

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The role of Probiotics in colorectal cancer patients: A systematic review protocol of randomized controlled trial studies
<b>AUTHORS</b>	Dikeocha, Ifeoma; Al-kabsi, Abdelkodose; Hussin, Salasawati; Alshawsh, Mohammed

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Zhou, X Zhejiang University
<b>REVIEW RETURNED</b>	21-Mar-2020

<b>GENERAL COMMENTS</b>	<p>The authors declared that "we found out that most of the systematic reviews which have been done were not entirely specific to colorectal cancer, and those that are specific to probiotics and colorectal cancer patients focus on one outcome either on postoperative complications, surgical site infection, diarrheaa from chemotherapy. We see this as a limitation of these studies, hence we intend to study more than one outcome in order to get a wholisitc idea of how probiotics administration affect colorectal cancer patients who are recieving different types of treatment on different levels", then my worry comes:The bigger the focused topic is, the harder the conclusion to make.</p>
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<b>REVIEWER</b>	Grégoire Wieërs Clinique Saint Pierre Ottignies, Belgium I receive research grants from Metagenics
<b>REVIEW RETURNED</b>	15-Apr-2020

<b>GENERAL COMMENTS</b>	<p>Dear authors,</p> <p>The sujet you propose is very interesting, and the method could be appropriate. It is disappointing that there is neighter results nor meta-analysis in this article which is limited to the description of the method.</p> <p>The text suffers from multiple naming errors and typos. The definition of the pathologies you want to review remains unclear as you mention colic but also rectal cancers which a two distinct diseases. As well you do not mention the concept of pathobiont which is interesting in this context.</p>
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<b>REVIEWER</b>	Carlo Genovese Department of Biomedical and Biotechnological Sciences - University of Catania - Italy
<b>REVIEW RETURNED</b>	25-Apr-2020

<b>GENERAL COMMENTS</b>	<p>The Authors investigated the role of probiotics in colorectal cancer patients (systematic review). The work is clearly written, the different parts are well organized and the topic has been discussed in a comprehensive manner. However, the Authors provide too old references, while there are many recent paper on the same topic:</p> <ul style="list-style-type: none"> <li>- Brasiel P.G.A. et al. 2020. Preclinical Evidence of Probiotics in Colorectal Carcinogenesis: A Systematic Review. Digestive Diseases and Sciences, 1-14.</li> <li>- Cruz B. et al. 2020. Preclinical and clinical relevance of probiotics and synbiotics in colorectal carcinogenesis: a systematic review. Nutrition Reviews.</li> <li>- Sivamaruthi B.S. et al. 2020. The Role of Probiotics in Colorectal Cancer Management. Evidence-Based Complementary and Alternative Medicine, 2020.</li> <li>- Vivarelli S. et al. 2019. Benefits of using probiotics as adjuvants in anticancer therapy. World Academy of Sciences Journal, 1(3), 125-135.</li> <li>- Eslami M. et al. 2019. Importance of probiotics in the prevention and treatment of colorectal cancer. Journal of cellular physiology, 234(10), 17127-17143.</li> </ul>
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### VERSION 1 – AUTHOR RESPONSE

#### REVIEWER 1

REPLY- Thank you for your feedback and comment

We believe that making a conclusion in our systematic review will not be a hassle As we will asses several outcomes, these outcomes will be categorized and discussed based on if they are primary or secondary outcomes. Our systematic review is unique and different from previously published reviews in which we intend to include only randomized clinical trial (RCT) studies and asses the effects of the administration of various types of probiotics on colorectal cancer patients. As you know RCT studies considered one of the highest levels in evidence-based medicine. This has been explained further in the revised manuscript (page 4).

#### REVIEWER 2

REPLY- Initial screening of the relevant RCT studies showed that most of the outcomes of the included studies are not homogenous and cannot be pooled together, therefore meta-analysis most likely will not be carried out. Instead, a qualitative analysis will be performed to synthesize the studies included in the systematic review as well as a critical appraisal of the outcomes will be considered for all studies. However, after we complete the data extraction of all included studies if we find out that any of the outcomes is homogenous across some of the studies, then a meta-analysis of those outcomes will be carried out.

This also has been elaborated more in the revised manuscript page 7.

REPLY- Thank you for the comments and corrections.

All typo mistakes have been corrected.

This systematic review focuses on patients who were diagnosed with colorectal cancer which refers to cancer that starts at the colon and spread to the rectum, therefore the search syntax includes both

colon cancer and rectal cancer as well as colorectal cancer to ensure that all relevant studies were retrieved.

The concept of pathobionts has been discussed (page 3) as the probiotics also inhibit the activity of pathobionts such as *Clostridium difficile*, *Clostridium perfringens*, and *Klebsiella pneumoniae* which are potential pathogenic microorganisms and could also be symbiotic microorganisms under certain gut environment conditions.

#### REVIEWER 3

REPLY- Thank you for the comments. The suggested recent references have been added to the reference list (references No. 20, 21, 26, 27, and 28) and cited in the text (page 4).

#### REQUIRED AMENDMENTS

The name Abdelkodose Mohammed Al-kabsi is the correct one for this author, instead of Abdelkodose M. Al-kabis; a slight error was made when filling the name to the ScholarOne system. I have changed the email address to correct the name

ORCID for Abdelkodose Mohammed Al-kabsi is <https://orcid.org/0000-0003-0660-6049>

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Genovese, Carlo Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy
<b>REVIEW RETURNED</b>	14-May-2020
<b>GENERAL COMMENTS</b>	The Authors have fully implemented the corrections, I have no suggestions for further changes.