

REPLY TO REVIEWERS' COMMENTS 26149

All corrections in the manuscript have been highlighted in yellow.

<u>Reviewers</u>	<u>Comments</u>	<u>Clarification</u>
03548332	It will contribute to a literature review, well written. Printable.	Thanks for your appreciation.
00646291	Illustrations similar to that provided for metformin transporters in Figure 1 should be provided for sulfonylureas and thiazolidinediones explaining their molecular mechanism of action and exemplifying the relation between the therapeutic failure of these drugs and the mutations in the genes associated with their function. For example: Page 11: An explanation of how mutations in the genes encoding SUR1 (ABCC8) and Kir6.2 (KCNJ11) could lead to altered signaling cascades needs to be described clearly as the relation between these mutations and the SUs' therapeutic failure is not apparent.	We wish to draw attention of respected reviewer in that the illustration for metformin transporters is in Figure 2. As suggested, we have added Figure 3 to explain the mechanism of action of sulfonylureas. Necessary modifications have been incorporated in the text (Page 11).
	Page 12: What is the function of the Transcription factor 7-like 2 (TCF7L2) and how mutations in this transcription factor can lead to alterations in the SUs' therapeutic efficacy?	Necessary corrections have been incorporated. The exact molecular mechanism by which SUs act on TCF7L2 is still not clearly understood (Page 13).
	Page 14: How PPARgamma signaling affects the response to	The necessary corrections have been incorporated

	thiazolidinediones treatment?	(Page 15). We have added the figure 4 to understand the correlation of PPAR gamma and thiazolidinediones (Page 16).
	Page 5: Please delete “Such type of” in the sentence “Such type of inter-individual differences can be attributed to polymorphisms of certain candidate genes involved in drug absorption, transportation, distribution, metabolism...”	The necessary corrections have been made (Page 5).
	Page 7: Please delete “Such a” in the sentence “Such a metformin-induced AMP kinase activation leads to transcriptional inhibition of hepatic gluconeogenesis.”	Necessary correction has been incorporated (Page 6-7).
	Page 9: Please delete the word “been” in the sentence “However, compared to OCT1 and OCT2, very few studies have “been” reported about OCT3 variants and metformin therapeutics.”	The necessary corrections have been made (Page 9).
	Page 11: Please rephrase the sentence “KCNJ11 located on chromosome 11p15.1 has reported 219 SNPs.” “Two hundred nineteen (219) SNPs have been reported for the KCNJ11 gene located on chromosome 11p15.1.	The necessary corrections have been made (Page 12).
	Page 11: Please rephrase the sentence “Only 6 SNPs viz. rs5210, rs5215, rs5218, rs5219, rs886288, rs2285676 were	The necessary corrections have been made (Page 12).

	reported for significant association with diabetes” “Only 6 SNPs viz. rs5210, rs5215, rs5218, rs5219, rs886288, rs2285676 have been reported to be associated with diabetes”	
	Page 13: Please delete “has been reported to” in the sentence “On binding with PPAR γ , TZDs stimulate adipocytes differentiation and “has been reported to” decrease plasma glucose level in T2DM patients.”	The necessary corrections have been made (Page 14).
	Page 15: Please separate the words metabolized/by	The necessary corrections have been made (Page 17).
	byPage 15: Please rephrase the sentence “Genetic polymorphisms in SLCO1B1 have been reported for significant influence on repaglinide pharmacokinetics with reduced exposure after administration of a single dose of repaglinide.” “Genetic polymorphisms in SLCO1B1 have been reported “to exert” significant influence on repaglinide pharmacokinetics with reduced exposure after administration of a single dose of repaglinide.”	The necessary corrections have been made (Page 17-18).
	Page 17 Please correct the typo “catalized” to “catalyzed”	The necessary corrections have been made (Page 19).