

Technical Report

Significance of Berberine Hydrochloride in CanXida Remove (Formula RMV)

In CanXida Remove (Formula RMV), Berberine HCl plays a crucial role in inhibiting Candida albicans and supporting gut health through its antimicrobial, anti-inflammatory, antioxidant bioactive components and properties.

Contents

Executive Summary	1
1. Introduction	2
2. Components of Berberine HCl	2
3. Functional Properties of Berberine hydrochloride:	3
3.1. Antimicrobial:	3
3.2. Anti-inflammatory:.....	4
3.3. Antioxidant:.....	4
3.4. Cholesterol-lowering:.....	4
3.5. Prebiotic-like effects:	4
4. Bioactive Compounds.....	4
5. Health Benefits of Berberine Hydrochloride:.....	5
5.1. Modulation of gut microbiota:	5
5.2. Improvement of gut barrier function:.....	5
5.3. Regulation of gut motility:	5
5.4. Gastrointestinal effects:.....	5
5.5. Neuroprotective:.....	5
5.6. Improved Women Health	7
6. Biosafety Profile of Berberine HCl	7
7. Effective Targets of Berberine HCl.....	8
8. Significance of Berberine HCl Extract in CanXida Remove	9
References.....	11

Executive Summary

Berberine hydrochloride, a potent isoquinoline alkaloid derived from various Chinese herbs, offers a multitude of pharmacological actions, including antidiabetic, anti-inflammatory, and antimicrobial effects. Despite its beneficial properties, its poor water solubility limits its effectiveness. Berberine hydrochloride's functional properties, such as antimicrobial, anti-inflammatory, antioxidant, and cholesterol-lowering effects, make it a valuable compound in traditional and modern medicine. It has shown promising results in modulating gut microbiota, improving gut barrier function, regulating gut motility, and exerting neuroprotective effects. Additionally, it has potential benefits for women's health, including menstrual regulation, PCOS management, and menopausal symptom relief.

While generally considered safe, it can have side effects, particularly with excessive use. It may also interact with certain medications and should be used with caution in individuals with specific medical conditions. Overall, berberine hydrochloride's multifaceted properties and bioactive compounds make it a valuable component in healthcare, particularly in formulations targeting gut health and candida removal *.

** These statements have not been evaluated by Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.*

1. Introduction

Berberine hydrochloride is an isoquinoline alkaloid isolated from several Chinese herbs. It possesses a variety of pharmacological actions, including antidiabetic, antilipidemic, anti-atherosclerotic, neuroprotective, and polycystic ovary syndrome-improving properties. Additionally, it is known for its antibacterial, antifungal, and anti-inflammatory effects, making it a popular gastrointestinal remedy in China (Tan et al., 2011).

Despite its promising effects, berberine hydrochloride has poor water solubility, limiting its absorption and effectiveness. This challenge has spurred interest in developing novel drug delivery systems, such as polymeric nanoparticles, nanocapsules, liposomes, solid lipid nanoparticles, and nanoemulsions, to improve its solubility and bioavailability (Tan et al., 2011).

2. Components of Berberine HCl

Berberine hydrochloride (HCl) is made of two components:

- **Berberine**
- **Hydrochloric acid (HCl)**

2.1 Berberine

Since the beginning of time, berberine has been utilized in both traditional Chinese medicine and Ayurvedic medicine (Funk et al., 2018).

It is a nonbasic and quaternary benzyloisoquinoline alkaloid with a complex chemical structure. This compound is widely recognized for its significant role in the creation of various bioactive derivatives. Through the process of condensation, modification, and substitution of functional groups, scientists are able to strategically design new drugs that are both selective and potent (Neag et al., 2018).

Berberine is a compound that plays a significant role in pharmacology and medicinal chemistry.

Source:

Berberine has been detected in various plant families (Arayne et al., 2007) i.e.

- *Annonaceae*
- *Berberidaceae*
- *Menispermaceae*
- *Papaveraceae*

- *Ranunculaceae*
- *Rutaceae*

2.2 Hydrochloric Acid (HCl)

Hydrochloride is an acid that possesses a remarkably low pH level and is classified as an acid. Produced by the stomach, this substance plays a crucial role in supporting immunity, facilitating nutrition absorption, and aiding in digestion. It is widely recognized as a natural disinfectant and digestive agent within the human body. A healthy digestive system produces approximately three to four quarts of hydrochloric acid on a daily basis. The acidity of the stomach is a natural and vital component of our digestive system (Block & Rowan, 2020; Dionisio et al., 2018; Ravindran & Reza Abdollahi, 2021).

Source:

Naturally produced by parietal cells in the gastric glands of the stomach and can also be made synthetically (Dionisio et al., 2018)

Roles:

- **For Better bioavailability:** HCl in berberine serves as a salt-forming agent, increasing the compound's solubility in

water and aiding in its absorption in the gastrointestinal tract. This improved solubility is particularly important for oral medications, as it enhances the bioavailability of berberine, allowing for better absorption and effectiveness in the body*.

- **For Better stability:** Additionally, the HCl salt form can enhance the stability of berberine in formulations, prolonging its shelf life*.

3. Functional Properties of Berberine hydrochloride:

Berberine hydrochloride has been studied for its various functional properties, particularly in traditional medicine and more recently in modern research. Here are some of its key functional properties:

3.1. Antimicrobial:

Berberine hydrochloride exhibits broad-spectrum antimicrobial activity against bacteria, viruses, fungi, and protozoa. It can inhibit the growth of various pathogens, making it potentially useful in treating infections (Sahibzada et al., 2018).

* These statements have not been evaluated by Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

3.2. Anti-inflammatory:

Berberine hydrochloride has been shown to reduce inflammation by inhibiting inflammatory pathways and cytokines. This property may be beneficial in treating inflammatory conditions (Chen et al., 2014; Sahibzada et al., 2018).

3.3. Antioxidant:

Berberine hydrochloride has antioxidant effects, which means it can neutralize harmful free radicals in the body. This property is important for reducing oxidative stress and protecting cells from damage (Ezabadi et al., 2019).

3.4. Cholesterol-lowering:

Some studies suggest that berberine hydrochloride can help lower cholesterol levels by inhibiting the production of cholesterol in the liver and increasing the clearance of cholesterol from the blood (Chen et al., 2014).

3.5. Prebiotic-like effects:

Berberine hydrochloride has been shown to promote the growth of beneficial bacteria such as *Akkermansia muciniphila*, which is

associated with improved metabolic health (Dong et al., 2021).

4. Bioactive Compounds

Berberine, a bioactive compound found in various plants, is known to produce several metabolites with potential health benefits. Some of the bioactive compounds produced by berberine include (Belwal et al., 2020; X. Guo et al., 2023):

- **Thalifendine:** This compound is a metabolite of berberine and has been studied for its potential anti-inflammatory properties.
- **Columbamine:** Another metabolite of berberine, columbamine, has been investigated for its antioxidant and anti-inflammatory effects.
- **Jatrorrhizine:** Jatrorrhizine is a berberine metabolite that has shown potential antidiabetic and anti-inflammatory properties in studies.
- **Palmatine:** Palmatine is a related alkaloid found in some plants along with berberine. It has been studied for its antimicrobial, anti-inflammatory, and antioxidant properties.

- **Berberrubine:** This metabolite of berberine has been studied for its potential antidiabetic and anti-inflammatory effects.

These metabolites, along with berberine itself, contribute to the overall pharmacological profile of berberine-containing supplementation*.

5. Health Benefits of Berberine Hydrochloride:

Berberine hydrochloride, has been studied extensively for its potential health benefits. Some of the key benefits include:

5.1. Modulation of gut microbiota:

Berberine hydrochloride has been shown to modulate the composition of the gut microbiota, promoting the growth of beneficial bacteria while inhibiting the growth of harmful bacteria. This can help improve overall gut health and function (Habtemariam, 2020).

5.2. Improvement of gut barrier function:

Berberine hydrochloride may help strengthen the gut barrier (Cao et al., 2022), which can

become compromised in conditions such as leaky gut syndrome. By improving gut barrier function, berberine hydrochloride may help prevent the entry of harmful substances into the bloodstream.

5.3. Regulation of gut motility:

Some studies suggest that berberine hydrochloride may help regulate gut motility, which can be beneficial for individuals with conditions such as irritable bowel syndrome (IBS) (Chen et al., 2014; Yang et al., 2023).

5.4. Gastrointestinal effects:

Berberine hydrochloride has been studied for its effects on the gastrointestinal tract, including its ability to inhibit diarrhea-causing pathogens and reduce intestinal inflammation (Chen et al., 2014).

5.5. Neuroprotective:

There is emerging evidence suggesting that berberine may have neuroprotective effects, potentially helping to protect against neurodegenerative diseases like Alzheimer's (Dan et al., 2023).

* These statements have not been evaluated by Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

Table 1: List of specific clinical trials utilizing berberine hydrochloride as an active component for therapeutic or preventive purposes. Source: clinicaltrials.gov

Clinical trial ID	Health Condition	Status
NCT04479202	<ul style="list-style-type: none"> • Berberine • COVID-19 	<i>Completed</i>
NCT03333265	Colorectal Adenomas	<i>Completed</i>
NCT04434365	<ul style="list-style-type: none"> • Percutaneous Coronary Intervention • Stable Coronary Artery Disease 	<i>Completed</i>
NCT02365480	Ulcerative Colitis	<i>Completed</i>
NCT02633930	<ul style="list-style-type: none"> • Dyspepsia • Gastritis • Peptic Ulcer 	<i>Completed</i>
NCT02296021	<ul style="list-style-type: none"> • Dyspepsia • Gastritis • Peptic Ulcer 	<i>Completed</i>
NCT03420976	<ul style="list-style-type: none"> • Small Intestinal Bacterial Overgrowth 	<i>Withdrawn</i>
NCT04697186	<ul style="list-style-type: none"> • Chronic Gastritis • Dyspepsia • Helicobacter Pylori Infection 	<i>Completed</i>

5.6. Improved Women Health

Berberine, a compound found in several plants, has been studied for its potential benefits in women's health. Some of its notable roles include:

- **Menstrual Health:** Berberine may help regulate menstrual cycles and alleviate symptoms of premenstrual syndrome (PMS), such as mood swings and cramping (Caliceti et al., 2015; Di Pierro et al., 2023).
- **Polycystic Ovary Syndrome (PCOS):** Berberine has shown promise in managing PCOS by improving insulin sensitivity, reducing testosterone levels, and aiding in weight management, all of which are beneficial for women with PCOS (Li et al., 2018).
- **Fertility:** Berberine may improve fertility in women by regulating menstrual cycles and improving ovulation, although more research is needed in this area (Di Pierro et al., 2023).
- **Menopause:** Berberine may help manage some symptoms of menopause, such as hot flashes and mood swings, although more research is needed to confirm its effectiveness (Caliceti et al., 2015).

- **Infections:** Berberine has antimicrobial properties that may help prevent or treat infections that can affect women, such as urinary tract infections (UTIs) and vaginal infections (Neag et al., 2018)

6. Biosafety Profile of Berberine HCl

Berberine hydrochloride, sourced from plants such as barberry and goldenseal, is of organic origin, which often indicates a potentially safer product. The extraction processes involved in isolating berberine from these plants are typically designed to be non-toxic, ensuring the safety of the final product. These extraction methods aim to retain the beneficial properties of berberine while eliminating any harmful substances that may be present in the raw plant material. As a result, berberine hydrochloride is generally considered safe for consumption when used appropriately*. However, like any compound, it can have side effects, particularly when consumed in excess.

The symptoms, such as arterial hypotension (low blood pressure), dyspnoea (difficulty breathing), flu-like symptoms, gastrointestinal discomfort, constipation, and

* These statements have not been evaluated by Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

cardiac damage, can occur with excessive use (“Berberine,” 2020; Caliceti et al., 2015).

Berberine is also not FDA-approved for treating conditions. Dietary supplements, including berberine, do not require FDA approval.

However, it is also approved and experimented to be used for therapeutic purposes by DRUDBANK under the accession ID DB04115

Furthermore, it is also important to note that berberine hydrochloride may interact with certain medications, particularly those metabolized by the CYP450 enzyme system, which could lead to adverse effects or reduced efficacy of these medications (Guo et al., 2011).

Additionally, individuals with specific medical conditions like liver disease, kidney disease, or cardiovascular disorders should be cautious when using berberine hydrochloride, as it could worsen these conditions*.

7. Effective Targets of Berberine HCl

Berberine has demonstrated antimicrobial effects against various pathogens relevant to gut health, including (Chen et al., 2014; Dash et al., 2020; Xie et al., 2020; C. Zhang et al., 2022; L. Zhang et al., 2020):

- **Salmonella:** Salmonella can cause foodborne illnesses, leading to symptoms like diarrhea, fever, and abdominal cramps.
- **Clostridium:** Certain species, like *C. difficile*, can cause gut infections, especially after antibiotic use, leading to severe diarrhea and other complications.
- **E. coli:** Certain pathogenic strains can cause intestinal infections, leading to diarrhea and abdominal pain.
- **Helicobacter:** *H. pylori* can infect the stomach lining, leading to gastritis and peptic ulcers, affecting gut health.
- **Candida:** Candida overgrowth can lead to infections like oral thrush and vaginal yeast infections, affecting gut flora balance.

* These statements have not been evaluated by Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

- ***Giardia***: *Giardia* infections in the gut cause symptoms such as diarrhea, abdominal cramps, and bloating.
- ***Entamoeba***: *Entamoeba histolytica* infections can cause amoebiasis, leading to symptoms like diarrhea and abdominal pain, affecting gut health.
- ***Staphylococcus***: It can cause food poisoning when ingested through contaminated food, leading to symptoms like nausea, vomiting, stomach cramps, and diarrhea.
- ***Streptococcus***: Certain pathogenic species can cause infections such as strep throat and pneumonia, potentially leading to serious health complications.
- ***Klebsiella***: Can cause infections, particularly in the lungs and urinary tract, which can be severe, especially in immunocompromised individuals.

7. Significance of Berberine HCl Extract in CanXida Remove

Berberine hydrochloride can play a crucial role in candida removal formulas due to its multifaceted properties.

Its potent antimicrobial action may target *Candida* species, especially *Candida albicans*,

inhibiting their growth and aiding in their elimination*.

The anti-inflammatory effects of berberine can further support this process by reducing inflammation caused by *Candida* overgrowth, which can help alleviate symptoms and promote healing*.

Additionally, berberine's ability to modulate the gut microbiota and improve gut barrier function can enhance its efficacy in candida removal and improve gut health*.

By creating a healthier gut environment, berberine may support the absorption of other drugs and nutrients in the formula, potentially leading to better bioavailability and overall effectiveness*.

Berberine's bioactive compounds, like thalifendine and columbamine, enhance candida removal formulas by complementing berberine's antimicrobial action. They can reduce inflammation and support gut health, aiding in *Candida albicans* inhibition. Additionally, berberine hydrochloride improves women's health by regulating menstrual cycles, managing PCOS symptoms, and potentially enhancing fertility

* These statements have not been evaluated by Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

and menopause management. This dual benefit makes berberine hydrochloride a valuable addition to candida removal formulas*.

Moreover, berberine's promotion of gut health may help restore microbial balance, which is often disrupted during candida overgrowth, further aiding in the elimination of Candida species*.

Berberine's bioactive compounds, like thalifendine and columbamine, enhance candida removal formulas by complementing berberine's antimicrobial action. They can reduce inflammation and support gut health, aiding in Candida albicans inhibition. Additionally, berberine hydrochloride

improves women's health by regulating menstrual cycles, managing PCOS symptoms, and potentially enhancing fertility and menopause management. This dual benefit makes berberine hydrochloride a valuable addition to candida removal formulas.

When combined with other antifungal ingredients, such as caprylic acid or oregano oil, berberine's effectiveness in combating Candida overgrowth may be enhanced*.

Overall, berberine hydrochloride's diverse functional properties make it a potentially valuable component in candida removal formulas, offering a holistic approach to managing candidiasis*.

* These statements have not been evaluated by Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

References

- Arayne, M., Sultana, N., of, S. B.-P. journal, & 2007, undefined. (2007). The berberis story: Berberis vulgaris in therapeutics. *Europepmc.OrgMS Arayne, N Sultana, SS BahadurPakistan Journal of Pharmaceutical Sciences*, 2007•*europemc.Org*.
<https://europemc.org/article/med/17337435>
- Belwal, T., Bisht, A., Devkota, H. P., Ullah, H., Khan, H., Pandey, A., Bhatt, I. D., & Echeverría, J. (2020). Phytopharmacology and Clinical Updates of Berberis Species Against Diabetes and Other Metabolic Diseases. *Frontiers in Pharmacology*, 11.
<https://doi.org/10.3389/FPHAR.2020.00041>
- Berberine. (2020). *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*.
<https://www.ncbi.nlm.nih.gov/books/NBK564659/>
- Block, M. S., & Rowan, B. G. (2020). Hypochlorous Acid: A Review. *Journal of Oral and Maxillofacial Surgery*, 78(9), 1461. <https://doi.org/10.1016/J.JOMS.2020.06.029>
- Caliceti, C., Rizzo, P., & Cicero, A. F. G. (2015). Potential Benefits of Berberine in the Management of Perimenopausal Syndrome. *Oxidative Medicine and Cellular Longevity*, 2015.
<https://doi.org/10.1155/2015/723093>
- Cao, J. W., Chen, M. Y., Xu, R., & Guo, M. Y. (2022). Therapeutic Mechanisms of Berberine to Improve the Intestinal Barrier Function via Modulating Gut Microbiota, TLR4/NF-κB/MTORC Pathway and Autophagy in Cats. *Frontiers in Microbiology*, 13.
<https://doi.org/10.3389/FMICB.2022.961885/FULL>
- Chen, C., Yu, Z., Li, Y., Fichna, J., & Storr, M. (2014). Effects of berberine in the gastrointestinal tract - a review of actions and therapeutic implications. *The American Journal of Chinese Medicine*, 42(5), 1053–1070. <https://doi.org/10.1142/S0192415X14500669>

- Dan, L., Hao, Y., Li, J., Wang, T., Zhao, W., Wang, H., Qiao, L., & Xie, P. (2023). Neuroprotective effects and possible mechanisms of berberine in animal models of Alzheimer's disease: a systematic review and meta-analysis. *Frontiers in Pharmacology*, *14*, 1287750. <https://doi.org/10.3389/FPHAR.2023.1287750/BIBTEX>
- Dash, S., Kumar, M., & Pareek, N. (2020). Enhanced antibacterial potential of berberine via synergism with chitosan nanoparticles. *Materials Today: Proceedings*, *31*, 640–645. <https://doi.org/10.1016/J.MATPR.2020.05.506>
- Di Pierro, F., Sultana, R., Eusaph, A. Z., Abrar, S., Bugti, M., Afridi, F., Farooq, U., Iqtadar, S., Ghauri, F., Makhduma, S., Nourin, S., Kanwal, A., Bano, A., Bugti, A. A., Mureed, S., Ghazal, A., Irshad, R., Recchia, M., Bertuccioli, A., ... Khan, A. (2023). Effect of Berberine Phytosome on reproductive, dermatologic, and metabolic characteristics in women with polycystic ovary syndrome: a controlled, randomized, multi-centric, open-label clinical trial. *Frontiers in Pharmacology*, *14*. <https://doi.org/10.3389/FPHAR.2023.1269605/FULL>
- Dionisio, K. L., Phillips, K., Price, P. S., Grulke, C. M., Williams, A., Biryol, D., Hong, T., & Isaacs, K. K. (2018). Data Descriptor: The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products. *Scientific Data*, *5*. <https://doi.org/10.1038/SDATA.2018.125>
- Dong, C., Yu, J., Yang, Y., Zhang, F., Su, W., Fan, Q., Wu, C., & Wu, S. (2021). Berberine, a potential prebiotic to indirectly promote Akkermansia growth through stimulating gut mucin secretion. *Biomedicine & Pharmacotherapy*, *139*, 111595. <https://doi.org/10.1016/J.BIOPHA.2021.111595>
- Ezabadi, A., Peeri, M., Azarbayjani, M. A., & Hosseini, S. A. (2019). The Effects of Resistance Training and Berberine Chloride Supplementation on Oxidative Stress Markers in the Cerebellum Tissue of Diazinon-Poisoned Rats. *Middle East Journal of Rehabilitation and Health Studies* 2019 6:3, 6(3), 92870. <https://doi.org/10.5812/MEJRH.92870>

- Funk, R. S., Singh, R. K., Winefield, R. D., Kandel, S. E., Ruisinger, J. F., Moriarty, P. M., & Backes, J. M. (2018). Variability in Potency Among Commercial Preparations of Berberine. *Journal of Dietary Supplements*, *15*(3), 343. <https://doi.org/10.1080/19390211.2017.1347227>
- Guo, X., Xiong, X., Zhao, L., Zhong, G., & Zhu, X. (2023). The anti-aging mechanism of Berberine associated with metabolic control. *Anti-Aging Pharmacology*, 305–327. <https://doi.org/10.1016/B978-0-12-823679-6.00020-5>
- Guo, Y., Pope, C., Cheng, X., Zhou, H., & Klaassen, C. D. (2011). Dose–response of berberine on hepatic cytochromes P450 mRNA expression and activities in mice. *Journal of Ethnopharmacology*, *138*(1), 111–118. <https://doi.org/10.1016/J.JEP.2011.08.058>
- Habtemariam, S. (2020). Berberine pharmacology and the gut microbiota: A hidden therapeutic link. *Pharmacological Research*, *155*, 104722. <https://doi.org/10.1016/J.PHRS.2020.104722>
- Li, M. F., Zhou, X. M., & Li, X. L. (2018). The Effect of Berberine on Polycystic Ovary Syndrome Patients with Insulin Resistance (PCOS-IR): A Meta-Analysis and Systematic Review. *Evidence-Based Complementary and Alternative Medicine*, 2018. <https://doi.org/10.1155/2018/2532935>
- Neag, M. A., Mocan, A., Echeverría, J., Pop, R. M., Bocsan, C. I., Crisan, G., & Buzoianu, A. D. (2018). Berberine: Botanical Occurrence, Traditional Uses, Extraction Methods, and Relevance in Cardiovascular, Metabolic, Hepatic, and Renal Disorders. *Frontiers in Pharmacology*, *9*(AUG), 557. <https://doi.org/10.3389/FPHAR.2018.00557>
- Ravindran, V., & Reza Abdollahi, M. (2021). Nutrition and Digestive Physiology of the Broiler Chick: State of the Art and Outlook. *Animals : An Open Access Journal from MDPI*, *11*(10). <https://doi.org/10.3390/ANI11102795>
- Sahibzada, M. U. K., Sadiq, A., Sfaidah, H., Khurram, M., Amin, M. U., Haseeb, A., & Kakar, M. (2018). RETRACTED ARTICLE: Berberine nanoparticles with enhanced in vitro

bioavailability: characterization and antimicrobial activity. *Drug Design, Development and Therapy*, 12, 303–312. <https://doi.org/10.2147/DDDT.S156123>

Xie, Y., Liu, X., & Zhou, P. (2020). In vitro Antifungal Effects of Berberine Against *Candida* spp. In Planktonic and Biofilm Conditions. *Drug Design, Development and Therapy*, 14, 87. <https://doi.org/10.2147/DDDT.S230857>

Yang, F., Gao, R., Luo, X., Liu, R., & Xiong, D. (2023). Berberine influences multiple diseases by modifying gut microbiota. *Frontiers in Nutrition*, 10, 1187718. <https://doi.org/10.3389/FNUT.2023.1187718/BIBTEX>

Zhang, C., Li, Z., Pan, Q., Fan, L., Pan, T., Zhu, F., Pan, Q., Shan, L., & Zhao, L. (2022). Berberine at sub-inhibitory concentration inhibits biofilm dispersal in *Staphylococcus aureus*. *Microbiology (Reading, England)*, 168(9). <https://doi.org/10.1099/MIC.0.001243>

Zhang, L., Wu, X., Yang, R., Chen, F., Liao, Y., Zhu, Z., Wu, Z., Sun, X., & Wang, L. (2020). Effects of Berberine on the Gastrointestinal Microbiota. *Frontiers in Cellular and Infection Microbiology*, 10. <https://doi.org/10.3389/FCIMB.2020.588517>