and its wound healing" to "Application of metal-organic framework in diagnosis and treatment of diabetes".