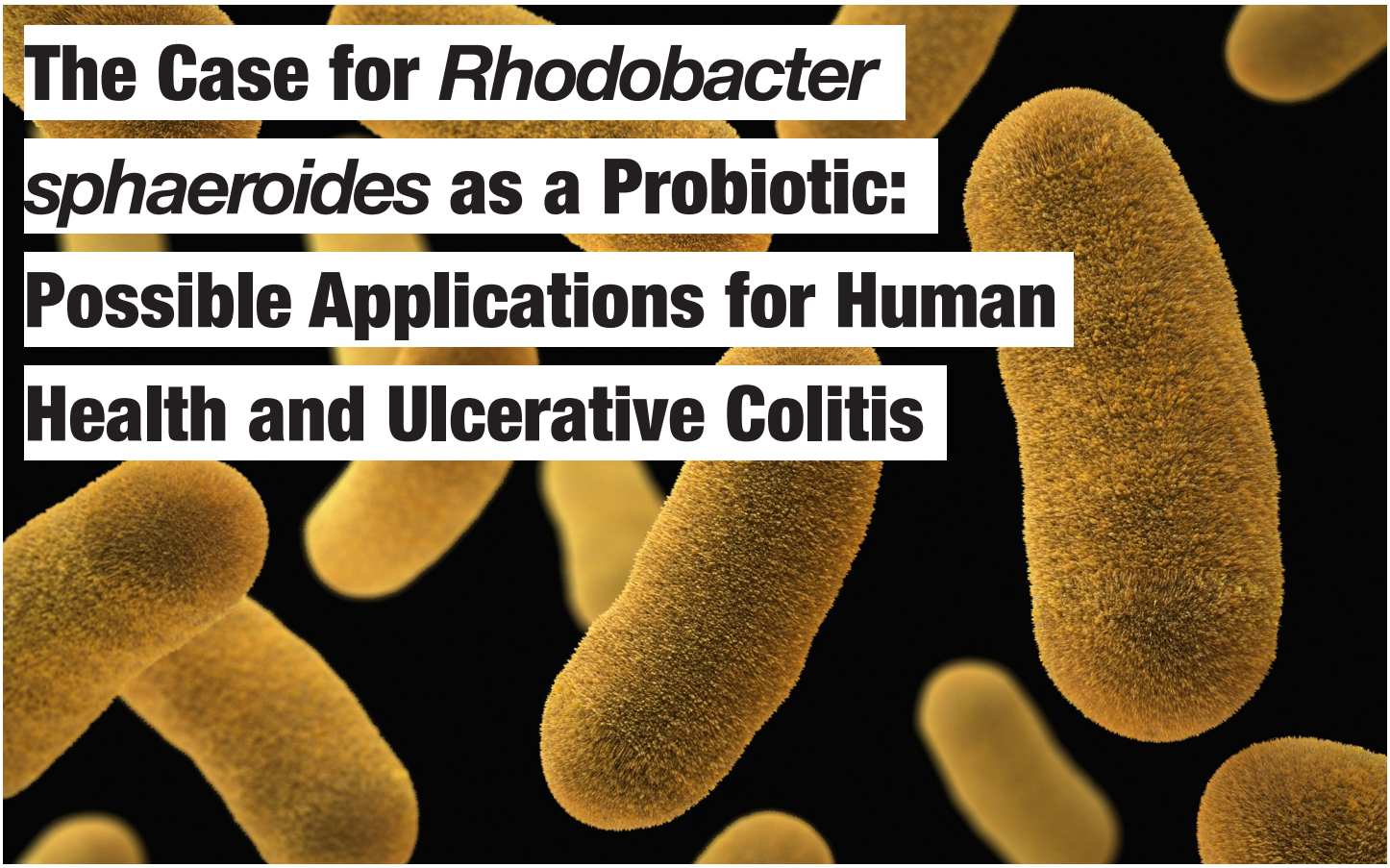
The Case for *Rhodobacter sphaeroides* as a Probiotic: Possible Applications for Human Health and Ulcerative Colitis



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Date Submitted: December 7, 2021
Date Accepted: January 19, 2022
Date Published: July 7, 2023

DOI: https://doi.org/10.18192/uojm.v12i1.6149

Keywords: *Rhodobacter sphaeroides, probiotic, ulcerative colitis*

ABSTRACT

In this short narrative review, the mechanisms through which the probiotic administration of non-pathogenic bacterium *Rhodobacter sphaeroides* could contribute to human health in general, and more specifically, the treatment of ulcerative colitis, are explored. This review is built around the concept that the mitochondrion is a key player in the pathogenesis of ulcerative colitis, and proposes ways that the probiotic could contribute to a more optimal environment for mitochondrial functioning, namely through reduction of inflammation and production of beneficial compounds like ubiquinone and bacteria-derived carotenoids. It concludes with the current state of the research involving *Rhodobacter sphaeroides* as a probiotic, identification of current gaps in the literature, and suggestions of possible future directions.

RÉSUMÉ

Cette brève analyse narrative explore les mécanismes par lesquels l'administration probiotique de la bactérie non pathogène *Rhodobacter sphaeroides* pourrait contribuer à la santé humaine en général et, plus spécifiquement, au traitement de la colite ulcéreuse. Cette étude s'articule autour du concept selon lequel la mitochondrie est un acteur clé dans la pathogenèse de la colite ulcéreuse et propose des moyens par lesquels le probiotique pourrait contribuer à un environnement plus optimal pour le fonctionnement des mitochondries, notamment par la réduction de l'inflammation et la production de composés bénéfiques tels que l'ubiquinone et les caroténoïdes dérivés de la bactérie. Il conclut sur l'état actuel de la recherche concernant *Rhodobacter sphaeroides* en tant que probiotique, sur l'identification des lacunes actuelles dans la littérature et sur des suggestions d'orientations possibles pour l'avenir.

Rhodobacter sphaeroides is a gram-negative, non-pathogenic bacterium with impressive metabolic flexibility. For instance, it is capable of both aerobic and anaerobic respiration and photosynthesis.[1] It is capable of producing many factors that contribute to human health, such as vitamin B12, short-chain fatty acids (SCFAs), and ubiquinone.[1–3] It also produces bacteriochlorophylls and carotenoids in photosynthetic conditions, though whether these compounds are still produced to an appreciable degree in lightless, anaerobic conditions is not well characterized, it is understood that the production is suboptimal.[1,3,4]

R. sphaeroides has been the subject of interest over the past 20 years in bioengineering processes involving mass synthesis of ubiquinone,[2,5,6] environmental detoxification,[7,8] and optimization of animal health in the context of aquaculture.[9–11] The viability of *R. sphaeroides* as a probiotic does appear to extend to mammalian health, as shown by Yang et al. (2020) in a murine model where *R. sphaeroides* administration significantly increased acetate production by the microbiota, increased abundance of predominant microbiota and α-diversity, and decreased creatinine and aspartate aminotransferase levels.[12] To echo the concluding remarks of Yang et al. (2020), some interesting next steps would be to determine the effects of *R. sphaeroides* administration on oxidation parameters in vivo, as the presence of the bacteria with the Caco-2 cell line has already been shown to mitigate H2O2-related oxidative damage via increased endogenous activity of superoxide dismutase, catalase, and glutathione peroxidase *in vitro*.[13] To further support the therapeutic potential of this bacterium, an *R. sphaeroides* extract named Lycogen™ already has demonstrated antioxidant and anti-inflammatory effects[14] with significant protective effects against dextran sodium sulfate (DSS)-induced colitis[15] and cisplatin-induced renal injury.[16] The extract itself is highly concentrated in the bacterium's carotenoids[14] and is not necessarily representative of the outcome of the administration of the whole bacterium, but it does demonstrate the potential strength of the effect of the bacterium's endogenously produced compounds. Although applications of *R. sphaeroides* probiotics could extend to general human health, its administration would present numerous advantages in the context of inflammatory bowel diseases like ulcerative colitis (UC), whose exact cause remains unknown but has multifactorial pathogenesis involving a complex interaction between genetics and environment. With mitochondria gaining much recent attention as the centrepiece of the pathogenesis of ulcerative colitis (see Figure 1), this review will examine some mechanisms through which *R. sphaeroides* probiotic administration could be beneficial as a complementary treatment for this debilitating disease (see Figure 2) whose incidence and prevalence continue to increase globally.[17]

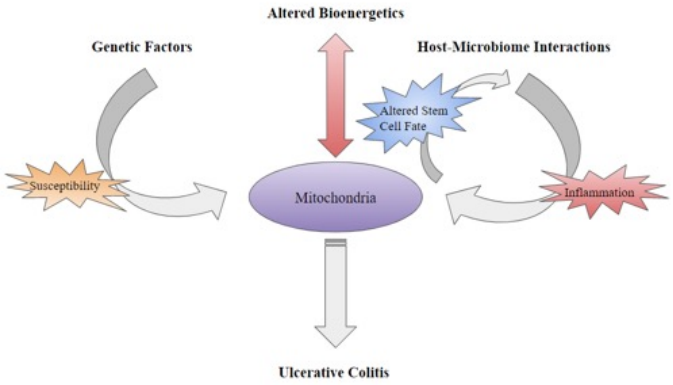

Figure 1. Simplification of the Mitochondrion as a Centrepiece in the Pathophysiology of Ulcerative Colitis. Mitochondria have been gaining attention as the key player in ulcerative colitis pathogenesis in recent years. Beyond the impaired mitochondrial function which contributes to UC's expression, reduced oxidative phosphorylation specifically has been shown to decrease the differentiation of intestinal stem cells into Goblet cells.[35,36] The loss of Goblet cells is followed by decreased production of protective mucus, which leaves the intestinal epithelium vulnerable to insult from intestinal microbiota, thus generating a vicious cycle. On the left-hand side, there are genetic factors which are also important drivers of the disease expression,[62–65] many of which affect the mitochondria directly or through inflammatory processes. Relative overexpression of some mitochondrial proteins through gene polymorphisms even rescue the UC phenotype in mouse models,[62] but further discussion of genetic factors is outside the scope of this review.

MECHANISMS THROUGH WHICH *R. SPHAEROIDES* ADMINISTRATION COULD ALLEVIATE INAPPROPRIATE HOST-MICROBIOTA INTERACTIONS

It is unclear whether the dysbiosis associated with UC is a result of the pathology or a causative agent. When developing treatments, however, it would be best to work with the principle that dysbiosis is a vicious cycle since mechanistically, dysbiosis causes intestinal damage and the damaged environment seems to encourage the growth of pathogenic and undesirable bacteria. The dysbiosis associated with UC is generally described as a decrease of abundance in some beneficial butyrate-producing bacteria, decreased overall diversity, and increased prevalence

of pathogenic bacteria such as *Campylobacter spp.* and *Escherichia coli*.[18–20] Considering this, it is natural that an interest in performing studies examining the effect of probiotics on UC has been generated in the past. Results are rather mixed in this regard; on one hand, a large meta-analysis has found that probiotic administration has beneficial effects on clinical remission rates of active UC,[21] while other studies demonstrate that such administration carries the risk of intestinal side effects like diarrhea, and even increased disease activity.[22] *R. sphaeroides* is particularly interesting in the context of UC, where both dysbiosis and inflammation are contributing factors. Beyond simply promoting a beneficial intestinal environment and producing short-chain fatty acids (SCFA) like many probiotics, *R. sphaeroides*, a gram-negative bacterium, releases lipopolysaccharide (LPS). However, in contrast to the intensely pro-inflammatory hexaceylated LPS (like in the case of *E. coli*), *R. sphaeroides*' LPS is pentacylated, which antagonizes the Toll-like receptor 4 (Tlr4).[23,24] It has been found that 88% of UC patients in a particular study demonstrated significant endotoxemia.[25] In addition, the role of LPS in UC is rather well characterized as a contributing factor by promoting chronic inflammation.[26–28]

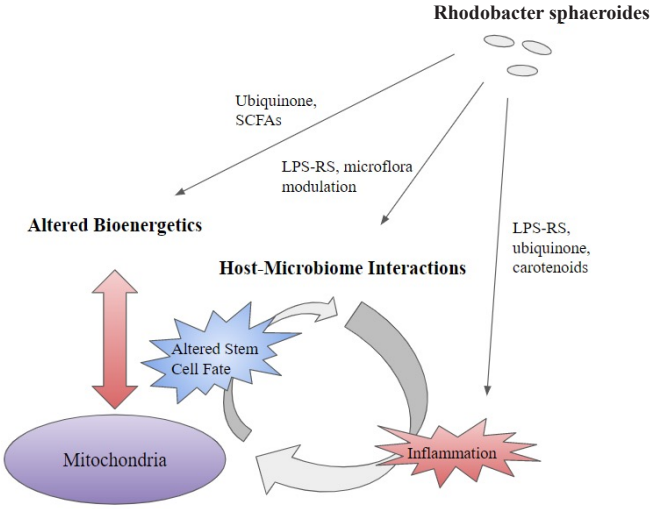

Figure 2. Simplified Rendition of *Rhodobacter sphaeroides*' Proposed Actions on Mitochondria in Ulcerative Colitis. Probiotic administration of *R. sphaeroides* is proposed to improve bioenergetics directly through production of ubiquinone and short chain fatty acids and indirectly through reduction of inflammation, improve dysbiosis by modulating intestinal microbiota, and alleviate inflammation by the antagonism of Tlr4 and through the antioxidant and anti-inflammatory effects of ubiquinone and *R. sphaeroides*' carotenoids.

Accordingly, recent studies examining the effects of Tlr4 antagonism have shown promising results in UC models.[29] Through *R. sphaeroides* administration, dysbiosis could be alleviated as suggested by data that shows its capacity to modulate microbiota to a certain extent in a murine model.[12] Furthermore, chronic inflammation could be decreased due to *R. sphaeroides*' Tlr4-antagonizing LPS. Tlr4 activation is also an important subject of discussion to relate intestinal microbiota to the mitochondria in UC.

MECHANISMS THROUGH WHICH *R. SPHAEROIDES* ADMINISTRATION COULD ALLEVIATE ALTERED BIOENERGETICS

Ulcerative colitis was classically theorized to be an energy deficiency disease. This idea was supported by data demonstrating the intestinal epithelium's decreased ATP, butyrate utilization, and fatty acid oxidation.[30–33] It wasn't until research linked the relative usage of oxidative phosphorylation to stem cell fate that a mechanism explaining the connection between altered bioenergetics and disease characteristics could be described.[34] Sünderhauf et al. (2020-2021) performed studies that may prove to be pivotal, which demonstrated that decreased ability of intestinal stem cells to perform oxidative phosphorylation impacted their ability to differentiate into Goblet cells,[35,36] the cells that produce the protective mucus lining of the intestine.[37] Pairing this information with the data that shows altered oxidative phosphorylation and electron transport chain function in UC,[38–41] we have an explanation for the observed reduced Goblet cell count and protective mucus production,[37,42,43] which seems to occur early on in the pathogenesis of UC.[43] The impaired barrier function naturally facilitates the inappropriate host-microbiota interactions, which provoke inflammatory responses.[44] Moreover, these responses contribute to mitochondrial dysfunction, which establishes a vicious cycle. Tlr4 activation is one relevant pathway which contributes to mitochondrial dysfunction and could be alleviated by the presence of *R. sphaeroides*. Building on what was previously discussed, Tlr4 activation was shown to unfavourably alter mitochondrial dynamics in both myocytes and macrophages[45,46] and cause direct mitochondrial damage.[47] In the context of intestinal stem cells, Tlr4 activation shown to reduce proliferation and increase rates of apoptosis.[48]

Beyond antagonism of Tlr4, *R. sphaeroides* could alleviate the ROS-induced mitochondrial stress through its demonstrated antioxidant effects. The ubiquinone, produced by the bacteria, is a powerful antioxidant and electron

acceptor in the electron transport chain. Consequently, it would contribute to both the mitigation of ROS damage and the promotion of electron transport chain function, thus promoting appropriate bioenergetics. Ubiquinone has shown to alleviate disease expression in animal models,[49–54] reduce apoptosis through mitochondrial mechanisms,[55,56] and in the context of clinical trials for UC, decrease disease expression and increase patient quality of life.[57] Although studies assessing the production of ubiquinone by *R. sphaeroides* in an intestinal environment are lacking, it was found that administration of *R. sphaeroides* in bovine significantly increased the ubiquinone content of the milk by over 70%,[58] thus suggesting that production in a mammalian intestinal environment is not only possible but of significant yield.

Besides this, *R. sphaeroides*' carotenoid content, as exploited in the extract Lycogen™, could also contribute to the bacteria's antioxidant and anti-inflammatory effect, which is supported by data showing protection against DSS-induced colitis, as previously mentioned.[15]

GAPS IN LITERATURE AND PROPOSED FUTURE DIRECTIONS

R. sphaeroides has already been exploited in different ways for its separate components (LPS-RS, carotenoids, and ubiquinone), yet surprisingly, very few pre-clinical studies have been conducted to verify its probiotic effects. The only mammalian studies performed to date are one murine study, which explored the effects of its administration on microbiota and general health parameters like weight, creatinine and aspartate aminotransferase.[12] Furthermore, one bovine study was conducted, which did not study any health parameters but did report increased ubiquinone content in milk.[58] Therefore, more pre-clinical studies examining the effects of *R. sphaeroides* probiotic administration on health parameters relating to UC (disease expression, cytokine release, mitochondrial function, intestinal microbiota, Goblet cell count, and mucus barrier integrity) are warranted.

The viability of supplemented *R. sphaeroides* in humans should be assessed. There is an important weakness to the conclusion that the bacteria remain viable after administration, if this conclusion is based on the fact that there is a significant change in biochemical or clinical parameters alone. Since the bacterium contains bioactive membrane-bound components and beneficial metabolites, it could be argued that in the two mammalian studies,[12,58] the observed effects could still happen following bacterial death and release of its contents in the GI tract, especially considering the relatively high and frequent dosing used. However, for a counterargument , it should be noted that *R. sphaeroides* viability has been tested in simulated human gastric and intestinal conditions. In the harshest gastric condition of pH = 2.0 for 180 minutes, *R. sphaeroides* demonstrated over 50% retention of viable colony forming units.[59] In the two small intestine simulations that were assessed, *R. sphaeroides* colony-forming units increased significantly in the absence of bile salts and did not change significantly in presence of 0.3% bile salts.[59] Therefore, the current evidence suggests that *R. sphaeroides* is able to survive the human GI tract in non-competitive conditions. It is the capacity to colonize that remains untested in mammalian GI tracts and is thus a gap in the literature. This could be addressed in murine models by adding a washout period following probiotic administration, followed by a characterization of the microbiota or screening for the presence of the bacteria, for instance.

As *R. sphaeroides* is the subject of much bioengineering research to optimize a specific function (carotenoid production, ubiquinone production, etc.), the question of which strain to use in pre-clinical studies does, in fact, arise. Hence, research examining the viability of different strains in the intestinal environment, and their respective effects on valued health parameters, could also be an avenue of further research.

There is also a need for more research examining the effects of administration on intestinal microbiota composition. As reported by Yang et al. (2020), increased α-diversity and increased abundance of anaerobic bacteria could be a beneficial outcome,[12] though, in UC, it is less clear. For instance, even if lower diversity and lower levels of major anaerobic have been found in UC,[60] an increase in total bacterial content in active inflammatory bowel disease compared to healthy controls has also been reported.[61] This highlights the importance of determining which bacteria benefit from the administration of *R. sphaeroides*, particularly the bacteria that are generally found to be less abundant in UC patients and those that may be pathogenic. Considering this, it could be that the timing of probiotic treatment is an important factor in its own right. For example, perhaps probiotic treatment with *R. sphaeroides* could be better suited for a prophylactic role to maintain periods of remission, as many of its proposed mechanisms are protective, though there is no way to know without further research.

CONCLUSION

Rhodobacter sphaeroides is a non-pathogenic bacterium that could offer benefits to human health as a member of the intestinal microbiota. There are several mechanisms through which these benefits could be conferred, all of which could be of particular interest in the context of inflammatory bowel diseases like ulcerative colitis. Although the proposed mechanisms are theoretically effective for many aspects of ulcerative colitis, some important studies examining the strength of their impact and thus therapeutic potential, remain unconducted. Furthermore, there is a need for studies evaluating the viability and effects of administration of the bacteria in humans. In conclusion, *Rhodobacter sphaeroides* is a strong candidate for future probiotic research, and could be envisioned as a possible complementary treatment for inflammatory bowel disease.

CONFLICTS OF INTEREST DISCLOSURE

The author declares no conflicts of interest.

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