

## ESPS Peer-review Report

**Name of Journal:** World Journal of Diabetes

**ESPS Manuscript NO:** 7503

**Title:** Exploration of natural enzyme inhibitors with hypoglycemic potentials amongst Eucalyptus Spp. by in vitro assays

**Reviewer code:** 00506409

**Science editor:** Qi, Yuan

**Date sent for review:** 2013-11-22 20:06

**Date reviewed:** 2013-11-24 17:56

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input checked="" type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

In this manuscript a detailed in vitro pharmacologic evaluation of extracts from three Eucalyptus species in in vitro assays for activity of a variety of enzymes and assays for anti-oxidant activity is presented. The selection of enzymes and anti-oxidant activity is based on the hypothesis that these activities are involved in the pathogenesis of type 2 diabetes. The three extracts show broad enzyme inhibitory activity and anti-oxidant activity, which differs in magnitude between the three extracts. The authors conclude that the extracts might serve as starting material for new therapeutic modalities for type 2 diabetes, and that their data fit with the idea that leaves from trees could provide a base material for drug discovery and development programs. Essentially, the work is interesting but far away from any application as therapeutic treatment of type 2 diabetes. The lack of specificity, i.e., a general inhibitory effect on a variety of enzymes combined with a general anti-oxidant activity, is one item for discussion, and another item is evidently the high magnitude of IC<sub>50</sub> values associated with the fact that the extracts do not present pure compounds. This comment is not given to criticise the work and mission of activities by the authors, it is just given to enable the authors to bring their work in the correct perspective. The mission of pharmaceutical development is rather contrary, namely obtaining a high specificity with low IC<sub>50</sub> value to enable targetting a specified pathway without adverse effects on other metabolic pathways. Pharma companies have used now for decades large-sized extract/compound libraries (maybe including Eucalyptus extracts, but evidently also others like extracts from fungi and other sources from the natural environment) in so-called Lead-Finding-Units (enormous-high throughput screening programs, spending millions of dollars/euros/pounds) to identify therapeutic drug moieties. In this respect the work of the authors



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is not new but rather presents an old-fashioned approach: having stated this, results of Lead-Finding-Units in pharmaceutical companies are never disclosed in public and in this respect the work of the authors has news value. It could be discussed whether these extracts serve the diabetes community in the form of nutritional supplements rather than leads for pharmaceuticals: for sure, it serves Lead-Finding-Units in pharmaceutical companies but that is a different issue that is far away from targetting specific disease conditions. Following the above, there is little actual scientific criticism on the actual work presented in the manuscript, but rather a comment on the context in which the work was initiated. It is highly recommended to bring the work in the right perspective, i.e., presenting biological activity of extracts from environmental natural materials, which could have the perspective of being the start of new drug targets. Blood pressure management has the same likelihood of success as diabetes management and treatment of infectious disease, as is obesity and Alzheimer disease: it could therefore be discussed whether the 'World Journal of Diabetes' presents the correct medium to publish these data. Apparently, from the accompanying correspondence between the authors and the journal it appears that this manuscript was written on invitation. If this is indeed the case, it could be recommended to rewrite the manuscript as an opinion paper or as a minireview, bringing the perspective of what extracts from natural products could bring the diabetes community that is in need of proper treatment modalities (including nutritional supplements). The introduction of the present paper could serve as a basis, and the results as an illustration. In this way, the data could be presented in a more informative format to the readership of the journal. There is a major comment on the way in which the studies are presented in this manuscript. First, there are numerous editing issues, no

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**Reviewer code:** 00225280

**Science editor:** Qi, Yuan

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
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## COMMENTS TO AUTHORS

This article by Dey et al is addressing an important health problem in relation to possible new therapeutic strategies. However, the manuscript is lacking in several aspects. To begin with, the introduction is far too long (about 1400 words). In addition, the methods section is also long and with some of the methods too analytical. The results are not adequately presented in the text (for instance lacking p values) and the discussion fails to consider how these results relate to other studies and where future research should focus. For example they do not comment on the content of other infusions like green tea or try to explain how the phenolic content of their extracts relate to the enzyme inhibitory effect. Finally, language needs minor to major polishing in several parts of the manuscript. More specifically: ? In the abstract, 'prevalence' is mostly used in epidemiology. Use more appropriate alternative, such as 'presence and potency or efficacy'. ? Re-writing the methods is advised, omitting 'playing pathogenic role in type 2 diabetes', as this is more suitable for the aim section of it. Furthermore, it should be made clear that phenolic and other content was first investigated and then the inhibitory potential of the extracts was. The sentence needs to be re-written for clarity. ? In the results, add values e.g. ng/ml or / 100 gr dried extract etc. ? An R2 value of 0.99 is surprisingly high. Please confirm. ? 'Potentiality' is not commonly used and 'unconventional' may be omitted as it gives a wrong impression. ? In the core tip, the phrase 'but hyper-expression... to processes' need rephrasing. ? The introduction is too long and not to the point. Some parts would be more relative to the Discussion. ? I would advise a shorter paragraph on diabetes, possibly including the key aspects of diabetes's related enzymes. For example a short sentence about DDP4 with a reference from a large clinical trial would be sufficient instead of an entire paragraph. ? The aim of

the study should be clear. Identifying the major phytochemicals in the extracts seems to be the first objective and exploring the anti-diabetic potential of the extracts by means of performing the enzyme inhibition assays the second. The phrase 'existence of NEIs...' is confusing, whereas in fact the purpose is to explore the potential of the extracts to inhibit these enzymes in vitro. ? An effort should be made to shorten the methods as well. Also, delete phrases like 'The enzymes mentioned above... of eucalyptus'. ? Statistical analysis is poorly described. P values are often missing and the coefficient correlation is not described either. ? GC analysis is not included in the results adequately. A chromatogram and an effort to identify the remaining 'important compounds'. ? Some of the tables (for example tables 1 and 5) are not necessary as they only include symbols or just 3 values. ? P values are not included in some of the tables, which would allow the reader to evaluate possible differences among the three species studied. ? Figure 1 seems to be describing exactly the same as table 2. Therefore it might be preferable to exclude it. The same for figure 7. ? The discussion is, unlike the rest of the manuscript, short; poorly written; repeats findings, such as the 1.8 cineole results, unnecessarily and fails to critically compare these findings with the literature and suggest how these findings could advance in future research (e.g. experiments in infusions, animal studies and human clinical trials).

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**Science editor:** Qi, Yuan

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## COMMENTS TO AUTHORS

Dey et al. investigated the potential hypoglycemic actions of Eucalyptus extracts in vitro. The extracts were found to potently inhibit a number of enzymes related to T2DM, such as amylase, glucosidase, and DPP4. The rationale of this study and methodology were adequately described. Major comments 1. Please clearly add statistical symbols and/or error bars (+/- SD) in all figures and tables. 2. The authors should include the limitations of the study, such as no clinical study, toxicity tests, etc. Minor comments 1. The introduction section is too long. Please shorten by 30-40%. 2. Please make abbreviations more consistent (e.g., type 2 diabetes vs. type 2 DM). 3. Do not capitalize generic terms (e.g., Reactive Oxygen Species)

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