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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 53772

Title: Probiotic mixture VSL#3: An overview of basic and clinical studies in chronic diseases

Reviewer's code: 05306383
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: France
Author's Country/Territory: China

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Reviewer chosen by: Jin-Zhou Tang
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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[Y] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

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SPECIFIC COMMENTS TO AUTHORS

In this review, the authors reported the current state of the art regarding the potential effects of the probiotic mixture VSL#3 in a wide range of chronic diseases. To my knowledge, there is no other review summarizing the potential effects of VSL#3 probiotic, which makes this publication really interesting for the scientific community. The authors carrefully reviewed the litterature on the topic in a large number of diseases and summarized all the data into tables. This review gives an essential input to the field regarding the summarized knowledge on VSL#3. Comments : To me, the title, abstract, key words and core tip reflect closely what is in this review. In the abstract, authors said « We observed that VSL#3 had a therapeutic or preventive effect in various systemic diseases ». Even if authors previously published on VSL#3, this statement is not appropriated. In the Core Tip, authors said « The imbalance of intestinal microbiota is the causal factor and concurrent cause of multiple diseases. ». This is a very strong assumption which has not been yet demonstrated. All along the manuscript, mainly before page 11, some of the authors statements requires more precautions regarding the effects of the probiotic product : - p.5 : « VSL#3 has a protective effect on intestinal barrier function (IBF), which is the major mechanism in treating all kinds of chronic diseases. » - p.7 : « The positive effect of VSL#3 on intestinal biological barrier function was also mediated by SCFA acetate ». This sentence does not prove that acetate is responsible of the positive effects of VSL3. Author statements require more precise and scientific explanations. - p.8 : « Besides, a culture of HT-29 monolayer cells with VSL#3 DNA was shown to inhibit IL-8 secretion induced by Salmonella in the presence of proinflammatory stimuli ». The sentence does not mean that VSL3 inhibits IL-8 secretion in stimulated HT-29 cells. The sentence has to be modified. - p.9 : « Interestingly, Lactobacilli and Bifidobacteria from VSL#3 did not induce IL-8, and a high concentration

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of streptococcal strains induced IL-8 when HT29/19A monolayers were cultured with cell extract fractions from a single strain of VSL#3 ». This sentence is hard to understand, and authors need to discuss what does this observation mean. - p.10 : « Then, a study in IL 10-knock out (KO) mice showed that VSL#3 down-regulated the signaling pathway of toll-like receptors (TLR) ». This sentence is not clear when compared to the original publication. This has to be modified. - p. 10 : « In the review, VSL#3 was proven to be effective in gastric ulcer, diarrhea-predominant enteritis, irritable bowel syndrome (IBS), ulcerative colitis (UC), pouchitis, colitis and so on. ». This review has not proven any effect of VSL3 in these diseases. Authors should revise the sentence carefully. - p.11 : « The use of antibiotics generally suppresses the normal intestinal microbiota, which leads to the overgrowth of resistant microbiota (Clostridium difficile). » This is a strong statement and fortunatelly not every single people using antibiotics had CD infection. - p.14 : « They are a group of heterogeneous diseases caused by an overreaction of intestinal immune systems to intestinal commensal bacteria ». Are authors sure of this statement ? What about food components ? - p.15 : « The fecal microbiota of patients with UC was not significantly different from that of controls » This is the statement from only one study from 1991 on the fecal microbiota. Is this the same conclusion in more recent studies? Many studies have since demonstrated that the composition and function of intestinal microbiota in UC patients are compromised. - p.16 : « Several studies have provided evidence about the effect of VSL#3 in dextran sulphate sodium (DSS)-induced murine colitis, which is similar to human UC. » This statement is not appropriated. - p.16-17 : « The different results indicated that the efficacy of VSL#3 was dependent on the dosage of VSL#3. ». Authors cannot compare two different studies from different labs and conclude that the difference is only due to the dosage of the probiotic, unless the negative controls of the two studies have been compared. - p.20 : « One study showed that VSL#3 could retard the development of colonic inflammation to dysplasia

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and cancer, accompanied by an increase of antiangiogenic factor vitamin D receptor (VDR) ». Authors need to mention that this study has been done on rats (moreover, the use of rats instead of mice in CRC models is discussable). - p.22 : « It encompasses a system of histopathological change from simple liver steatosis to cirrhosis or fibrosis, and NAFLD might be caused by intestinal dysbiosis, which increases intestinal permeability to bacterial products and harmful substances. » Dysbiosis might participate to NAFLD, but the authors of reference 107 never assumed that dysbiosis is the cause. - p.28 : « Atherosclerosis is caused by bacterial translocation from the oro-gastrointestinal tract to circulation ». Authors cannot make this statement. First atherosclerosis is multifactorial and secondly, the reference 155 never reported this information. I would suggest to authors to revise the writting of their paper according to the « Radiation-induced enteritis » (p.11) paragraph which has been well written. A proper definition of the term « probiotic » could be appreciated in the introduction section. The use of the expression « a kind of » to refer to a certain type of probiotics or strains does not mean what authors want to say and is not appropriated in a scientific paper. All bacterial names are supposed to be in italic. p.7 « Furthermore, the production of short-chain fatty acids (SCFAs) by intestinal mucosal cells reduces the intestinal pH and plays an important role in maintaining intestinal biological barrier function[5]. » This statement is partially wrong. SCFA are not produced by intestinal cells but by bacterial fermentation only. p.11 : « CDAD » has to be defined. p.16 : « DAI » has to be defined. p.21 : « The reason for the two different results may be that the administration time of VSL#3 was after the onset of inflammation and dysbiosis in the second study ». What does this conclusion mean in regard of the use of VSL3 in CRC patients? Authors should discuss more this conclusion. p.31 : « Apart from this, we also demonstrated that VSL#3 had a benefit on obesity and diabetes, allergic diseases, nervous systemic diseases, AS, bone diseases and female reproductive systemic diseases. » Authors did not

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demonstrated all these potential effects, but reported and participated to it. In their manuscript and Tables, authors should talk about probiotic intake in terms of CFU per day when possible, rather than volumes or masses. Are Figure 2 and «3 original figures made by authors ? A recent publication by Razafindralambo H et al. (Probiotics Antimicrob Proteins. 2019) showed variability in the probiotic formulation VSL#3 which could impact effects of the product. Do authors can comment this work ? Authors should not only discuss the « side effects related to VSL3 » (p.30) but also discuss the limits of this formulation in their review. The conclusion is a bit long and should fit into one paragraph. Some informations in the Conclusion could move to Introduction section. The language and grammar is not accurate all along the manuscript. The language requires a deep revision. A strong review of the English is required before publication of the review.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

[ ] The same title

[ ] Duplicate publication

[ ] Plagiarism

[Y] No

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Reviewer's code: 00503345
Position: Editorial Board
Academic degree: PhD
Professional title: Professor
Reviewer's Country/Territory: Canada
Author's Country/Territory: China
Manuscript submission date: 2019-12-30
Reviewer chosen by: Ying Dou
Reviewer accepted review: 2020-02-05 20:40
Reviewer performed review: 2020-02-11 23:15
Review time: 6 Days and 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[Y] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

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SPECIFIC COMMENTS TO AUTHORS

The manuscript is a systematic review of the literature on the therapeutic use of VSL#3, a probiotic mixture of bacterial strains, for treatment of various chronic diseases. Many studies have reported that VSL#3 can decrease the severity of chronic diseases, including but not limited to those of the gastrointestinal tract. The mechanisms of action of VSL#3 include the synthesis of small molecules and reduced colonization of the gastrointestinal tract by armful bacteria, which have beneficial effects on the function of the intestinal barrier and of gut immune cells.

General comment: This is an interesting review. In its present form, the manuscript requires substantial editorial correction of the English. Several sentences need to be revised throughout the manuscript. Instead of using the words "improve" or "ameliorate" at all sauces, it would be preferable to use other words (reduce, decrease, dampen) depending on the context. Treatment does not improve tissue damage or disease severity but can improve tissue functions or decrease (reduce, dampen) disease severity.

Specific comment:

The following sentence (underlined words) should be revised since the current literature suggests that PTPN2 has anti-inflammatory properties.

"Sometimes, the influence of VSL#3 on tight junction protein is achieved by increasing the protein level and enzymatic activity of T-cell protein tyrosine phosphatase (TCPTP), an inflammatory bowel disease (IBD) candidate gene PTPN2 protein product."

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The following sentences should be revised/rewrote:

-The stimulation effect required the temporary colonization of high-dose VSL#3 in the intestinal lumen[26].

However, VSL#3 (105 organisms/ml) did not change the immature phenotype and costimulatory molecules expression of DC, and high-dose VSL#3 (107 organisms/ml)…

At the earliest stage of DC antigen presentation, VSL#3 potentially induced IL-10 by DC from blood and intestinal tissue[31].

Additionally, a placebo-controlled study showed that VSL#3 expressed an anti-inflammatory effect…

One study of rats demonstrated that VSL#3 was effective at high concentrations (1.2 × 1010 bacteria) at enhancing acetic acid-induced gastric ulcer healing by stimulating the production of angiogenesis-promoting growth factors…

The up-regulation of the innate immune response against invasive microbiota was the main mechanism underlying the therapeutic effect of VSL#3 in patients with enteritis submitted to radiotherapy[40].

It is possible to treat IBD through a variety of the mechanisms mentioned above, such as by altering

…. which accelerated the recovery of colitis in Muc2 mucin-deficient mice[15].

Besides, a significant reduction of iNOS scores in the VSL#3 group suggested the ameliorative inflammatory status of the disease, and the trial had limitations due to a small sample size and a short therapeutic time[94].

However, the trial had such a small number of patients enrolled that it could not clarify the conclusion completely.

Thus, VSL#3 can correct glucose intolerance and obesity in Lepob/ob mice, and significantly increased proopiomelanocortin (POMC) levels and decreased neuropeptide Y (NpY) and agouti-related protein (AgRP) levels (were observed) in the hypothalamus

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of VSL#3-treated mice.

Moreover, Th2-secreted cytokines IL-5 and IL-13 reduced and Treg/Th1 cytokines IL-10 and IFN-γ increased, and VSL#3 supplementation could induce TGF-β, which reduced the Th2 inflammation through inducing or maintaining regulatory T cells expressing FOXP3[148,149].

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