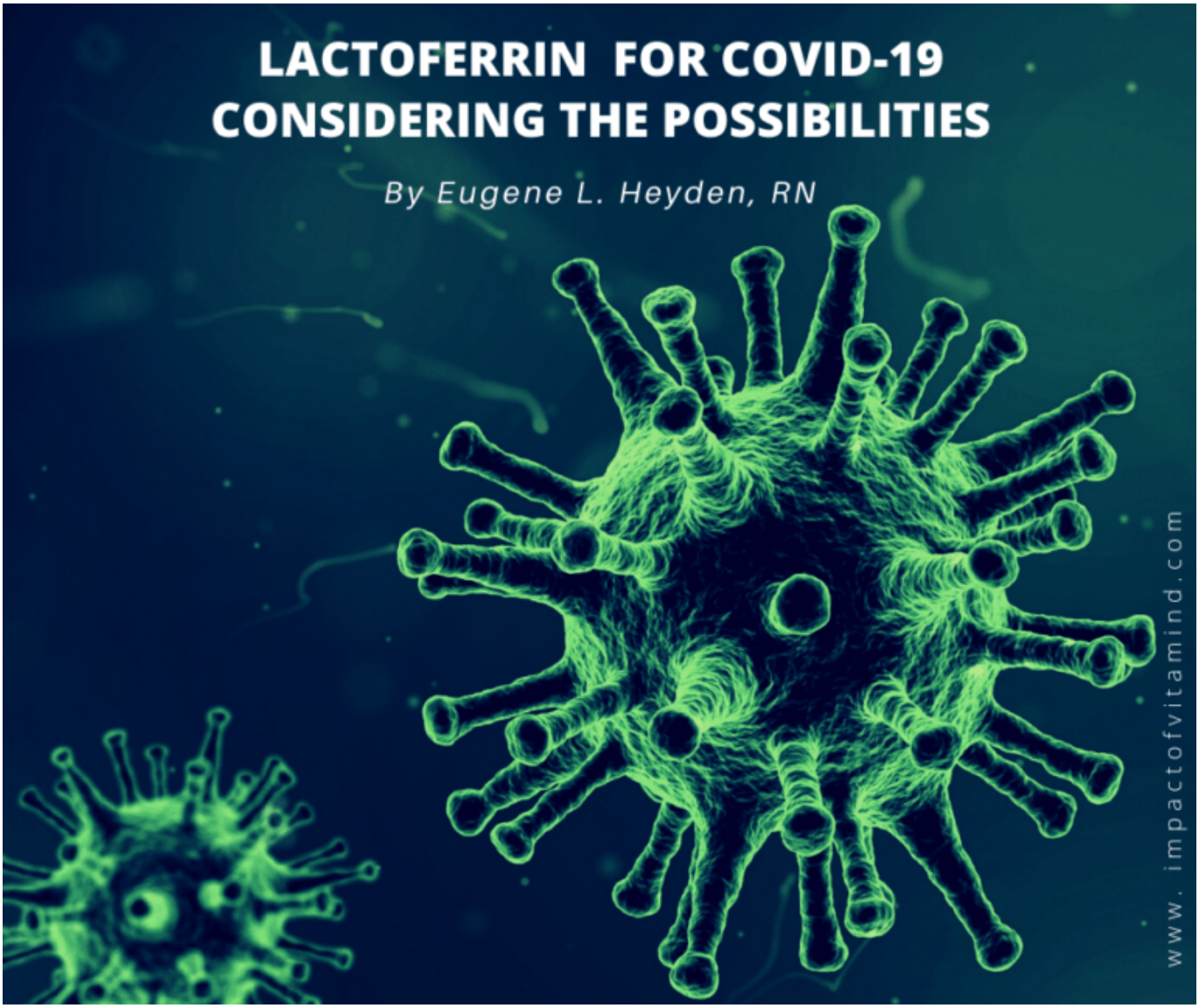
Lactoferrin for COVID-19: Considering the Possibilities

written by Eugene L. Heyden, RN. | April 30, 2020



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"Comparative studies showed that breast-fed children are less susceptible to viral infections than artificially fed children." **~Seganti et al., 2004**

"A key function of colostrum is to provide neonates with essential components for the development of their immune system, and it therefore exerts a protective function." **~Moreno-Expósito et al., 2018**

*"**LF [lactoferrin] inhibits the entry of viral particles** into host cells, either by direct attachment to the viral particles or by blocking their cellular receptors."* **~Redwan et al., 2014, emphasis added**

Our individual battle against viruses begins before birth. I know mine did. Whatever Mom sent my way through the placenta to protect me from this threat was meaningful, and I'm certainly glad I did not turn any of it down, but the real battle starts immediately after birth, a time when an ongoing exposure to a myriad of viruses begins and lasts for a lifetime. And to get me off to a good start, quite literally, Mom had the solution.

The solution is the first milk a mother provides to her newborn, called colostrum. And tucked inside "the solution" is a remarkable component, a protein called lactoferrin. Lactoferrin has antiviral written all over it. You will see.

One of the antiviral actions exhibited by lactoferrin is the ability to bind viruses, a wide variety of viruses, holding them in suspended animation to block their entry into cells (Redwan et al., 2014; Wakabayashi et al., 2014). In addition, lactoferrin can block the cellular mechanisms viruses use to gain access to the interior of a cell (Lang et al., 2011; Redwan et al., 2014). And if that wasn't enough, lactoferrin has another trick up its sleeve. It can enter an infected cell and stimulate the complex antiviral responses a cell can mount to destroy an invader (Wakabayashi et al., 2014). And amid this current coronavirus pandemic, I hope we will pay close attention to the lessons we have learned from our study of the antiviral activity of lactoferrin.

In the beginning

"LF plays an important role during the first stages of life, and human colostrum contains high concentrations (7 g/L), while breast milk has a lower concentration (1

g/L).” **~Moreno-Expósito et al., 2018**

“In all non-human mammals, ***colostrum is <u>crucial</u>*** *to the survival of the newborn because* ***high concentrations of immune factors are transferred to the newborn via colostrum.*** *<u>In humans</u>, some immunofactors are transferred through the placenta. Human colostrum is particularly beneficial; however,* ***if a human newborn does not receive colostrum, death is not imminent as it is in other mammals.*** *Like in other mammals,* ***a newborn’s first meal of colostrum significantly impacts its health and well-being, and the effect lasts the rest of its life.*** *Because a newborn’s immune system is not fully developed, it is* ***highly susceptible*** *to pathogens, antigens and allergens.”* **~Siqueiros-Cendón et al., 2014, emphasis added**

If my memory serves me correctly, colostrum didn’t taste all that bad. Actually, it was an improvement over what I was used to. During my last two trimesters, amniotic fluid was just about it—and I drank a ton of it as I recall. Somehow, I knew I could get valuable things from Mom just by drinking what was readily available. Only recently, however, did I learn that amniotic fluid contains lactoferrin, and in ever increasing amount,s as gestation progressed to its conclusion (Niemelä et al., 1989). It sounds a lot like Mom wanted me to be protected from pathogens, including viruses, and she was using lactoferrin to do this, even before birth. *Aren’t moms great?!!*

Shortly before my birth, Mom was busy preparing colostrum for my immediate use—and loading it with a large amount of lactoferrin. I can’t thank her enough. And after colostrum gave way to standard-issue breast milk, she continued to supply me with relevant amounts of lactoferrin. At the time, I remember feeling invincible, knowing that this remarkable protein was still on the menu, protecting me from viruses and other threats to my very existence.

I’ll leave my playful tribute to Mom and we’ll get down to business. Let’s see if lactoferrin could be useful in our battle against COVID-19. My hunch: it can.

Why lactoferrin?

*"**Coronaviruses cause** a variety of diseases in mammals and birds ranging from enteritis in cows and pigs and upper respiratory disease [in] chickens to **potentially lethal human respiratory infections**."* **~Fehr and Perlman, 2015, emphasis added**

*"LF [lactoferrin] has efficacious antibacterial and antiviral activities against a wide range of Gram-positive and Gram- negative bacteria and against both naked and **enveloped** DNA and **RNA** viruses. In its antiviral pursuit, **LF acts predominantly at the acute phase of the viral infection or <u>even at the intracellular stage</u>**, as in hepatitis C virus infection."* **~Redwan et al., 2014, emphasis added**

It seems so unreal, but a virus is not exactly a living thing. It is more like a machine, a killing machine. It finds its way inside a host cell, uses the cellular machinery within to clone itself and create hundreds if not thousands of identical viruses, and does so at the expense (death) of the infected cell. One virus becomes many. And if not stopped, the many become many more. If things get way out of hand, the infected individual will die. But until death is reached (or not), the numbers of clones created become an immense army of pathogens that can advance and invade other individuals (one sneeze or cough at a time). And others, so infected, can pass the virus in great numbers on to others, who, in turn, can pass it on to others. Unless measures are taken to stop the spread of the virus, the momentum builds, things spiral out of control, and a viral pandemic is unleashed upon the world. I'm watching it happen right now, in real time. I'm not happy with what I see.

Fortunately, individually, we battle viruses all day long, pandemic or no pandemic. We usually win the battle. And we do this in many ingenious ways. The immune system has the capability to recognize viruses and create neutralizing antibodies which bind viruses to prevent their entry into an uninfected cell. The viruses so bound are sitting ducks, easily picked off (destroyed) by specialized immune cells. The immune system employs other strategies, too, such as allowing lactoferrin to enter the cell and activate the anti-viral mechanisms within (Wakabayashi et al., 2014). Such actions allow you to prevent and/or recover from a cold, a flu, and from another viral diseases as well. And speaking of the flu,

*"A human study found that nutritional supplementation with **colostrum was***

<u>equally efficient</u> in preventing episodes of the flu *compared to a vaccine."* (Siqueiros-Cendón et al., 2014)

Colostrum! Effective as a flu vaccine! Could it be the lactoferrin? I think it is the lactoferrin, at least in great measure. And I am not alone. Much is written about the antiviral properties of the remarkable protein tucked inside "the solution" Mom had in mind. And what have we learned?

Lessons learned

*"**The competition between Lf [lactoferrin] and virus for common binding sites prevents the internalization into cells and accounts for the decreased infectivity."*** **~Florian et al., 2009, emphasis added**

*"**Lactoferrin** (LF) . . . prevents virus attachment to the target cells by binding to the virus receptor on the target cells or binding to the virus. In addition, lactoferrin induces IFN a/b production and thereby **inhibits virus replication after entry of the virus into the cells.*** **~Wakabayashi et al., 2014, emphasis added**

Perhaps a most valuable lesson we have learned along the way is this: **The battle against a virus is, in essence, a battle to prevent viral replication.** If a virus can't replicate, it can't destroy. Fortunately, once exposed, an individual has the tools to prevent viral replication, and can do so on multiple levels. Lactoferrin is one of the tools used by the immune system for this very purpose. And the beauty of **lactoferrin** is, it is **not restricted to combating a specific virus** but can be active against a wide range of viruses (Lang et al., 2011; Redwan et al., 2014; Siqueiros-Cendón et al., 2014).

Lactoferrin can come to our aid in the battle against viral replication, for the following reasons:

- Lactoferrin binds viruses and their particles, preventing their entry into the target cell (Redwan et al., 2014; Wakabayashi et al., 2014)

- Lactoferrin blocks receptors used by viruses to access the interior of a cell (Florian et al., 2009)

- Lactoferrin can activate natural killer cells, a specialized immune cell that can detect a viral-infected cell and kill it, preventing further replication (Redwan et al., 2014)

- Lactoferrin can enter a cell and trigger antiviral responses (Wakabayashi et al., 2014)

I could add more, but I seem to have run out of those big black dots. But I'm sure, by now, you get the point. Lactoferrin has antiviral written all over it. Which leads us to the following question: Could lactoferrin help us in our battle against COVID-19?

Application to COVID-19?

"Prior to the SARS-CoV outbreak, coronaviruses were only thought to cause mild, self-limiting respiratory infections in humans.

"Over the past 50 years the emergence of many different coronaviruses that cause a wide variety of human and veterinary diseases has occurred. It is likely that these viruses will continue to emerge and to evolve and cause both human and veterinary outbreaks owing to their ability to recombine, mutate, and infect multiple species and cell types." **~Fehr and Perlman, 2015**

We've been here before—a coronavirus attacking people, extinguishing their lives, devastating families and communities.

"Since first identified in 1960s, Human CoVs were considered relatively benign and usually cause mild upper respiratory tract infections (common cold) until the emergence of the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and later the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. The latter two CoVs could result in severe lower respiratory tract infection which would rapidly progress to pneumonia and caused thousands of cases and hundreds of deaths in about 30 countries, respectively." (Sun et al., 2020)

Due to the close similarity between the SARS virus and SARS-CoV-2, we can learn lessons from the former and justifiably apply them to the latter.

One important lesson learned in the study of the SARS virus is lactoferrin can block receptor-mediated viral entry into a target cell, and does this by attaching to a molecule (HSPG) which is anchored to the surface of a wide variety of cells and assists the virus in its goal to attach to a nearby cellular receptor called ACE2, also available on a wide variety of cells including the lung alveolar epithelial cell (Hamming et al., 2004; Lang et al., 2011; Cagno et al., 2019). And when you prevent viral entry into a cell, you prevent viral replication, one cell at a time. **As in SARS, COVID-19 infection involves viral binding to both HSPG and ACE2 for viral entry into a target cell** (Lang et al., 2011; Hondermarck et al., 2020; Fang et al., 2020). (HSPG = Heparin Sulfate Proteoglycans; ACE2 = Angiotensin-Converting Enzyme 2)

Another important lesson learned in the study of the SARS virus is lactoferrin increases the activity of natural killer cells (Lang et al., 2011; Redwan et al., 2014), cells that detect and destroy the infected cell. Killing an infected cell is one way to stop the creation of more and more and more viruses, reducing the viral load in the infected individual and subsequently reducing the degree of transmissibility of the virus to others.

A most unfortunate lesson we have learned from SARS that has application to COVID-19 is that both lead to pneumonia and kill by pneumonia. (Lang et al., 2011; Mehta et al., 2020). Furthermore, COVID-19 is substantially more contagious than SARS-CoV (Fehr and Perlman, 2015; Wilder-Smith et al., 2020) and is therefore a more accomplished killer. Now, as I write (in 2020), COVID-19 has so far claimed

over 224,000 lives, worldwide. (Excluding the many lives lost in China that the ruling Chinese Communist Party does not want you to know about.)

Because of the similarities between SARS and COVID-19, it is reasonable to assume, that since lactoferrin can help protect from the SARS virus (Lang et al., 2011), it can also help protect from, and possibly treat, COVID-19. We don't know this for sure. But perhaps the Chinese people do. Surprisingly, the sales of lactoferrin to China have dramatically increased since the beginning of the COVID-19 outbreak. One Australian company reported an "unprecedented demand" of lactoferrin from China and is boosting production to meet the demand (https://rb.gy/ar9uks).

Whether supplemental lactoferrin can successfully prevent or treat COVID-19 is currently unknown. But since lactoferrin *"**possesses strong antiviral activity** against a broad spectrum of RNA and DNA viruses"* (Lang et al., 2011, emphasis added), and COVID-19 is an RNA virus (Aronson, 2020), confidence is high that lactoferrin can be of help in our battle against this most aggressive killer.

Which brings us to this:

Lactoferrin supplementation strategies

"Bovine lactoferrin (bLf) has been recognized as a potent inhibitor of different viruses and has been often reported to exhibit higher antiviral activity than human lactoferrin (hLf)." **~Superti et al., 2019**

"No adverse effects of its use have been reported to date." **~Moreno-Expósito et al., 2018**

Fortunately, bovine (cow) lactoferrin has been found to be a more effective antiviral than human lactoferrin (Superti et al., 2019). And we're in luck. Bovine lactoferrin can easily be purchased online. But to maximize its effectiveness, lactoferrin should be done right and taken in adequate amounts.

For most supplements, following the instructions on the supplement bottle is usually satisfactory—a safe dose, one deemed sufficient to meet the needs of the average

individual and with a typical objective in mind. But are the typical dosing and directions suitable in the era of COVID-19? Probably not. We just don't know. But we do know there are ways to take lactoferrin to achieve a greater benefit.

The lactoferrin I personally use has the following instructions printed on the label: *"DIRECTIONS: Take one (1) capsule daily with or without food, or as recommended by a health care practitioner."* (LifeExtension, Product # 01681) But to achieve a targeted effect, I prepare my lactoferrin in a unique way. I enteric coat it (in a special way). The reason?

In my studies over the years, I learned that taking enteric-coated lactoferrin is the best way to get supplemental lactoferrin, unaltered, into the bloodstream—compared to lactoferrin taken in its standard, capsule form (Takeuchi et al., 2006; Ono et al., 2010). Enteric coating allows lactoferrin to escape the actions of the enzymes found in both the stomach and initial portion of the small intestine, and thereby will remain intact for receptor-mediated uptake and eventual transport into the circulatory system (Kawakami et al., 2015).

"In adults, LF is hydrolysed by gastric pepsin, preventing it from reaching the small intestine in a form that is capable of binding to LF receptors. Consequently, delivery systems such as ***enteric-coated tablets are necessary to assure the physiological activity of LF in adults."*** (Kawakami et al., 2015, emphasis added)

It has been disocvered that enteric-coated lactoferrin increases blood levels of lactoferrin (in rats) by 10-fold (Takeuchi et al., 2006). For those of us (humans) who want to increase our blood levels of lactoferrin, this is good news. This phenomenon is based on the fact that **the receptors in the small intestine that transport lactoferrin into the lymphatic system, then into the blood stream, require lactoferrin to be in whole form or transport cannot occur** (Kawakami et al., 2015). So, in light of the COVID-19 pandemic, a possible 10-fold increase in lactoferrin blood levels could be helpful, which may be accomplished by supplementation with enteric-coated lactoferrin.

My personal use of lactoferrin began as a strategy I initiated to deal with a problem we all face, a little troublemaker called LPS. LPS is short for lipopolysaccharide, a bacterial cell wall component that is highly immunostimulatory. LPS promotes

(creates or makes worse) a variety of diseases. If you have diabetes, you have a problem with LPS. If you have cardiovascular disease, you have a problem with LPS. If you have fatty liver disease, you have a problem with LPS. If you are obese, you have a problem with LPS. (see Ono et al., 2010; Neves et al., 2013) And if you have Alzheimer's disease, you don't know you have a problem with LPS, but you do (Pretorius et al., 2016).

So, it should be of no surprise that I turned to enteric-coated lactoferrin to deal with all the madness. It is the metabolic syndrome (from internalized LPS) that is out to kill us all (as well as those darn viruses). Lactoferrin can bind LPS and reduce its negative impact, helping to ameliorate the metabolic syndrome (Ono et al., 2010; Kawakami et al., 2015) Enteric-coated lactoferrin gets more LPS-binding lactoferrin into the bloodstream, which is why I use enteric-coated lactoferrin.

Unfortunately, it is nearly impossible to find enteric coated lactoferrin on the market. (Let me know if you succeed.) But I have a work-around. And it's easy! This is what I do:

I purchase regular lactoferrin online, making sure it comes in a capsule, size 0. Then, I manually place it into a larger size, size 00, empty enteric-coated capsules, also purchased online. It's that easy. There are three companies (perhaps more) that sell empty enteric-coated capsules online. They are: **Capsuline**; **CapsuleSupplies.com**, and **SuperDosing.com**. All three companies sell size 00 empty enteric-coated empty capsules. Depending on the company, the cost of each capsule ranges from 2 to 4 cents each. It takes me about 10 minutes to "enteric-re-encapsulate" an entire bottle of lactoferrin.

If enteric re-encapsulation, described above, is just not for you, there is another way to get more lactoferrin into the circulation. I'll let Lepanto and colleagues fill you in. (LF = lactoferrin; bLF= bovine lactoferrin)

"Another pivotal parameter influencing the Lfs efficacy is the in vivo bioavailability. In this respect, the ***oral administration of bLf should be performed before meals*** *to avoid the protein degradation due to the low pH of gastric juice during digestion (about 1.5). Conversely, at pH about 4, characteristic of gastric juice before meals, 90% of the administered bLf arrives undigested to the intestine."*

(Lepanto et al., 2019)

My belief is enteric coated lactoferrin is a better way to go, should increasing blood levels of lactoferrin be your goal. However, taking lactoferrin before meals as described above is a close second.

Now about that dose

"In published studies, there have been no signs of toxicity in mice or monkeys treated with oral and i.v. lactoferrin up to 5,000 mg/kg. In human studies, no toxicity in i.v. lactoferrin have been reported." **~Wolf et al., 2007**

Because of the *"exceptional safety profile,"* even at high dose (Wolf et al., 2007), those who become interested in investigating the use of lactoferrin as a treatment for COVID-19 will likely choose a high-dose regimen for testing and should choose a method of delivery that will likely offer the best opportunity for success.

Enteric-coated lactoferrin appears to be the best choice for delivering lactoferrin into the bloodstream, possibly 10-fold more effective in this regard than lactoferrin administered in regular form. As far as a dose suitable for COVID-19, we just don't know. But high dose lactoferrin would likely pose no danger. *"In a recent non–small cell lung cancer trial, 10 patients were given oral lactoferrin up to 9 g/d without any hematologic, hepatic, or renal toxicities."* (Wolf et al., 2007) So, pushing the envelope on the dose may be reasonable in testing its effectiveness for COVID-19, as lactoferrin has safety written all over it **and** we are fighting an aggressive enemy.

Lactoferrin given in the usual way, non-enteric coated, has not been all that effective as a treatment for another viral infection, hepatitis C (Okada et al., 2002; Ueno et al., 2006; Berlutti et al., 2011). Lactoferrin at 1.8, 3.6, and 7.2 g/day did not resolve the established viral infection (Okada et al., 2002; Ueno et al., 2006). The problem here may have been the delivery method and not so much the dose. In view of the evidence that enteric-coated lactoferrin allows substantially more lactoferrin uptake, studies using lactoferrin in regular form may have not achieved success due to the method of delivery which substantially limited the amount of lactoferrin entering the

circulation.

Frequency of administration may also be an important consideration. It may be that the intestinal transport receptors involved in the uptake of lactoferrin become saturated after a given dose of lactoferrin, preventing further uptake for a period of time before they can resume active transport and transfer lactoferrin into the circulation (Wolf et al., 2007). If this turns out to be the case, perhaps lactoferrin taken every 6 hours would be best course of action than dosing all at once or a couple times a day.

There is a novel way to administer lactoferrin that should be placed under consideration. Lactoferrin can be aerosolized and given as a breathing treatment (Lepanto et al., 2019). This mode of delivery may be particularly relevant since COVID-19 infects the gas exchanging alveolar cells of the lungs. Someone, please put this to the test.

These are just a few of my thoughts on dose and method of delivery, for what it's worth. I'll leave it up to the researchers and health care professionals to determine the lactoferrin dose and route of administration that offers the best opportunity for success with COVID-19. Confidence is high that lactoferrin does have something to offer us in the treatment of this disease.

Conclusion

"In conclusion, lactoferrin consumption may protect the host from viral infections through inhibiting the attachment of a virus to the cells, replication of the virus in the cells, and enhancement of systemic immune functions." **~Wakabayashi et al., 2014**

It is my hope that this article will draw attention to lactoferrin as a promising therapy in the battle against COVID-19. Lactoferrin has antiviral written all over it. And I believe it should be put to the test. Enteric-coated lactoferrin may be a key to its success, as enteric coating allows for greater uptake of lactoferrin into the circulation by preserving its original form, the form that is favored for uptake by

intestinal transport receptors.

For more information:

Earlier this year I was invited to be a coauthor of a scientific paper on the potential lactoferrin has in the prevention and treatment of COVID-19. I am pleased to announce that the paper is now in print. To read the paper, entitled ***The Biology of Lactoferrin, an Iron-Binding Protein That Can Help Defend Against Viruses and Bacteria***, **click here**.

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