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PEER-REVIEW REPORT

Name of journal: *World Journal of Diabetes*

Manuscript NO: 67818

Title: Antidiabetics and antimicrobials: Harmony of mutual interplay

Reviewer's code: 05227830

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Croatia

Author's Country/Territory: Egypt

Manuscript submission date: 2021-05-03

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-03 13:49

Reviewer performed review: 2021-05-06 08:17

Review time: 2 Days and 18 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



SPECIFIC COMMENTS TO AUTHORS

Dear Author/s, It was a pleasure to review your manuscript, since it is interesting, relevant, nicely written and up-to-date. I believe it is already very good; however I suggest few minor adjustments in order to improve the quality even more (to become excellent and even more up-to-date). I strongly believe latter is going to result in publication of your manuscript in a prestigious Journal such as World Journal of Diabetes. Comment on several criteria from checklist: Title reflects the main subject of the manuscript. Abstract summarizes and refelects the work described in the manuscript. Key words reflect the focus of the manuscript. Table and figures are of adequate quality, nicely presented, easily understandable and relevant. References are correctly chosen and up-to-date. To deduce, this review article is very good, easy to read and relevant.

Minor suggestions/comments: -Before the COVID-19 pandemic 650 million adults (13% of the world's adult population) were obese. Kelly et al. (2008) estimated that 19.7% of the world's population will be obese by the year of 2030. In addition, momentarily due to COVID-19 pandemic and quarantine measures, it is higly certain that global burden of obesity will escalate even more. Since diabetes type 2 is one of the most prevalent complications of obesity; if I were you I would take into account latter (and provide a short note/comment) in introduction paragraph were you give projection regarding diabetes rates (especially since the reference 1 was before pandemic situation and secular trends have potentially changed now). -When dividing diabetes to types, I would maybe also add that it depends on pathophysiological cascade, besides age of onset and the need for external insulin (especially since insulin is also a common therapeutic measure among T2DM patients also). -Regarding your comment on IL-1B and TNF inhibitors, I would paraphrase or remove that statement, since it is not routinely prescribed at the moment (grade <B of evidence) and not in guidelines of head societies. -I suggest you to make some modifications in Diabetes and immunity



interplay paragraph: maybe you should put more emphasis on autoimmunity when talking about T1DM (on top of that the triggering events are still not clarified; hence I would use terms like may, probable/plausible, one may believe ... when talking about the triggers); maybe you can update pathogenesis of T2DM by adding some data on low-grade chronic inflammation (Wensveen FM et al. The "Big Bang" in obese fat: Events initiating obesity-induced adipose tissue inflammation. *Eur J Immunol.* 2015). -I suggest you to update Imbalance in gut microbiota in diabetes by adding comments/data on e.g. Belančić A et al. Gut microbiome dysbiosis and endotoxemia - Additional pathophysiological explanation for increased COVID-19 severity in obesity. *Obes Med.* 2020. ; Larsen N et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One.* 2010. ; Qin J et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature.* 2012 ; Wu X et al. Molecular characterisation of the faecal microbiota in patients with type II diabetes. *Curr Microbiol.* 2010., etc. -Is there a difference between gut microbiome composition between T1DM and T2DM patients (due to obesity and other associated comorbidities, as well per se)? Please elaborate in this paragraph/provide a comment with references. -It would be interesting to add some more comments on the effects of individual antidiabetic agents on gut microbiome. For instance you can refer to articles on metformin (besides already given comment on shift towards SCFAs-producing bacteria), GLP-1RAs, etc. ... such as e.g. refer to Wu H et al. Metformin alters the gut microbiome of individuals with treatments-naive type 2 diabetes, contributing to the therapeutic effects of the drug ; Belančić et al. Glucagon-like peptide-1 receptor agonists in the era of COVID-19: Friend or foe? *Clin Obes.* 2021., etc. -In your paragraph Diabetes promotes microbial infections, I suggest you to provide info on diabetes and COVID-19 relation (susceptibility, severity) in order to achieve that your manuscript is even more up-to-date -When you talk about antimicrobials with antidiabetic activity it is great that you took into account potential



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drug-drug interactions (e.g. clarithromycin ...). If I were you I would probably even add a separate lines (sub-paragraph here) on drug-drug interactions of the mentioned antimicrobials and associated (due to interaction) effect on glucose levels. ; On top of that, one should be careful when interpreting antimicrobials antidiabetic activity since infection/inflammation can also impact glucose levels (potential confounding effect when interpreting somewhere/sometimes)? -Please add info on individual antidiabetics' antimicrobial activity regarding COVID-19. For example please see previously mentioned manuscript by Belančić A. et al. (Clin Obes, 2021) regarding GLP-1RA. Provide comments in your sup-paragraphs of paragraph Antidiabetics with antimicrobial activities. On top of that, GLP-1RA also pose anti-inflammatory properties - please add in your sentence where you talk about anti-inflammatory properties of glitazones, metformin, sulfonylureas and DPP-4 inhibitors. -In order to avoid selection bias please include also the references regarding insulin that have contrary results if any ... -Provide a short comment on manuscript Plotkin et al. Effect of insulin on microbial growth. Curr Microbiol. 2000. -Please provide here also the elaboration on the effect of individual antidiabetics (for each were applicable) on gut microbiome in more details (as already explained/asked before). -Please provide/include a comment on Faiza Malik. Is metformin poised for a second career as an antimicrobial? Diabetes Metab Res Rev. 2018. -Please add info that pioglitazone enhanced the antibacterial activity of amoxicillin, cephalexin and ciprofloxacin (and not of co-trimoxazole) (your ref. 197). -I believe you have accidentally put "pioglitazone is a direct PPAR inhibitor" in a sentence "Sulfonylureas were reported to decrease M1 macrophage activity ..." (paragraph on Sulfonylureas and Meglitinides). -In Table 1 please put either antidiabetic drug or antidiabetic class in first column; I suggest antidiabetic drug; however if so please precise which GLP-1RA and alfa-glucosidase inhibitor then. Also update after modifications in text according to peer-reviewer's comments. -Please provide more



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extensive data on antimicrobial/antivirulence activity of GLP-1RAs, as well as their effect on gut microbiome and COVID-19 (besides other, please refer to previously mentioned manuscript of Belančić A et al. on GLP-1RAs published in Clin Obes in 2021.)

-Since this is still not a high grade evidence I suggest you to add that additional adequately constructed preclinical and human/clinical RCTs and subsequent meta-analyic data is needed to draw the final conclusions on antimicrobial and antivirulence activities of individual antidiabetis. What is more, new/upcoming data needs to be constantly evalated based on EBM priniciples. On top of that, I would maybe more emphasize the possibility of indirect antimicrobial/antivirulence effect due to euglycemic, anti-inflammatory and anti-oxidative properties of some antidiabetics. -As I previously suggested, I believe that by including facts regarding COVID-19 (in paragraphs were applicable), this manuscript would be even more popular, cited and useful in practice. Best regards, Reviewer



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PEER-REVIEW REPORT

Name of journal: *World Journal of Diabetes*

Manuscript NO: 67818

Title: Antidiabetics and antimicrobials: Harmony of mutual interplay

Reviewer's code: 05458177

Position: Peer Reviewer

Academic degree: MD

Professional title: Assistant Professor, Surgeon

Reviewer's Country/Territory: Indonesia

Author's Country/Territory: Egypt

Manuscript submission date: 2021-05-03

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-03 12:58

Reviewer performed review: 2021-05-12 10:06

Review time: 8 Days and 21 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

1. The figures need overhaul, the texts placement and the designs were poor.
2. The manuscript has to be more focused according to its title, not too much discuss irrelevant topic, despite it's associated.



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PEER-REVIEW REPORT

Name of journal: *World Journal of Diabetes*

Manuscript NO: 67818

Title: Antidiabetics and antimicrobials: Harmony of mutual interplay

Reviewer's code: 05309430

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Egypt

Manuscript submission date: 2021-05-03

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-05-06 12:57

Reviewer performed review: 2021-05-14 02:11

Review time: 7 Days and 13 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



SPECIFIC COMMENTS TO AUTHORS

This is a comprehensive review that discussed the interplay between immunity, diabetes and microbial infections (Fig. 1). The influence of diabetes on worsening of microbial infections and antimicrobial agents that can harbor antidiabetic activities were discussed. Special interest focused on the antidiabetic drugs that have antimicrobial and anti-virulence activities through multiple mechanisms (Table 1), The review could add to our understanding of diabetes and microbial infections (Fig. 2) and antimicrobial activities of antidiabetic drugs (Table 1). Listed below are minor suggestions: 1. The title cannot summarize the whole content of the review, i.e., the interplay between diabetes, infection and immunity. 2. The font size in Fig. 1 is too small to read, which could be condensed to make the key points larger. 3. English abbreviations should be introduced for the first time with the full name and then followed by direct use of abbreviations. 4. Page or line should be numbered. Typos for example: a) Fig. 2: "Nf-KB" should be "NF- B". b) Page 13, line 6: "reduced glutathiones" should be "glutathione". c) Page 28, line 18: "repoting" should be "reporting".



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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Diabetes*

Manuscript NO: 67818

Title: Antidiabetics and antimicrobials: Harmony of mutual interplay

Reviewer's code: 05458177

Position: Peer Reviewer

Academic degree: MD

Professional title: Assistant Professor, Surgeon

Reviewer's Country/Territory: Indonesia

Author's Country/Territory: Egypt

Manuscript submission date: 2021-05-03

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2021-07-30 17:06

Reviewer performed review: 2021-08-10 12:58

Review time: 10 Days and 19 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The comments had been addressed well.