University of Veterinary Medicine Budapest
Department of Obstetrics and Food Animal Medicine Clinic

# The effects of bovine colostrum in human medicine

# A szarvasmarha kolosztrum hatása a human gyógyászatban

By:
Cassandra Traynor Muñoz

Supervisor:
Dr. Szenci Otto, PhD, DSc, Dipl. ECBHM

Budapest, Hungary
2023

## ABSTRACT

Bovine colostrum is a white, nutrient-rich, milk-like secretion that is produced by cows following parturition, in order to nourish their offspring. It serves as a vital source of nourishment and immunological components for newborn calves, giving them the strength and defences needed for growth and development. Colostrum is rich in immunoglobulins, growth factors, cytokines, vitamins, and minerals, which all play a crucial role in the development of the immune system, gastrointestinal growth, and general health of the calf. In recent years, the fascinating properties of bovine colostrum and its effects on calves have piqued the interest of researchers, prompting investigations and its potential application in the field of human medicine. In this thesis, I propose to outline several areas which have been explored to determine the effects of bovine colostrum in human medicine.



## ABSZTRAKT

A szarvasmarha-kolosztrum egy fehér, tápanyagban gazdag, tejszerű szekréció, amelyet a tehenek közvetlenül az ellés előtt termelnek, hogy táplálni tudják utódaikat. A kolosztrum az újszülött borjak táplálékának és immunológiai komponenseinek létfontosságú forrásaként szolgál, így a növekedéshez és a fejlődéshez szükséges energiát és védekezéshez szükséges ellenanyagokat biztosítva számukra. A kolosztrum gazdag immunoglobulinokban, növekedési faktorokban, citokinekben, vitaminokban és ásványi anyagokban, amelyek mindegyike döntő szerepet játszik az immunrendszer kialakulásában, a gyomor-bél rendszer fejlődésében és a borjú általános egészségi állapotában. Az utóbbi években a szarvasmarha-kolosztrum lenyűgöző tulajdonságai és a borjakra gyakorolt hatása felkeltette a kutatók érdeklődését, és számos vizsgálatokat végeztek annak potenciális alkalmazását illetően az emberi orvoslás területén. Ebben a tézisben összefoglalom mindazokat az eredményeket, amelyeket feltártak a szarvasmarha-kolosztrum jótékony hatásainak meghatározására a humán orvoslásban.

# TABLE OF CONTENTS

## ABBREVIATIONS

BC = Bovine colostrum

IGF-1 = Insulin-like growth factor

GIT = Gastrointestinal tract

Ig = Immunoglobulin

OPV = Oral polio vaccine

LGS = Leaky gut syndrome

TGF-β = Transforming growth factor-beta

I-FABP = Intestinal fatty acid-binding protein

IBD = Inflammatory bowel disease

NSAID = Nonsteroidal anti-inflammatory drugs

SBI = Serum-derived bovine immunoglobulin/protein isolate

PG = Prostaglandin

ASD = Autism spectrum disorders

*E. coli* = *Escherichia coli*

ETEC = Enterotoxigenic Escherichia coli

HBC = Hyperimmune bovine colostrum

BRV = Bovine rotavirus

MIC = milk immunoglobulin concentrates

*Cl. difficile* = *Clostridium difficile*

RTI = Respiratory tract infection

URTI = Upper respiratory tract infection

NK = Natural killer cells

SARS = Severe acute respiratory syndrome

EIMD = Exercise induced muscle damage

# 1. INTRODUCTION

The extent of this study includes publication papers, articles and factual materials outlining the breakdown of the biochemical composition of bovine colostrum (BC), all the parameters on how it differs to mature milk, and its importance to neonate calves to receive BC immediately and the right supply quantically, especially for the development of the gastrointestinal and immune systems [1]. It has been known for centuries how important BC is to the postnatal and preweaning calf, however, in recent years the benefits are emerging on exactly how vital it is, and all its elements which play key roles in the survival of a healthy offspring.

Studies have shown that managing the feeding of calves has consequences on their growth and maturation of tissues and organs, and the lack of which results in high rates of morbidity and mortality. What is detrimental to a calf in the perinatal period is colostrum from the mother cow, providing nutrient and non-nutrient factors, which in turn leads to the mandatory development of all organ systems, but in particular the microscopic functional bodies that make up the gastrointestinal tract, allowing them to flourish naturally, and develop their roles of absorption and digestion of nutrients present in the BC and later on, the mature milk [1]. It can also be said that if the calf consumes BC within the corresponding time frame, it will most likely have a successful effect on its health as it continues throughout the rearing stages and into adulthood, with a healthy, more abundant performance outcome in later years.

Furthermore, this emerging scientific research on BC has attracted more interest from research scientists in human medicine, and in how the results may be integrated into future human medical research topics. Since BC is packed with such nutritious values and statistics [1], each of its constituents has been a subject of interest to researchers investigating its properties in relation to the calf itself and in relation to how its findings can be implemented into research in the field of human medicine. With research backing the enhancement benefits in a variety of aspects with humans, this study sets out to highlight the main findings, and the importance of further research in this area is needed.

This thesis provides an overview on the diverse approaches that researchers have implemented, to investigate the potential benefits of BC supplementation in humans. BC emerged as a particularly intriguing subject due to its numerous advantages for neonate

calves. Researchers were curious about whether similar positive outcomes could be observed in humans. However, like many of these emerging novel substances, while the predominant findings are positive, there may be negative aspects to consider. Therefore, this thesis review aims to analyse the current literature comprehensively, to uncover potential therapeutic benefits associated with BC in humans. Simultaneously, it seeks to assess the potential risks, identify challenges, and examine any adverse effects of this increasingly popular, naturally occurring substance.

## 2. OBJECTIVES

Throughout the course of this thesis, the primary objective is to systemically search, thoroughly read and analyse the current literature and studies that have implemented BC into various facets of human medicine. First, it will endeavour to outline, the major differences between BC and mature bovine milk, highlighting the rich nutritional profile that makes it an essential resource for neonate calves. It will delve into the historical aspects of BC's use within traditional medicinal systems and explore how the scientific community has introduced this nutritionally dense substance into the world of Western Medicine. The review aims to elucidate the various ways in which BC supplementation has been researched and implemented in human health. Simultaneously, it intends to uncover and present the potential benefits that BC may offer to individuals, taking from an array of scientific studies and clinical trials. Finally, this thesis will aim to assess any risks, challenges and potential adverse side-effects associated with BC usage in humans. Ultimately, the goal is to contribute a comprehensive insight into the research, clinical applications and outcomes associated with the use of BC in human medicine.

# 3. LITERATURE REVIEW

## 3.1 Composition of Bovine Colostrum

Colostrum in all mammals is well known for its importance in neonates, its outstanding line of defence and protection/nutrition which could mean the difference in survival or death for some young animals; also, its diversity to milk, which lacks the high levels of beneficial components compared to colostrum.

Differentiating between bovine colostrum (BC) and milk involves several distinct factors. Though both are derived from the cow postpartum, they contain a variety of elements that differ. Timing of the production is different; colostrum is produced immediately postpartum for a few days, averaging around 3 days, but can vary, while milk is produced after colostrum has stopped, and this signifies the beginning of the lactation period of the cow. The lactation cycle will last for about ten months.

### 3.1.2 Biochemical Composition Differences

Bovine colostrum contains higher levels of immunoglobulins, growth factors such as insulin-like growth factor (IGF-1), and cytokines [2]. Immunoglobulins (Ig), which are also called antibodies, provide the newborn calf with maternal antibodies through passive immunity, as their intestinal tract at this time is permeable for the passage of large Ig's, giving essential immune protection to the calf for its survival in the first few days of life. It was shown that the earlier the calf consumes colostrum, with an essential adequate supply, the better, as there is a larger amount of Ig's available in this period, and the permeability of their intestinal tract declines within 24 hours. Colostrum which was collected and tested at 6, 10 and 14 hours postpartum had significantly reduced Ig levels compared with the sample taken after 2 hours postpartum [3]. This is important as immunoglobulins, especially IgG cannot pass through the placenta, and therefore, can only be consumed in order for the calf to receive the beneficial Ig's [4]. Growth factors, aid in developing and maturing the cells of the gut. This growth will ensure the gut is efficiently adapting to the calf's growth and consequently establishes a smooth transition of liquid feed to solid feed, as well as the development of the rumen. Cytokines, known for being small core proteins that promote the maturation of, and influence signalling pathways for blood cells and other cells that make up the immune system, are found in abundance in BC compared to mature milk. This high level of cytokines produced and

secreted by the mammary gland, will provide immunomodulatory activity and progress the newborns' immune system [5].

### 3.1.2 Nutrient Composition Differences

Total protein is found to be at a much higher level than milk, comprising of two components: whey and casein. Whey is a soluble protein that may possess an immune-modulatory function, as it has been shown to be a potent modulator of cellular immunological function in livestock species [6]. Casein is an insoluble protein, makes up most of the protein found in milk, and gives the white colour. A literature review by R. Playford and Weiser [2] found that casein, not only is a source of energy, but also may hold "immune-regulatory, antibacterial and anti-inflammatory properties" [2]. This triple pack protection gives an insight into how important and vital colostrum is to the offspring.

Carbohydrates such as lactose, oligosaccharides, glycoprotein, and glycolipids are found in BC, however, it is lactose which maintains significantly lower levels in BC than that of mature milk. Lactose is the principal sugar found in milk, and contrary to the other constituents, its level rises as colostrum transitions into milk post-partum. Lactose is believed to play a major role in the osmotic pressure of milk; water flows via osmosis from the epithelial cells of the mammary tissue into the secretory vesicles and therefore into the milk [7]. This osmotic control monitors the amount of milk produced, and its level of viscosity. The lower levels of lactose, and subsequently water content, correlate with a more viscous fluid [8], which can be observed in colostrum. The increase in lactose as milk matures from BC, signifies its importance and contributions to the development of the growing calf, including being the main energy source currently for the maturing internal organs.

Oligosaccharides are made up of a number of simple sugars called monosaccharides, which form a chain, and are linked to one another by glycosidic bonds. They are seen to be approximately double the levels in BC when compared to mature milk. In a review to seek the functionality of oligosaccharides from bovine milk in human health, it was shown that the oligosaccharides from bovine origin mimicked human oligosaccharides, which are known to promote the growth of two main beneficial bacteria, Bifidobacteria and Lactobacilli, while simultaneously creating an acidic environment which does not

benefit the bacteria that can become harmful when in excess [9]. They act in the colon, as they are not broken down in the upper quarter of the gastrointestinal tract. Here, they influence and advocate for healthy and diverse microbiota. However, only trace elements of these oligosaccharides are found in bovine milk, out of which they can be found in a greater abundance in BC. Having this knowledge of these microbiome enhancement properties, therefore, it may be stated that BC oligosaccharides act as prebiotics in human health.

Fat content in BC has a higher percentage than mature milk [10] and is estimated at about 7% in BC, mainly as milk fat globules [2]. The reason for this is, that newborn calves need a fast and efficient energy source to maintain body temperature and thermogenesis, as their stores are very low immediately after birth. The fat contained in colostrum is a very important factor in meeting these requirements and in extending the calf's chances of survival. Phospholipids, which are an element of the lipid fraction in fat, have been shown to be of particular importance in the development of the offspring. A study using milk phospholipids on neonatal piglets found that the treated group had an increase in neurocognitive activity, including elevated learning and memory capacity, compared with the control group [11]. Moreover, the study also measured acetylcholine, one of the main neurotransmitters in the body, which is associated with brain function and memory, in the hippocampi, and was found to be at a higher level. Piglets were used in this study because they possess cognitive growth and brain development similar to that of humans. Phospholipids have also been closely looked at for their role in decreasing and possibly even regulating inflammatory processes which may come from harmful pathogens or diseases. Their mechanisms of action give them the advantage of encouraging the pharmacokinetics of certain drugs, like non-steroidal anti-inflammatories, and of enhancing anti-inflammatory and analgesic properties, when studied against acute and chronic arthritis models [12].

Vitamins and minerals are also core elements that make up part of the profile of BC and milk, and like the other constituents, bare important roles for a healthy developing calf. Vitamins can be fat-soluble; they are absorbed into the body system with dietary fat and the excess stored in the liver, meaning they stay long-term, or they can be water-soluble, readily absorbed and the excess is excreted with urine, having no storage capacity. Fat-

soluble vitamins include Vitamin A, D, E and K, and water-soluble are Vitamin C and all the B's.

Vitamins A and E are known to be concentrated in much higher amounts in BC [13]. This may be due to their limited passage via the placenta, meaning the newborn is primarily deficient and must be provided with them through colostrum [13]. Vitamin A has several fundamental roles for the healthy development of neonates, such as normal cell growth and tissue development; it helps maintain organ function and matures the reproductive system. It is mostly known for its indispensable involvement in vision; here, vitamin A is in a form known as retinal, and combined with other molecules, allows the absorption of light which is absolutely necessary for vision. A deficiency in vitamin A can result in the animal experiencing visual impairments. Both Vitamins A and E contribute in aiding the immune system, and therefore, optimising protection against diseases, prompting their crucial ingestion by neonate calves. Vitamin E's main function is as an antioxidant, where it scavenges to eliminate free radicals that have the potential to cause harm.

It was shown in another study, that Vitamins D and K also possess higher levels in BC compared to milk [10]. The main objective for Vitamin D is to work alongside calcium and phosphorus to assist in their absorption into the skeletal framework to build and preserve strong, healthy bones, as well as calcium reabsorption from the kidneys back into the body system when needed. It also overlooks and regulates the calcium/phosphate balance in the blood, by stimulating their absorption from the gut [14], this mechanism ties in with the parathyroid hormone, which when released in excess into the blood, due to low calcium levels, will send signals for the release of skeletal calcium into the blood. Vitamin D has been shown to promote and stimulate osteoclast formation [15]; whose role is to degrade and resorb aged bone so new bone can form. Vitamin K is involved with the production of fundamental proteins that are responsible for both the process of the normal coagulation of blood, as well as proteins used to produce the structure and integrity of strong bone formation.

Essential minerals are nutrient molecules that organisms need, to carry out daily functions on a biomolecular scale and contribute to the pivotal normal growth of offspring. Like vitamins, minerals are also seen to possess significantly higher levels in BC [2], and therefore, make it an incredibly valuable resource for newborn calves (Table 1). Such

minerals include calcium, phosphorus, magnesium, zinc, iron, and many more. Calcium, which was discussed earlier in this paper, has a fundamental involvement in the healthy development of bone structure and density, the intricate contraction of muscles, and in the transmission of nerve signals between the brain and body, maintaining a functioning nervous system. Phosphorus, mainly known for working together with calcium to maintain the integral structure of bones for strength and stability in the growing calf, also has a critical role in energy metabolism which fuels the bases of all physiological processes. Magnesium participates in assisting enzyme activity, which is important for energy production on a cellular level; it additionally functions as a co-factor for hundreds of enzymatic reactions involved in metabolic processes including muscle contraction, nerve function and neurotransmitter release [16]. Moreover, magnesium also has a connection with the immune response to tackle pathogens, participating in the generation of immune cells and aiding in their functionality in various ways [17].

Table 1. The content of minerals (%) in colostrum and milk (Puppel et al. [19])

| Testing Time | Calcium | Magnesium | Potassium | Sodium Chloride | Phosphorus | Chloride |
|---|---|---|---|---|---|---|
| **At the time of calving** | 0.256 | 0.037 | 0.137 | 0.074 | 0.235 | 0.118 |
| **After 11 days** | 0.130 | 0.011 | 0.153 | 0.036 | 0.113 | - |

### 3.1.3 Other Factors

The volume and duration of production is another variant; though colostrum is only produced and consumed in the first 3-4 days once the calf is born, milk is produced for months after, providing the essential and beneficial nutrients and macromolecules to encourage and support growing calves, as every physiological system is developing at this stage. Time is a critical component for colostrum and its super nurturing properties. With the rates of the macromolecules decreasing drastically as the hours pass, and their ability to be absorbed thoroughly also declining, it is of utmost importance that colostrum is given immediately after birth [18].

Bovine colostrum is a biologically produced substance, and thus a range of variations can exist in its composition among individuals, with many factors affecting its overall structure and physical properties. Genetics may play a notable impact, for example, different cattle breeds can have a range of different genetic traits, including colostrum and milk production capacities and quality. Holstein cattle are regarded as having a lower Ig concentration in their colostrum compared to other dairy breeds [19]. Some cows may naturally produce colostrum with higher specific nutrients, due to individual genetic variation. Adequate nutrition in well-fed cows with a balanced diet, especially during the dry period and leading up to calving, are more likely to produce high-quality colostrum. However, milking cows prematurely or very close to calving, can disrupt the natural dry period, which is typically around five weeks, and lower the levels of Ig's in the colostrum. During this period, the secretory epithelial cells of the mammary glands undergo regeneration and lactogenesis begins, as well as the changing composition of precolostral Ig's. A reduced Ig concentration can result in colostrum that is less effective in passing on passive immunity to the newborn calves [19].

The environment is very important, including temperature, humidity, dirty, wet bedding, and exposure to stress factors can negatively impact a cow's ability to produce high quality and quantity of colostrum. Animal husbandry including the treatment of the cow by the farmer, the general living conditions, well-being, and the immune challenges such as vaccination programmes and exposure to diseases that the cow has experienced over the course of her life.

It is also known that age and parity affect the volume and quality of the colostrum. It appears that older multiparous cows have a better-quality colostrum then first calving heifers, possibly because of increased pathogenic exposure, body condition scoring, and higher functioning immunity [18].

Disease, such as mastitis, which is an inflammatory disorder of the mammary gland tissue of the udder, can subsequently cause a decrease in the quality of colostrum, and has been shown to lower the levels of IgG, compared to cows without mastitis or infected mammary glands [20]. Other udder diseases, chronic acidosis and ketosis have also shown to lower Ig levels in colostrum [19].

The significance of colostrum for neonate calf well-being and viability is indisputable, given its distinct characteristics compared to milk. The process of harvesting, handling, and storing colostrum, along with overall management, holds the key determining factor ensuring calf health and survival [18]. By implementing sound management practices, farmers can make a substantial impact on protecting calves from disease and providing the foundation for their future growth and well-being.

This importance of bovine colostrum has naturally piqued the interest of scientists, leading them to explore its properties and potential applications in human health and medicine. The unique composition of colostrum, rich in immunoglobulins, growth factors, nutrients, and other bioactive compounds, presents promising avenues for research and innovation, raising the possibility of positive applications in various aspects of human health, including immunology, gastrointestinal health, nutrition, and agility.

Table 2. Bovine colostrum and mature milk composition (Arslan et al. [10])

| Colostrum component | n[a] | Mean | Minimum | Maximum | SE | Mature milk |
|---|---|---|---|---|---|---|
| **Bovine colostrum** | | | | | | |
| Fat mg/mL | 1,226 (29) | 64.00 | 41.00 | 83.00 | 33.20 | 39.00 (28) |
| | 54 (30) | 67.00 | 20.00 | 265.00 | 41.60 | |
| Protein mg/mL | 1,226 (29) | 140.00 | 116.00 | 166.00 | 36.70 | 36.00 (28) |
| | 55 (30) | 149.20 | 71.00 | 226.00 | 33.20 | |
| Casein mg/mL | – (31) | 43.00 | – | – | – | 25.00 (31) |
| Whey mg/mL | – (31) | 120.00 | – | – | – | 5.10 (31) |
| Lactose mg/mL | 1,226 (29) | 27.00 | 23.00 | 31.00 | 5.50 | 49.00 (28) |
| | 55 (30) | 24.90 | 12.00 | 52.00 | 6.50 | |
| Dry matter mg/mL | 55 (30) | 276.40 | 183.00 | 433.00 | 58.40 | 125.00 (28) |
| Ash mg/mL | 55 (30) | 0.50 | 0.20 | 0.70 | 0.10 | 7.00 (28) |
| IgG mg/mL | 1,239 (29) | 55.00 | 38.10 | 67.80 | 25.75 | 0.257 (32) |
| IgA mg/mL | 55 (30) | 1.66 | 0.50 | 4.40 | 0.50 | 0.04–0.06 (12, 30, 33, 34) |
| IgM mg/mL | 55 (30) | 4.32 | 1.10 | 21.00 | 1.10 | 0.03–0.06 (12, 30, 33, 35) |
| Oligosaccharides mg/mL | – (36) | – | 0.70 | 1.20 | – | 0.3–0.5 (36) |
| Lactoferrin mg/mL | 55 (37) | 0.82 | 0.10 | 2.20 | 0.10 | 0.10–0.30 (37) |
| Lactoperoxidase mg/mL | – (38) | – | 11.00 | 45.00 | – | 13–30 (38) |
| Ca mg/kg | 55 (30) | 4,716.10 | 1,898.00 | 1,775.10 | 8,593.50 | 1,220.00 (39) |
| | – (40) | 1,518.60 | – | – | – | |
| P mg/kg | 55 (30) | 4,452.10 | 1,706.29 | 1,792.40 | 8,593.5 | 1,520.00 (39) |
| | – (40) | 1586.00 | – | – | – | |
| Mg mg/kg | 55 (30) | 733.24 | 286.07 | 230.30 | 1,399.60 | 120.00 (39) |
| | – (40) | 219.70 | – | – | – | |
| Na mg/kg | 55 (30) | 1,058.93 | 526.02 | 329.70 | 2,967.80 | 580.00 (39) |
| | – (40) | 516.70 | – | – | – | |
| K mg/kg | 55 (30) | 2,845.89 | 1,159.89 | 983.20 | 5,511.40 | 1,520.00 (39) |
| | – (40) | 1,297.50 | – | – | – | |
| Zn mg/kg | 55 (30) | 38.10 | 15.90 | 11.20 | 83.60 | 5.30 (39) |
| | – (40) | 151.00 | – | – | – | |
| Fe mg/kg | 55 (30) | 5.33 | 3.09 | 1.70 | 17.50 | 0.80 (39) |
| | | 34.66 | – | – | – | |
| Mn[b] mg/kg | 23 (30) | 0.10 | 0.11 | 0.00 | 0.36 | 0.20 (39) |
| | – (40) | 2.62 | – | – | – | |
| Vitamin A mg/kg | 55 (30) | 4.90 | 1.82 | 1.40 | 19.30 | 460.00 (39) |
| Vitamin E mg/kg of fat | 55 (30) | 77.17 | 33.52 | 24.20 | 177.90 | 2.10 (39) |
| Vitamin B12 μg/mL | 5 (30) | 0.60 | 0.35 | 0.20 | 1.10 | 4.50 (39) |

[a] *Number of colostrum samples reported in the referenced study.*
[b] *Part of the samples were quantified as <0.05 and therefore not included in averages.*

## 3.2 THE APPLICATION OF BOVINE COLOSTRUM IN HUMAN MEDICINE

### 3.2.1 Historical Aspects

The use of bovine colostrum in human medicine appears to have been employed for many years in different cultural practices, consumed for health benefits, medicinal advantages, and spiritual rituals. It has been documented in the ancient Ayurveda, a traditional Indian medicinal system, which is an alternative practice of medicine in existence for thousands of years in India, with a fundamental belief in the interconnectedness of body, mind, and spirit. It therefore utilizes a holistic approach that encompasses a variety of components including natural remedies, nutrition, meditation, along with other wellness practices to treat and prevent illnesses, with consideration given to the physical, psychological, philosophical and spiritual health of the individual [21]. According to Godhia et al. [22], 'India have used bovine colostrum for both medicinal and spiritual purposes since the cows were first domesticated', indicating the ancient knowledge of its therapeutic potential, clear understanding of the nutritional value BC possesses and its effects on human health and well-being.

In 1799, Hufeland first established a direct correlation between the ingestion of colostrum by calves and their strong optimal development [23], initiating an emphasis into researching BC and its properties. Over the next couple of years, with growing scientific interest and improved research facilities, researchers were able to identify abundant levels of antibodies in the colostrum matrix when compared to mature milk [23].

In the 1950s, Dr. Albert Sabin, renowned for his groundbreaking work in developing the oral polio vaccine (OPV), thought to integrate BC in his efforts to combat polio [109]. Astutely, Dr. Sabin recognised the immune boosting properties of BC, and the idea that introducing inactivated poliovirus into the cow would produce antibodies against it, possibly enhancing the effectiveness of the vaccine [109]. He proceeded to conduct pivotal research that employed the use of these BC antibodies to improve the immune response of children receiving the OPV, aiming to boost their immunity against poliovirus. A study was conducted of eleven three-day-old infants during a sixteen-day observation period. These infants consumed BC that contained poliovirus neutralising antibodies, and subsequently were administered the Sabin Type 2 vaccine, to evaluate its efficacy in preventing viral infection of the gastrointestinal tract. The study revealed that

while the ingestion of BC did not significantly impact the occurrence of infection, it did seem to postpone infection or possibly disrupted, for a brief time, the detection of the virus from faeces samples. Furthermore, the consumption of BC lacking the poliovirus neutralising antibodies had no apparent effect on the rate of infection [24].

### 3.2.2 Bovine Colostrum in Association with the Gastrointestinal Tract

Due to the high-quality composition of BC, many areas of its benefits have been researched to explore potential enhancements in human medicine. Given that BC has an increased ability to protect young calves with maternal antibodies, bolstering their resistance against infectious diseases and heightening their immunity, this concept was extended to human subjects for investigation to determine if similar outcomes would be observed. It was of major importance to discover that BC exhibits properties comparable to human colostrum, and that it can be acquired in substantial quantities [25]. This knowledge was crucial for furthering investigations into the various ways BC could be utilised in different applications for humans, with a focus on safe outcomes and avoiding toxicological side-effects.

Products derived from BC have been used for a long time, recognised for containing numerous bioactive molecules, promoting their health benefits, and are widely considered safe to consume [26]. However, Davis et al. [26] noticed the absence of a comprehensive evaluation of BC's long-term safety, especially in young individuals. Considering this, it was imperative to ascertain the safety of BC human consumption, in particular for young children and infants, in order to gain approval for its production.

It is worth emphasising that BC contains hormones and growth factors, making its extended use in children of particular importance. In a study conducted in New Zealand, weanling rat subjects were used to evaluate potential toxicological levels associated with the consumption of BC [26]. Weanling rats have been acknowledged as a valid model for studying humans, as recommended by the Organisation for Economic and Co-operative Development (OECD), for assessing the safety of chemicals. Weanling rats may also provide a closer representation of young humans during a critical time of growth and development [26]. At the end of the 90-day study period, no adverse physical, biochemical, or histopathological effects were observed, signifying the absence of harm or toxicity. Nonetheless, the authors mentioned the importance of conducting human

trials to validate the safety of long-term BC consumption, despite the lack of adverse effects observed in their 90-day trial, and of other studies conducted which used humans as the study subjects.

One of the most extensively researched areas of BC in human medicine has focused on its impact on the gastrointestinal tract (GIT). Studies have examined its potential to enhance GIT development and stimulate the growth of beneficial microorganisms, assisting in the management of various diseases or conditions within the digestive system. BC contains an array of growth factors, including insulin-like growth factors, which are integral for GIT development and maintenance on a cellular level. They help in repairing and regenerating the gut lining, support the growth of healthy gut epithelial cells, and contribute to the maturation of the mucosal immune system [2]. As a result, BC can help improve gut barrier function and reduce the risks of such conditions like leaky gut syndrome (LGS), which is also known as intestinal hyperpermeability [27]. It is a pathological condition associated with the disruption and weakening of tight junctions formed from intestinal epithelial cells and a mucosal barrier dysfunction. This weakening results in a decreased protective strength, allowing the passage of endotoxins from the gut lumen into the body's system to initiate systemic inflammatory responses [28].

Endurance sport athletes are often observed to have a strong link with the occurrence of gastrointestinal problems, with LGS being the most prevalent among these issues [29]. Moreover, rigorous physical activity has been shown to have adverse effects on the digestive system, 'causing symptoms like abdominal pain, colic, flatulence, nausea, vomiting, or diarrhoea, which affect nearly seventy percent of athletes' according to Dziewiecka et al. [27]. Considering that BC contains an immense level of immune-boosting molecules, it is no surprise that research began to explore the benefits of supplementing BC to athletes who suffered from LGS and other such digestive conditions. It found that BC has an intestinal sealing ability due to a specific cytokine it possesses called transforming growth factor-beta (TGF-β), which has a role in intestinal barrier integrity [27]. It also has another significant component, lactoferrin, which is an iron-binding glycoprotein, that can stimulate the development and maturation of epithelial cells in the small intestine, attributing to the volume, length and expression of digestive enzymes, as well as having enhancement properties to the immune system [30]. A research review carried out by Dziewiecka et al. [27] concluded BC supplementation

in athletes proved to be highly beneficial to improve and decrease gut permeability. Another study saw the positive effects of BC supplementation on the strengthening of the gut barrier and decreasing intestinal permeability in sixteen athletes during peak training for competition, with no significant side-effects [31].

In a separate study, the efficacy of BC supplementation was assessed in relation to exercise-induced intestinal permeability under high temperature conditions and circulating intestinal bacterial DNA over the duration of fourteen days in twelve male participants. The authors concluded that this is the first study to show the benefits of BC on intestinal injury post exercise in vivo. They observed that an increase in plasma I-FABP (Intestinal fatty acid-binding protein) coincides with increased intestinal permeability, and BC was found to counteract the rise of plasma I-FABP, but did not have any impact on the presence of circulating bacterial DNA [32].

Numerous studies have indicated that BC and some of its individual constituents have demonstrated effectiveness in a broad spectrum of GIT conditions. These conditions include inflammatory bowel disease (IBD), nonsteroidal anti-inflammatory (NSAID)-drug induced gut injury and chemotherapy-induced mucositis [33].

IBD can be described as a group of chronic conditions marked by recurrent episodes of inflammation in the GIT. It comprises two distinct types of idiopathic intestinal conditions, ulcerative colitis, and Crohn disease, which are distinguished by their specific locations and the depth of their involvement within the bowel. Ulcerative colitis is characterised by widespread inflammation of the mucous membrane in the colon and Crohn disease leads to ulceration that may extend to any part of the GIT [34]. The exact cause of IBD is not fully understood. While there is much speculation involving environmental and genetic factors, it is often considered an autoimmune disease, in which the immune system begins to target and attack the healthy gut tissue. However, the specific trigger for these immune attacks remains unknown, and this has led to a scarcity of effective therapeutic options. Currently, the focus of treatment aims to target the disruptions in the GIT. This includes the use of probiotics to balance the microflora, anti-inflammatory medications, immunosuppressants, carefully regulated diets, as well as exercise and lifestyle modifications [35].

The constituents of BC, particularly its immune-stimulating and anti-microbial properties, hold particular relevance in this context. Since BC is recognised for its role in maturing and shaping the digestive system in calves, facilitating their development and regeneration processes, it is reasonable to assume similar benefits could extend to promoting the gut function in humans. Though studies have struggled to find a direct correlation of immunoglobulins from BC directly alleviating IBD symptoms in patients [35], a study conducted using serum-derived bovine immunoglobulin/protein isolate (SBI), which is a special formulated protein preparation for oral use, on a co-culture model of the intestinal epithelium, demonstrated that SBI reduced the antigen-associated inflammation, by inhibiting cytokine induced proinflammation and immunoglobulins from the SBI binding to prevent bacterial translocation across the damaged barrier [36].

Sienkiewicz et al. [35] argues that given the limited research on the effects of BC on humans, it is crucial to conduct analysis encompassing not only the potential advantages but also the possible contraindications associated with its use. Subsequent research should aim to elucidate the impact of orally ingested BC on the human body, considering the possible alterations in the biological activity of its components during the process of digestion. As the reviewed studies may suggest, BC primarily acts to counteract the increase of proinflammatory cytokines, however, the intricate nature of cytokine storms in IBD patients indicates that BC may be working with other such mechanisms to exert its benefits. Consequently, it is imperative to gain a more comprehensive understanding of the favourable effects of BC in managing IBD [35].

NSAIDS are anti-inflammatories drugs, which are used to reduce inflammation and pain. They work by inhibiting the production of certain regulatory enzymes, known as cyclooxygenases (COX)/prostaglandin-endoperoxide synthase, which participate in the biosynthesis of prostaglandin (PG), and play a significant role in the process of inflammation. This, in turn, helps to alleviate pain and inflammation. They are used to manage a variety of conditions, including ‘chronic pain, osteoarthritis, rheumatoid arthritis, postoperative surgical conditions, menstrual cramps and even used extensively as analgesics and anti-pyrectics’ [37].

Although NSAIDs are a favourable choice of medication due to their effective results and lack of addictive properties, it is important to note that they carry potential side effects when used over extended periods or in high doses. GI damage is frequently observed in

association with NSAID intake for long-term periods or at high doses, causing irritation to the stomach lining and increasing the risk of GI issues such as gastritis, peptic ulcers and bleeding leading to chronic conditions and in some cases perforation. This is because NSAIDs inhibit the production of PG, which have a protective role in the stomach lining. As the PG is reduced, the stomach and intestines become more susceptible to damage from gastric acids and other such factors [38].

Recent research has shown that BC has the potential to decrease intestinal permeability, making it a promising complementary therapy when used in conjunction with NSAIDs for treating gastric damage. A randomised crossover trial was conducted by Playford et al. [39], comparing changes in the intestinal permeability, where indomethacin was administered as a control, and BC was co-administered along with a regular dose of NSAIDS in both groups. The study revealed that indomethacin led to a three-fold increase in intestinal permeability, while the participants in the BC group did not exhibit a significant rise. This finding suggests that BC may offer an innovative and unique therapeutic approach for the treatment of GI damage induced by certain drugs such as NSAIDs [39].

Diarrhoea, a condition characterised by loose and watery stool, is a common disorder that affects many people. Many GI disorders can trigger diarrhoea, resulting in an increased loss of fluids and nutrients from the body, which can lead to dehydration. Malabsorption is often a prime factor contributing to the presence of excess fluid in the gut lumen and a reduced absorption of these essential minerals and biomolecules. The primary causes of diarrhoea typically stem from bacterial, viral, parasitic, or fungal infections, but it can also be due to other issues like intolerances, medication side-effects or GI related diseases. Studies have suggested that diarrhoea originating from bacterial or viral infections may show significant improvement when BC is consumed. A randomised controlled trial was conducted utilising BC as a treatment for acute diarrhoea in children below the age of two. The aim was to prevent diarrhoea and its consequential complications, such as dehydration [40].

BC offers a diverse array of attractive and valuable components which are abundantly available to support the GIT, including Ig, growth factors, lactoferrin and antimicrobial properties, all of which play a role in nurturing and enhancing the gut. This can be particularly beneficial in cases where the gut is injured, and diarrhoea becomes an issue.

In a study in which one hundred and sixty children participated, half of whom received standard therapy in combination with BC, while the other half received standard therapy and a placebo, it was observed that the group consuming BC experienced a significant decrease in the frequency of vomiting and diarrhoea after forty-eight hours of treatment [40]. It is important to note that this study was conducted in a developing country where diarrhoea still poses a significant threat for morbidity and mortality. Therefore, given the potential advantages of BC as a beneficial nutraceutical product on the market, it is worthwhile to trial its benefits for addressing these healthcare needs and concerns.

Another study sought out to investigate the impact of a combined therapy involving BC products (BCP) for five weeks, and then probiotics and BCP for another five weeks on children with autism spectrum disorders (ASD); this is a population in which the majority commonly experience concurrent GI issues [41]. Sanctuary et al. [41] hypothesized that providing these children with a combination of probiotics, namely *Bifidobacterium longum subspecies infantis* and BC, which is rich in Ig and oligosaccharides, could promote a healthier gut microflora. The initial objective was to determine the tolerability of the supplement; then to evaluate the practicality of designing a potentially larger study in the future. The primary outcome measures were focused on assessing changes in the intestinal microbiota, and how well the participants tolerated it. Firstly, it is important to highlight that the participants in the group demonstrated great tolerance to both supplements, with no substantial side-effects reported, which is consistent with findings from other referenced studies. There were some noteworthy reductions in the occurrence of diarrhoea in the group receiving BCP treatment alone, and a significant decrease in pain during both treatments. Parents noticed a reduction of such behaviours like irritability and lethargy which would coincide with improved GI symptoms [41]. However, it is important to acknowledge certain limitations of the study. The research was conducted with a relatively small sample size, underscoring the necessity for a more extensive and controlled clinical trial. Also, children with ASD may encounter challenges in verbally expressing their physical sensations, such as improvements in GI health and reduced discomfort during bowel movements. Additionally, the taste of the supplement was not particularly palatable, making it a challenge to administer to the participants. With that in mind, it serves as a starting point for the desire to undertake further trials on a much larger scale, aimed at establishing solid evidence regarding the tolerance and advantages of BC in the GIT.

### 3.2.3 The use of BC in Infectious Diseases

In many developing countries, a significant proportion of diarrhoea cases can be attributed to bacterial and viral pathogens, such as HIV, Rotavirus, *Escherichia coli (E.coli),* Salmonella, Campylobacter, etc. There have been emerging studies exploring the use of BC and its components to combat against various viruses and bacteria, since it contains high amounts of antibodies and Ig. Previous studies have suggested that colostrum supplements have indeed been effective in ameliorating symptoms of diarrhoea in HIV-positive patients [42]. Therefore, to support this, an experiment was conducted in Northern Uganda, which involved eighty-seven adult participants who were living with HIV and experiencing HIV-associated diarrhoea. When given a colostrum-based supplement in addition to standard treatment, the results indicated a reduction in daily stool frequency, fatigue, and an increased general sense of wellbeing [42]. This suggests that BC preparations may be a valuable supplement in the managing of patients with HIV/AIDS who experience chronic diarrhoea, and further research should substantiate this finding.

As previously discussed, BC possesses antibacterial, antiviral, antiprotozoal, antifungal, and immunomodulatory properties, and partakes in various physiological, biochemical, and defensive functions. Within the realm of colostrum, hyperimmune BC has gained attention as a remarkable substance with potential health benefits. The idea is to deliberately expose cows against specific viral or bacterial antigens, by vaccinating them during gestation, which will stimulate the cows to produce colostrum with elevated levels of specific antibodies against these antigens. The colostrum will be rich in IgG, the antibodies that play a pivotal role in the body's defence against pathogens. The result is a colostrum with enhanced immune properties referred to as hyperimmune bovine colostrum (HBC). HBC has a broad spectrum of applications in various fields, particularly health, immunity, and disease prevention.

Bovine rotavirus (BRV) is one of the main causes of a condition in calves known as "calf scours", which is characterised by diarrhoea and can lead to significant dehydration and weakness to the neonate. Most calves are exposed early in their lives and can continue to be vulnerable for up to eight weeks. BRV can cause damage to the apical villous epithelial cells of the intestine causing villous atrophy and malabsorption [43]. This

disruption of the normal functioning cells, lead to the characteristic symptom of diarrhoea seen in affected individuals.

Parreño et al. [43] sought out to observe the impact of maternal antibodies in colostrum on the protection and development of the immune system in calves against BRV. Three distinct calf groups were organised: one group was deprived of colostrum (CD), the second group received control colostrum (CC) and the third group was provided with colostrum rich in IgG1 titre to BRV, referred to as immune colostrum (IC). All three groups were monitored and deliberately exposed to BRV, where it was seen that all groups became infected; however, the IC group had significantly reduced duration, by days, of diarrhoea compared to CD and CC. Both groups CC and IC also had a delayed onset of diarrhoea. Antibody secreting cells (ASC) were evaluated in the intestine's postmortem, and it was observed that the intestines indeed served as the primary location for the response of ASC against BRV, with large numbers of IgA detected here [43].

This study raised an intriguing question: if HBC can benefit calves in counteracting rotavirus, could it also offer potential advantages for children and adults who are infected with rotavirus? The promising findings have spurred the exploration of HBC applications in human health, particularly addressing rotavirus-related infections.

Rotavirus is recognised as a primary cause of infectious diarrhoea in infants and young children on a global scale. In GI infections, the most crucial protective factor is the existence of specific antibodies within the lumen of the small intestine. The predominant Ig in BC is IgG, while in humans it is IgA. However, bovine IgG can serve as an efficient method for conferring passive immunity, offering protection to both animals and humans against various diseases [44]. Over the past several decades, numerous researchers have focused their investigations on hyperimmunised milk from cows as a potential means for preventing and treating certain infectious diseases.

However, in recent years, there has been a shift in interest towards HBC, which has gained prominence as a promising subject for immune therapy and disease management. The effectiveness of HBC containing neutralising antibodies targeting human rotavirus, with the aim of offering passive immunity to children, has been explored. It was observed in one study that the HBC did not lead to symptom improvement in cases where the rotavirus infection had already been present; however, it was found to be successful in reducing

the severity of diarrhoea in children when it was ingested before the onset of the infection [45,46]. In another study, children treated with BC containing high antibody titre against human rotavirus, effectively gained passive immunity as none of them acquired the infection during the treatment [47]. In a double-blind, placebo-controlled investigation with eighty children experiencing rotavirus-induced diarrhoea, it found that children who received immunised BC exhibited several favourable outcomes. They had a reduction in the volume and rate of daily stools, and experienced quicker elimination of rotavirus from the stool compared to those in the placebo group; they also needed smaller quantities of oral rehydration solution [48].

These studies seem to indicate that the presence of high titre antibodies against rotavirus was the primary factor in mitigating the symptoms, rather than the BC constituents alone. It is probable that the higher the antibody titre, the more effective the protection against infection. Hilpert et al. [49] utilised a milk concentrate of Ig preparation, to treat infants with acute rotavirus gastroenteritis, and found a noteworthy decrease in the excretion of the virus in stool samples coinciding with the existence of neutralising activity from the antibodies [49]. Despite it being a bovine milk concentrate from rotavirus hyperimmunised cows, the Ig present would be produced the same as those in colostrum, potentially using BC as a source of these Ig's in future research.

*Enterotoxigenic Escherichia coli* (ETEC) is a major perpetrator behind the occurrence of travellers' diarrhoea, a common sickness afflicting individuals visiting regions with poor sanitation and hygiene standards. This bacterium also poses a serious threat to children in developing countries, where diarrhoea remains a leading cause of illness and mortality. ETEC infection typically results from the ingestion of contaminated food or water and produces specific toxins that disturb the normal function of the intestinal mucosa [50,51]. At present, the most widely used approach to manage travellers' diarrhoea primarily involves rehydration and alleviating symptoms. Antimicrobial agents are not commonly used due to concerns about potential adverse side-effects and a decline of efficacy caused by the appearance of antibiotic-resistant bacteria [52].

Given the challenges in developing an effective vaccine against ETEC, the pursuit of alternative therapeutic approaches has led to the suggestion that HBC might hold promise in reducing the risk of travellers' diarrhoea. As previously mentioned, BC is rich in antibodies, cytokines, growth factors and antimicrobial properties, and its therapeutic

potential in promoting human health has been acknowledged for quite some time, with extensive research for its use as a nutritional supplement against GI pathogens [50]. HBC, administered in a tablet form and enriched with pathogen-specific Ig against ETEC, demonstrated a remarkable protective effect in 90.9% of participants against the development of diarrhoea [52]. Huppertz et al. [53] carried out research focusing on children experiencing diarrhoea caused by diarrheagenic *E. coli*. The findings revealed that BC fortified with antibodies against Shiga toxin and enterohemorrhagic *E. coli* led to a significant reduction in the frequency of loose stools; it did not however have any apparent impact on the presence of the pathogen [53].

In another study conducted, the application of milk immunoglobulin concentrates (MIC) containing antibodies targeting enteropathogenic *E. coli* strains in children, resulted in the elimination of the *E. coli* strain from stool samples in 84.2% of the cases, offering compelling verification that MIC is successful in removing the *E. coli* strain from the gut [54]. This leaves an opportunity for researchers to expand upon this study using HBC and support the increasing evidence of utilising colostrum therapy. This research has the potential to pave the way to prevent or treat children in developing countries against ETEC, or any *E. coli* strains inducing diarrhoea.

HBC is becoming more popular in research proposals, as an antimicrobial substance rich in IgG, that appears to have the capability to maintain the integrity of the intestinal microbiome and may even serve as a potential substitute for antibiotic treatments. Therefore, it could alleviate the risk for any kind of new emergence of antibiotic-resistant organisms [55]. As I mentioned earlier in this thesis, HBC has been investigated for its therapeutic effects on enteric microorganisms, with a high rate of success.

Another bacterium known for inflicting gastro issues resulting in infectious diarrhoea is *Clostridium (Cl.) difficile*. *Cl. difficile* predominantly impacts elderly patients as a consequence of antimicrobial therapy, which appears to disturb the normal integrity and function of the gut microbial community [55]. Different *Cl. difficile* strains were starting to become more apparent in displaying increased tendencies of antibiotic resistance; therefore, an urge to delve into potential alternative treatment options was a necessity. Subsequently, it was evident to consider the use of HBC in treating *Cl. difficile*. Steele et al. [55] demonstrated HBC successfully prohibited the development of infections caused by *Cl. difficile* in piglet models, as well as reducing the occurrence of diarrhoea

[55]. Although additional evidence from human-based investigations is necessary, this preliminary study suggests that HBC may be a promising treatment for *Cl. difficile* in human patients in the future.

The outcomes of utilising immunoglobulins obtained from BC prepared from hyperimmunised cows in human diseases have displayed considerable promise in the reduction, prevention, and treatment of infectious diarrhoea.

### 3.2.4 Bovine Colostrum in Association with Respiratory Illnesses

Respiratory tract illnesses can affect the upper and lower respiratory system, extending from the nose to the lungs. These illnesses can be caused by a multitude of factors including genetics, environment, lifestyle, health status, exercise, and various pathogens such as bacteria, viruses and on occasion, fungi. Recurrent respiratory tract infections pose a significant public health issue in developing countries [56]. These infections often caused by a combination of limited access to healthcare, poor sanitation, overcrowding and malnutrition, particularly affect children, the elderly and immunocompromised individuals [57].

As previously discussed in detail, BC boasts a wide array of immune-promoting, antimicrobial properties, contributing to its substantial Ig content, which is believed to be almost a hundred-fold more than regular bovine milk [58]. Considering this, and with several successful studies demonstrating the efficacy of BC in addressing infectious diseases affecting the GIT, it was trialled for its potential in treating respiratory conditions. A study conducted in Jordan of a man experiencing recurrent viral respiratory tract infection (RTI) five times over the course of a year, was given oral capsules of BC in different phases for a year [58]. Nasal swabs were collected, and the investigators observed a notable reduction in the overall viral load. Furthermore, the individual taking the BC supplement did not experience any RTI throughout the year during the trial, suggesting that the supplement may have prevented the onset of such infections.

Immunoglobulin A is the main Ig for the immune system to protect mucosal surfaces, and research has shown a correlation between the levels of IgA in saliva and the body's ability to resist upper respiratory tract infections [59]. Therefore, children and adults suffering with IgA deficiency regularly experience disturbances to their respiratory and gastrointestinal systems with infections, etc. In a double-blind, placebo-controlled study,

thirty-one children with IgA-deficiency, who were suffering from viral upper RTI (URTI), were administered oral BC supplements with the aim to increase Ig levels. The results of the study indicated that while the BC group experienced a lower severity of infection, the levels of IgA in the saliva did not show an increase [59]. This suggests that BC may be helpful in reducing the symptoms of URTI, but additional research is necessary to further validate these findings. Previous studies have suggested similar outcomes, where symptoms were reduced, but more comprehensive investigations are required to further support the potential benefits BC may offer [60-62].

Many studies have supported the findings that engaging in rigorous physical activity can temporarily suppress the immune system, making individuals more susceptible to RTIs [27]. They indicate that URTI are the most predominant 'non-injury-related' complaints observed in sports medicine clinics [27]. However, there is limited data from studies exploring BC in athletes susceptible to URTI. Some reviews and meta-analyses on this topic have concluded that the evidence, derived from the studies they selected and deemed appropriate during their search, had reduced rates of upper respiratory symptoms and episodes; however, they also had limitations and exhibited substantial variations in results. Therefore, further research is imperative to draw more concrete conclusions [63].

Stress is another common factor that can lead to a depressed immune system, leading to a reduced ability to defend against invading microorganisms and increasing the risk of URTI. It is widely recognised that students in rigorous programmes, such as medical and scientific studies, experience significant stress during their university years. With this in mind, researchers aimed to investigate whether individuals with a weakened immune system, due to being under constant stress at university, and thus, at higher risk for potential URTI, would benefit from BC supplementation. It followed a group of medical students more 'at risk' and their counterpart health science students, who are not exposed to as much infectious agents or have the same level of workload, using a triple blind, placebo-controlled trial. It concluded that the colostrum group exhibited significant results in preventing URTIs, with a reduction in the number of days with symptoms, decreased severity of symptoms, and an overall improvement in general well-being [64].

Influenza, commonly known as the flu, is a highly contagious respiratory illness caused by influenza viruses. It affects a great proportion of people each year and presents a significant global public health safety concern [65]. It can be characterised by fever,

chills, cough, sore throat, runny nose, body aches and fatigue [66]. As the influenza virus is constantly evolving it is very difficult to maintain effective vaccines; however, the seasonal flu vaccine is recommended, especially to the elderly and immunocompromised individuals. Several studies have trialled the impact of BC supplements on human and animal models, to determine its effectiveness, with positive outcomes.

In a study comparing the effectiveness of the flu vaccine with BC consumption, four groups were formed: no treatment, vaccine and BC, vaccine only, and BC only. The study concluded that both BC groups had significantly lower episodes of the flu and three times less days experiencing the symptoms. Part two of the study included very-high-risk patients, with severe pulmonary hypertension and cardiovascular problems. The outcome suggests that individuals who took the colostrum supplement experienced less episodes, and hospital admissions were significantly reduced [67]. This study highlights the potential benefits of combining the influenza vaccine with BC to enhance its effectiveness and increase protective mechanisms against influenza viruses.

Scientists were intrigued by the mechanisms through which BC seems to combat certain viruses, such as the influenza virus, prompting them to investigate the molecular methods underlying these mechanisms. Uchida et al. [68] demonstrated that mice supplemented with concentrated bovine late colostrum had increased natural killer (NK) cell activity on Peyer's patch cells, splenocytes and lung cells, as well as significantly lower accumulated symptom rate when compared to the control group [68]. These findings suggest that the oral intake of BC triggers mechanisms at both a systemic and local cellular immunity level, activating an array of NK cells that contribute to combating influenza in mice. Similar scenarios may be seen in human-based trials with further investigations.

BC was seen to show some improvement in URTI, being biologically rich in Ig, growth factors, cytokines and very importantly lactoferrin, which has been reported to be effective in fighting against SARS-CoV-2 [69]. The biologically luxurious profile of BC has sparked a hypothesis about whether its benefits could be harnessed at a therapeutic level to aid in the treatment of patients who are suffering with severe acute respiratory syndrome (SARS) caused by COVID-19. The Coronavirus disease pandemic was a devasting event in recent history, bringing the world to a standstill and having profound implications on health, economies, and daily life, globally. This highly contagious virus led to widespread illness and loss of life, overwhelming healthcare systems and reshaping

the world in numerous ways. With so much at stake, there was a race against time in the scientific community to identify, isolate and develop protective measures, including vaccines to reduce the severity of symptoms and curb the spread of the infection, on a global scale.

The manifestation of the infection varied among individuals and depended on several factors. For the majority, a robust immune system response played a pivotal role in defending against the infection, by recruiting macrophages and monocytes. In contrast, immunocompromised individuals, whose immune system was not functioning at their optimal capacity, faced greater challenges to fight off the infection, leading to cytokine storms and eventually severe lung issues [70]. The immune promoting and antiviral activity of BC was what appealed to researchers when finding alternative methods of treatments. Lactoferrin in particular was of interest due to its antimicrobial properties and its ability to disrupt the binding of certain receptors by coronavirus [71]. A study conducted early in the pandemic aimed to determine whether there were elevated IgA levels in the breast milk of women who had been previously infected with COVID-19. It was concluded that an increase of IgA levels was observed, indicating that breastfeeding could potentially transmit adequate antibodies against COVID-19 to infants [72].

This concept could be applied using HBC, as there is up-to-date data suggesting BC and its constituents might serve as a non-pharmacological option for treatments of COVID-19 patients. Furthermore, there is outstanding research supporting the benefits of BC supplements to the immune system, strengthening its defences against bacterial and viral respiratory infections. Therefore, more research should be conducted in this area, through well-structured and trustworthy investigations [69].

### 3.2.5 Bovine Colostrum in Association with Athletes

Bovine colostrum has in recent years, gained attention in the context of athletic performance and recovery. Athletes, whether they are amateur or professional, are continually seeking ways to explore nutritional strategies to improve their performance and enhance recovery and well-being. BC offers a unique blend of bioactive compounds, as previously discussed, which have sparked a lot of studies and trials, exploring the potential advantages for athletes of all kinds. As mentioned previously, there is substantial support indicating the positive potential of BC for athletes, particularly in

association with their GI health, and to a lesser extent some evidence to suggest its potential in the respiratory systems, although additional studies are required to further explore this hypothesis. Although several studies have investigated the impact of BC supplementation on various facets of athletic performance and exercise, conflicting findings have emerged, likely attributing to several factors. Such factors may include, the quality of well-sourced BC and its bioavailable composition, the dosage regime, the layout of the investigation, the sample size, and the fitness condition of participants.

Many studies have focused on BC's rich profile of macro- and micronutrients, and enhancing factors such as growth factors, as a means to improve immune function, enhance performance, and promote muscle growth. A study carried out in 1997, was one of the first to examine the effects of BC on serum IGF-1, IgG, hormones, and saliva IgA during intense training [73]. Although most of these parameters showed no significant increase compared to the placebo, the notable exception was serum IGF-1, which displayed a noteworthy increase, marking an interesting find at the time. This discovery was especially intriguing because IGF-1 is thought to be the mediating factor through which growth hormone affects skeletal muscle [73]. Therefore, this finding suggested the potentials of BC in promoting the growth of muscles, and raised questions about its broader possible benefits, prompting the initiation of numerous subsequent investigations.

After evaluating various studies aimed at substantiating the claim that BC supplements could potentially increase muscle mass, conflicting results emerged, with some showing no significant differences [74]. However, Antonio et al. [75] investigated BC supplementation on body composition and exercise performance, namely muscle strength and endurance. The study found that the only significant result worth noting, was an increase of bone-free lean body mass; however, the precise mechanisms through which BC contributed to this increase is not yet understood, and is speculated to be possibly due to influence of increased IGF-1 [75]. Interest was piqued within the scientific community not just regarding the potential of BC to enhance muscle growth, but also to potentially apply it to muscle repair following intense exercise. A six-week study emerged of the effects of BC on soccer players who would undergo high-intensity physical activity, leading to exercise induced muscle damage (EIMD) and subsequently decreased performance. The degree of muscle damage ultimately dictates the duration of the repair

and recovery progress. The study utilised a long-term, low-dose regimen of BC and observed significant reductions in biochemical markers such as creatine kinase, C-reactive protein, and interleukin-6. Additionally, participants demonstrated improved performance in activities like squat jumping, suggesting that BC could potentially mitigate EIMD and enhance overall physical performance [76], leading to faster repair and recovery periods.

Intense exercise exerts a strenuous pressure on the body, affecting it physically, emotionally, and physiologically. This kind of rigorous physical activity results in muscle breakdown, which necessitates adequate periods of rest and recovery. These periods of rest can be quite lengthy, disrupting training schedules and causing inconvenience for many. Therefore, athletes of all levels are constantly in pursuit of methods or supplements that can minimise the risk of injury, aid in recovery and reduce physical stress on the body. Some studies observed that while they were initially seeking evidence of enhanced performance in these athletes through BC supplementation, it did not, in fact, impact performance. However, it may have had a positive effect on the recovery process. Thirty males partook in an eight-week trial, combining endurance running training with BC supplement consumption. The primary objective was to evaluate any impacts on IGF-1 levels, exercise performance and post exercise recovery. While IGF-1 levels did not show an increase, which contradicted Mero et al.'s findings [78], and there was no immediate improvement in performance during the initial running bout, there was a notable potential for enhanced recovery following repeated bouts of exercise, with up to 5.2% improvement in participants after the second bout of exercise, at the end of the eight-week period [77].

There is much to speculate concerning the underlying mechanisms of BC to elicit such recovery processes. BC supplementation has been shown to have the capacity to increase essential amino acids during recovery [78], these amino acids are crucial building blocks for synthesising protein and particularly muscle protein synthesis. They build and repair muscle tissue, and it has been reported that branched-chain amino acids reduce muscle damage caused by exercise, and in turn, promotes recovery [79].

Human blood possesses a natural buffering system which regulates the pH of blood. These buffers are carbonic acid and bicarbonate anions which create an acid-base balance. This system acts to counteract any significant changes in blood pH caused by substances

that enter the blood and cause alterations in hydrogen ion concentration. During exercise, hydrogen ions can increase significantly which causes blood pH to drop, leading to a more acidic environment [80]. Moreover, increased levels of lactic acid, which is a by-product generated during incomplete glucose breakdown in the anaerobic glycolysis process, occurring during exercise, can exacerbate the reduction of blood pH [81]. The acidity can result in muscle fatigue, discomfort, cramps, and delayed onset muscle soreness (DOMS), which are commonly experienced symptoms following exercise.

On the other hand, blood alkalosis, defined as an elevated blood bicarbonate concentration and therefore pH, has been demonstrated to be advantageous for exercise performance [80]. Hence, many athletes and exercise enthusiasts strive to keep their blood pH within an alkaline range, often resorting to supplements to boost their extracellular buffering capacity and, in turn, counteract exercise-induced acidosis. Various supplements with the potential to enhance buffering capacity have undergone extensive research, such as sodium bicarbonate, sodium citrate, and sodium/citrate lactate [82]. The ingestion of these substances prior to exercise leads to elevated blood pH, inducing alkalosis and subsequently enhancing exercise capacity and performance. Among them, sodium bicarbonate has demonstrated the greatest efficacy in improving high-intensity exercise performance; however, it is important to note that it can be associated with concerning side effects, notably GI distress [82]. For this reason, a growing interest in finding alternative supplements which will have minimal side effects, but cause a positive impact in blood buffering capacity, have been strongly sought after.

BC has been the focus of considerable attention in the world of sports and exercise, using mechanisms that remain unknown to scientists. A study conducted by Brinkworth et al. [83], revealed that supplementation of BC to female rowers for nine weeks, during a tailored training programme, resulted in improved blood buffer capacity, in contrast to the placebo group [83]. Since BC has shown no reported adverse side effects in any trial and has demonstrated no negative influence on the GI microbiome, this study ignited even greater interest in this field. Nevertheless, there are lingering questions about the precise mechanisms through which BC enhances blood buffer capacity. Some researchers wonder whether BC directly caused this outcome or if BC's components indirectly contributed to these effects during this trial [84]. Moreover, it is intriguing that despite

the expected benefits of increased buffering capacity for exercise performance, the study did not identify any positive impact on overall performance.

Brinkworth et al. [85] revisited the research one year later and obtained conflicting results. In their subsequent study, they found that BC supplementation had no impact on plasma buffer capacity or haemoglobin concentration. They suggested that the previous reported increase in buffer capacity, which resulted from BC supplementation, was likely due to adaptations in tissue buffer systems rather than changes in specific blood buffer parameters [85]. These findings leave a gap for further research to delve into and analyse this area in more depth.

As previously discussed, BC comprises a variety of compounds that may offer potential benefits for immunity and overall health amongst athletes. This is especially relevant since strenuous exercise is often associated with a temporary suppression of the immune system and it is widely acknowledged that this mechanism is a contributing factor to the elevated incidence of infections among athletes [86]. The 'open window' concept, is used in exercise physiology and immunology, suggesting that during and after intense physical activity or endurance exercise, there is a temporary period of increased susceptibility to infections [87]. There is compelling evidence to suggest that daily supplementation with BC over a period of weeks can help preserve the integrity of the intestinal barrier [88], enhance immune function [89] and lower the risk of athletes engaged in intense training from contracting infections [69].

A study which saw significantly increased salivary IgA levels in distance runners after twelve weeks of BC supplementation, demonstrated that BC may potentially induce these specific Ig to defend against URTI in susceptible athletes [90]. Again, a majority of these mechanisms responsible for the beneficial effects of BC have not been fully elucidated. However, there is substantial speculation that the bioactive molecules present play a pivotal role in these effects, and that they can withstand the digestive process without losing their beneficial properties and be readily available in the system. Nonetheless, further research is needed to gain a more comprehensive understanding of these mechanisms in athletes.

### 3.2.6 Bovine Colostrum in Immune Health/Supplements

Growing consumer demand for nutritionally beneficial and health-promoting foods is motivating food manufacturers and researchers to develop safe and economical food products, that can offer a variety of wellness within a single product. The bioactive components found in BC demonstrate cross-species bioactivity, rendering it a compelling option for the exploration and creation of food products and pharmaceuticals with applications in both veterinary and human domains [2]. Significant advancements have been achieved in the past twenty years to develop technologies designed to separate, fractionate, and isolate purified form of numerous proteins that are present in bovine colostrum and milk [91], making this a keen subject of interest for researchers, manufacturers and consumers alike. As BC gained increasing popularity within the scientific community, for its potential in enhancing immune systems, improving certain human diseases and managing their symptoms especially in the GIT, there was an opportunity in the market to create and develop supplements containing active BC biomolecules which could be deemed safe for human consumption. The focus was on immune health as BC contains antibodies, immunoglobulins, growth factors, and other immune-boosting compounds, that have the potential to enhance the human body's immune system and help protect against infections. BC also has an abundant supply of proteins and active peptides [92]. These active peptides can be released through processes like GI digestion or milk fermentation using proteolytic enzymes and have the potential to induce various physiological effects in vivo, impacting several body systems [91].

In the past, the lack of appropriate technologies and procedures restricted the development to retrieve these biomolecules on large industrial scales to produce such products; however, nowadays there are emerging techniques and instruments used to harvest, isolate and identify colostrum constituents, such as 'solid-phase extraction, transmission infrared (IR) spectroscopy, split trehalase immunoglobulin G assay (STIGA), proteomic analysis, isobaric tags for relative and absolute quantitation (iTRAQ), and lectin microarray profiling' [92].

Numerous studies have revealed a strong correlation between the consumption of BC and the enhancement of immunity in both neonate and adult humans. This led to the initiation for human supplementation trials, driven by the potential to enhance gastrointestinal health and function [10], and has now become widely available in the United States and

European Union, for its healthy immune boosting and anti-microbial properties in supplementation form, where it may be dried and made into a pill or tablet [10]. It is widely available in form of powder, lozenges, supplemented milk and beverages, yogurt, butter and even chewing gum [35]. Biomedical and pharmaceutical companies are rapidly advancing in their efforts to develop safe, durable, effective medications and supplements from extractions of the beneficial bioactive molecules in BC, terming them 'nutraceuticals'. The term nutraceutical, is a combination of 'nutrition' and 'pharmaceutical', signifying products that offer both nutritional value and serve as adjuvant therapies, providing health benefits beyond basic nutrition [93]. This has offered a natural and potent way to support immune function, improve gut health in an efficient and cost-effective way for both adults and children.

### 3.2.7 Bovine Colostrum in Association with Infants/Neonates

Maternal human colostrum is widely recognised for providing substantial benefits to newborns, particularly in terms of immune support and essential nutrients. Therefore, the understanding that BC shares similarities, are a hundred to a thousand times more concentrated in its bioactive compounds compared to human colostrum [94], and can be harvested in greater quantities, is of great significance, especially in situations where a premature baby or an infant with specific nutritional needs requires additional nourishment. In a randomised, controlled trial, infants within one or two weeks of life, whose maternal milk was lacking or limited were substituted with either BC, human donor milk or infant formula. The BC group seemed to excel as these infants received a higher intake of enteral proteins, and/or achieved full enteral feeding at an earlier stage compared to the other groups. Additionally, plasma tyrosine was shown to be elevated for a short period, which may be a good indicator of protein over-consumption [95]. BC appears to serve as a valuable alternative or supplement to maternal colostrum when needed, offering essential nutrients and bioactive compounds that contribute to the infant's health and development.

Until recent years, the prospect of utilising BC to address nutritional and immunological needs of this particularly vulnerable group in society had remained largely left out. BC and its constituents have, however, undergone thorough examination for their potential applications in nutrition, immune-boosting and perhaps antimicrobial supplementation for newborns of various farm animal species (lambs, kids, foals and piglets), with some

beneficial effects on immunity [96]. Research studies have even extended their focus to domesticated pets, such as dogs, with notable benefits like significant increases of a diverse intestinal microbiome and stability, as well as heightened vaccine responses [97]. These findings indicate that BC could potentially serve as a special nutritional and bioactive supplement for newborn infants, particularly in terms of supporting intestinal functions. Given that BC is acknowledged not to be strictly species-specific, its versatile application has been extended to various animal species, including human infants.

Many studies conducted over the years focused on preterm piglets as research models. Neonate pigs have been utilised as a longstanding model for studying human infant nutrition and gastroenterology, primarily due to the significant similarities they share with humans in terms of physiology, anatomy and metabolism [98]. A substantial number of these studies were focused mainly on the potential beneficial outcomes in the GIT of piglets and infants alike [40,48,99] confirming the benefits to the microflora in the gastrointestinal tract, in helping them heal and promote protection against harmful bacteria and other pathogens. Premature neonates of any species have an increased risk of infection, as their immune systems are less effective and underdeveloped, as well as immature organ systems, stunted growth and neurocognitive deficiencies. For this reason, it was speculated that preterm neonates may benefit from the enteral feeding of colostrum, and there is evidence to suggest that BC is effective to promote growth and improve resistance against system infection in preterm piglets [100]. These studies have emphasised the importance of using piglets as human models to assess the efficacy of BC in terms of nutrition, immune support, and milk supplementation purposes in human infants.

### 3.2.8 Bovine Colostrum in Association with Other Aspects

#### *3.2.8.1 Wound Healing*

With the knowledge attained regarding bovine colostrum having exceptional immune benefits, it sparked interest in the area of wound healing and its consequent potential for higher rates of rapid recovery in individuals. Wound healing is a complex and dynamic biological process that the body undergoes in response to injury or damage. It involves a sequence of well-coordinated events that aim to restore tissue integrity and function. The process can be divided into three continuous but overlapping phases: haemostasis/inflammatory phase, proliferative phase and remodelling phase [101]. BC

garnered interest due to its capacity to harness a multitude of anti-inflammatory properties, as well as 'immune, developmental, and tissue repair factors' [102]. Research studies have aimed to investigate whether BC holds the potential to facilitate wound healing and the process of the underlying mechanisms at which it may exert these effects. Kim et al. [102] showed the success of BC in wound healing with results of increased cell migration, proliferation and endothelial tube cell formation, as well as increased levels of IL-4, which promotes anti-inflammatory processes during the inflammation stage. The mechanisms were discovered to involve the upregulation of numerous proteins associated with the process of wound healing [102]. Other studies support this outcome, that BC can promote proliferation, migration and provide advantageous pro-healing activities [103-105]. These studies suggests that a natural bio-substance like BC, which can be collected on a large scale, may offer favourable and efficient approaches in supporting the wound healing process, with minimal or absent side effects.

#### *3.2.8.2 Diabetes*

Diabetes is a chronic medical condition characterised by high levels of glucose in the blood. It occurs when the body either does not produce enough insulin or cannot effectively use the insulin it produces. Insulin is a hormone that plays a crucial role in regulating blood sugar and allows it to enter cells for energy. There are two types: Type 1 is described as an autoimmune defect, and Type 2, which is more common, is a result of insulin resistance. The administration of BC to mice, with Type 1 diabetes, was regularly monitored for glucose levels, and revealed a noteworthy discovery. BC appeared to influence immune cells, resulting in a down-regulation of harmful responses directed towards pancreatic beta cells. Simultaneously, there was an up-regulation of IL-4 [106]. While this finding holds significant promise, further investigations are essential to substantiate and expand upon these initial observations.

## 4. METHODS

The aim of this thesis was to conduct a research literature review on the effects of bovine colostrum in human medicine. To identify relevant studies for the review, several research methods were conducted, utilising various platforms and sources. Initially, access to the University library's VPN was obtained, eliminating the need to rely on library computers. This granted access, via a personal laptop, to a wealth of databases, e-journals and e-books. This enabled the search for multiple scientific search engines, including PubMed, Scopus, etc. The next step was to define the research objectives and identify the key concepts and search terms. There was a wealth of articles available concerning bovine colostrum constituents and the utilisation of bovine colostrum in human medicine with its associated benefits. Therefore, the search needed to be refined to key word terms that would lead to the desired topics of interest. To apply the search, specific word terms were formulated and used to query the search functions of various websites, resulting in the retrieval of relevant research publications. The search criteria included restricting the language of publications to English.

Example of search terms: Bovine colostrum constituents terms: ("bovine colostrum constituents" OR "bovine colostrum components" OR "bovine colostrum bioactive molecules")

Determining the criteria for including or excluding sources involved the process of selecting the relevant criteria by entering the appropriate search terminology into the scientific platforms and subsequently choosing the papers, articles and journals that appeared to be relevant. Following a thorough reading and evaluation of their contents, the relevance, credibility and quality needed to be aligned with the topic of this thesis. The assessment considered factors such as publication date, investigation format, sample size and most importantly reliable sources that contributed directly to the literature review enhancing depth and comprehensiveness. After the full evaluation, it became evident whether the information provided was applicable to the specific focus of this thesis topic. During the course of reading selected articles, many of them contained extensive bibliographies, which significantly facilitated the inclusion of further research and exploration of the topics of interest. These references served as valuable guides, steering the research process in the appropriate direction and allowing for a broader understanding of the subject matter.

## 5. RESULTS

The purpose of this thesis was to overview the literature available on the effects of bovine colostrum in human medicine. Numerous scientific papers online, including those on platforms like Pubmed, spanned several years of research. For the purpose of this thesis, a meticulous selection process was employed to identify and analyse papers that would most effectively contribute to this literature review. Throughout writing this thesis, a total of 108 papers were cited and referenced to support the findings and generate a comprehensive perspective on whether BC can have a positive influence on various aspects of human medicine. Many of the scientific papers which were reviewed for the purpose of this thesis, predominantly fell into two categories: literature reviews investigating the existing studies, or double-blinded, placebo-controlled trials. These trials involved a range of subjects, including both human subjects and animal models such as piglets, mice and rats. The inclusion of diverse study types and models added depth and comprehensiveness to the research and analysis conducted for this thesis.

The following are the results from this literature review:

1. Bovine colostrum (BC) versus mature milk

    - In BC, higher levels of Ig, growth factors, cytokines, protein, oligosaccharides, fat, vitamins and minerals
    - There were lower levels of lactose in BC, but it was found to increase as the secretion became mature milk

2. Factors affecting quality of BC

    - Time of collection
    - Genetics: Individual genetic variation and types of cattle breeds
    - Quality of nutrition
    - Premature milking leads to colostrum deficiency of Ig and therefore is less effective in passing on passive immunity to the newborn calf
    - Environment e.g. temperature, humidity, wet, dirty bedding
    - Stress
    - Animal husbandry e.g. living conditions, well-being, vaccinations

- Age and parity produce better quality colostrum as older cows have more exposure to pathogens and therefore produce antibodies against them
- Mammary gland diseases e.g. Mastitis

3. BC affecting the GIT

Hyperpermeability:

- Safe to consume, there were no reports of any adverse side-effects or negative impacts on the gastrointestinal microbiome
- BC contains growth factors, such as insulin-like GF, can repair and regenerate the gut lining, support gut epithelial cells, and mature the mucosal lining in Leaky Gut Syndrome [2,27]
- Transforming GF-β is a specific cytokine found in BC which had intestinal sealing ability [27]
- Athletes consuming BC supplement had decreased gut permeability and strengthened gut barrier [27,31]
- BC found to counteracts the rise of I-FABP, however no impact on the presence of circulating bacterial DNA [32]

Inflammatory bowel disease (IBD):

- Studies struggled to find correlations of Ig from BC to directly alleviate IBD symptoms [35]
- Serum-derived bovine immunoglobulin/protein isolate on co-culture model of intestinal epithelium reduced antigen-association inflammation [36]

NSAIDs:

- BC consumed with NSAIDs observed no rise in intestinal permeability [39]

Diarrhoea:

- BC as treatment for acute diarrhoea in children observed a decrease in frequency of vomiting and diarrhoea [40]

- Autistic children with frequent diarrhoea, had decreased occurrence and pain after BC treatment [41]

Infectious diseases

- BC alleviated HIV-induced diarrhoea, leading to decreased frequency of daily stools, fatigue and an increase in well-being
- HBC used against rotavirus, although in one study it did not alleviate symptoms when rotavirus was present, it did reduce the severity of diarrhoea when consumed before the infection [45]. Another study observed HBC leading to positive passive immunity [47]. A third study showed a decreased volume of daily stools, eliminated rotavirus faster through the stools and patients needed less fluid to rehydrate [48]
- HBC used against *Enterotoxigenic Escherichia coli*, was found to have a protective effect of 90.9% of the participants against developing diarrhoea [52]
- HBC used against *Clostridium difficile*, stopped the development of infection in piglet models, as well as decreasing the occurrence of diarrhoea [55]

4. BC affecting the respiratory system

- Recurrent respiratory tract infection with BC supplement reduced the viral load on nasal swabs, and no recurrent RTI was recorded throughout the BC treatment [58]
- Patients with IgA deficiency and concurrent RTI, experienced lowered severity of symptoms with BC, however the level of IgA remained untouched in this study [59]
- In athletes suffering from RTI, some studies concluded reduced rates of symptoms, however, there are limitations and many variations in results [63]
- In stress cases, BC prevented URTI, reduced days and severity of symptoms, and improved well-being [64]
- BC lowered episodes of influenza and three times less days experiencing symptoms [67]

5. Athletes and BC

    - An early study found BC increased serum IGF-1 [73]. However, later studies had contradictory results [77]
    - BC found to increase bone-free lean body mass [75]
    - A study found IGF-1 was not elevated, no improvement in performance initially. However, in the second bout of exercise, performance improved by up to 5.2% potentially indicating enhanced recovery [77]
    - BC can increase essential amino acids during recovery [78]
    - BC improved blood buffer capacity [83]. However, the same researchers conducted another experiment and concluded no improved blood buffer capacity [85]
    - A study in distance runners observed an increase of IgA levels with BC [90]

6. BC in infants

    - BC infant group received higher enteral proteins, and/or achieved full enteral feeding faster [95]

7. Wound healing

    - BC treatment led to an increase in cell migration, proliferation, endothelial tube cell formation, an increase in IL-4 and up-regulation of proteins involved with the process of wound healing [102-105]

8. Diabetes

    - BC treatment led to a down-regulation of harmful responses directed towards pancreatic beta cells and an up-regulation of IL-4 [106]

## 6. DISCUSSION

In this comprehensive review, it has become evident that BC is a multifaceted bio-substance that has demonstrated intriguing results across various domains. Through the years, it has been recognised as a crucial element for survival of neonates in all species, providing them with a lifeline during the early, highly vulnerable stages of their lives. BC, the initial milk-like substance produced by a cow postpartum, is of utmost importance to be harvested within hours of its secretion. This is the time when it is richest in valuable, nutritionally dense compounds, teeming with immune-active molecules that are indispensable for neonates. As discussed throughout this literature review, it holds significant value in numerous aspects for humans as well.

BC is not a recent revelation to mankind; it is evident that it has been prepared and used for centuries within traditional medicinal practices [2], extending as far back as Ayurveda [21]. This ancient system of medicine presents a distinctive approach when compared to western medicine. In the early days of this particular culture, people discovered the richness of colostrum and its vital role in supporting the healthy development of newborns. They observed how colostrum helped neonates by nurturing their intestinal microflora, facilitating growth and bolstering their ability to combat invasive pathogens. Without these crucial defence mechanisms provided by colostrum, calves would have been vulnerable to potentially life-threatening infection.

BC differs immensely from mature milk, making it an essential component in the early life of a calf. Colostrum being the initial secretion produced by the cow immediately after giving birth, serves as a concentrated source of nutrients and bioactive molecules. Unlike mature milk, colostrum is rich in immunoglobulins, cytokines, a variety of growth factors that play crucial roles in strengthening the calf's immune system and providing passive immunity against a wide range of diseases. For this reason, it is of vital importance to ensure calves receive colostrum within hours of their birth. Additionally, colostrum has a higher fat content, offering essential energy for the calf during its early days of life. The difference in composition and the temporary nature of colostrum make it uniquely suited to meet the specific needs of the newborn calf. It is important to note that human infants primarily acquire maternal antibodies through the placental passage; however, calves must obtain these crucial antibodies through ingestion as there is no transfer through the placenta [98].

With rich amounts of Ig's, growth factors and cytokines, BC provides an immense contribution to helping the calf's immune system gain its defences, and combat against threatening infections early in life. These immune-boosting properties of BC piqued significant scientific interest, leading to eager investigations aimed at determining whether similar outcomes could potentially be observed in humans. Through numerous studies, research has demonstrated how it aids in supporting and strengthening the human immune system, positioning it as a potential agent that enhances the body's defence against various infections and conditions. The high concentrations of bioactive molecules such as lactoferrin and antimicrobial peptides play a vital role in promoting a healthy intestinal lining, reducing intestinal permeability and nurturing the flourishing of a balanced microbiome.

Numerous sources reviewed in this thesis provided compounding evidence to suggest that BC and its constituents have the potential to mitigate major GIT associated conditions that affect many people on a global scale. BC may be a promising natural remedy in addressing these GI challenges in humans. It has shown efficacy in managing conditions such as leaky gut syndrome, which involves increased intestinal permeability and potential immune system dysregulation through inflammatory responses. The bioactive components within BC's domain, including Ig, lactoferrin and growth factors, contribute to enhancing the integrity of the gut barrier and reducing inflammation. Furthermore, BC has demonstrated its worth in pathogen-induced diarrhoea, such as HIV, rotavirus, *E. coli,* and *Cl. Difficile*, by assisting in the prevention and treatment of infections, particularly in children, and those in underdeveloped countries. Its antimicrobial and immune enhancing properties make it an intriguing resource in combating pathogenic microorganisms. Moreover, BC has been explored for its potential to alleviate NSAID-induced gut damage, offering protection and support to the lining of the GIT, which is often seen to be irritated and injured after NSAID use. It is clear from these reviews, that BC seems to offer potentially diverse therapeutic applications within the GIT to promote health and well-being. However, not all studies yielded favourable outcomes.

Furthermore, BC extended its mode of actions onto the respiratory system, where increased interest has been mounting in this area, especially in light of the global COVID-19 pandemic. Once again, the immune enhancing compounds showed potential in aiding the defence against respiratory tract infections and the anti-inflammatory properties were

observed to reduce symptoms, even the reoccurrence of infection in some cases [58]. Additionally, it was interesting to observe how investigators explored the possible potentials of BC in the context of treating or preventing COVID-19, with a particular focus on BC's abundant level of lactoferrin and its strong antimicrobial properties [69,71]. While investigations are still in the early stages and evolving, there is no doubt that BC has the potential to support respiratory health and mitigate respiratory issues. BC may represent a holistic approach to enhance these body systems and well-being; however further research is needed.

BC has also made a notable impact on athletes and in the domain of sports and fitness, with advantageous outcomes, according to several studies conducted. BC being rich in growth factors and essential nutrients, demonstrated the potential to enhance exercise performance and recovery [76], increase muscle mass [75], reduce exercise-induced muscle fatigue and overall physical stress [77]. This highly favourable result has the potential to enable athletes to self-supplement, as a natural alternative, in a way that is not prohibited, will not have adverse effects on the body's physiology, and will not negatively impact gut bacteria. Additionally, it could lead to a reduced recovery time and muscle soreness, allowing athletes and active individuals to maintain a more consistent training regime, without the need for extended periods of rest to replenish muscle reserves. While research is still ongoing in this area, it is a promising natural supplementation that may pave the way to improved athletic performance and overall well-being.

The positive effects of BC leading to successful health outcomes, has caught the interest of major corporations and pharmaceutical companies [91]. They identified a niche in the market to create a safe and naturally occurring nutraceutical, bridging the gap between nutrition and therapeutic benefits, which is offered by BC, for a holistic approach to wellness [93]. The potential of BC to support immune health, GI well-being and overall vitality, is a very appealing concept for individuals who are seeking a natural alternative to dietary supplements. This development of BC as a nutraceutical, makes it convenient for consumers to access this versatile health promoting substance through a single product. With increasing interest in holistic health, the use of BC is likely to expand, and research will continue to explore this new and exciting substance for human health.

The wealth of supporting evidence underscores the vast potential that BC has to offer. It is remarkable how this naturally occurring secretion has gained widespread recognition for its beneficial effects in different aspects of human medicine.

However, it is important to acknowledge that not all studies succeeded in elucidating the potential benefits that BC may offer. Throughout the extensive research process conducted for this thesis, a few studies and trials surfaced, that unfortunately did not yield the anticipated beneficial results [107,108].

As discussed previously, BC appears to have a generally positive influence on the GIT in both children and adults. However, a specific study aimed at assessing the efficacy of BC in improving intestinal function in children with short bowel syndrome, revealed that BC treatment did not have a significant impact on or enhancement to the intestinal function [107]. This study was a randomised, double-blind, crossover study, with a sample size of nine children, may have limited the findings. Nonetheless, further research, with possibly a larger sample size, is required to gain more understanding.

BC was shown to have positive effects with certain infectious pathogens, however Ashraf et al. [108] demonstrated that HBC treatment did not show any beneficial effects to reduce stool frequency, duration or severity of shigellosis in children.

It is also worth mentioning some disadvantages that may impede the potential benefits of using BC for humans. Notwithstanding, that there is often an excess of colostrum produced postpartum, there may also be occasions where there is a borderline sufficiency of BC, due to various factors. Using BC for human purposes may raise some concerns regarding the welfare of calves, primarily as BC is the “liquid gold” they rely on for passive immunity to support their immune system for protection, as well as containing many other essential nutrients and antibodies crucial for their development and growth. Diverting collected BC for human use may raise an ethical concern, due to the possibility that calves may not receive the complete amount they require, if a portion is allocated for human consumption. If there is a potential shortfall in colostrum for calves, this deficit could jeopardise their ability to fight infections and receive the immunity their life depends on. Therefore, it is important to establish a realistic balance in the utilisation of BC, between the medicinal benefits for human use, and the welfare of calves.

Another crucial parameter to consider when collecting BC for human consumption, is the antibiotic treatment history of cows producing the colostrum. It is essential that these cows have not undergone any antibiotic treatment, in order to prevent the potential development of antibiotic resistance within the food chain; specifically, the practise of blanket dry cow treatment, which involves administering antibiotics to all cows in the same herd, regardless of whether they have an infection or not. This approach is commonly carried out as a preventative measure of mastitis control. Thus, particular attention should be given to the antibiotic treatment practices of the dairy cows involved, ensuring safe and responsible collection of pure colostrum intended for human use.

Furthermore, it should be mentioned that not all individuals may tolerate the consumption of BC without experiencing potential side effects. BC contains a certain amount of lactose, albeit less than mature milk, but nevertheless it may be problematic for those with lactose intolerances, and thus, it is advisable for these individuals to refrain from consuming BC. Additionally, allergic reactions to certain proteins present in colostrum, may pose a significant risk for those who may experience adverse reactions to these proteins. Consequently, individuals with known milk protein allergies, should be cautioned against consuming BC for medicinal purposes.

Having read through over a hundred scientific papers and trials involving BC, and its impacts on human medicine, it is clear to me that the majority had positive outcomes with some very significant results that will pave the way for further research, notwithstanding the fact that a small percentage of the literature did not observe any significant impacts of BC in certain areas for therapeutic approaches in humans. Based on my review of the scientific literature, I am of the opinion that with further research and inevitable growing interest in BC as a therapeutic application, it may potentially result in a major breakthrough within the scientific community, on a global scale, to treat human diseases and conditions using a naturally-based product with very little to no adverse side-effects.

## 7. SUMMARY

The aim of this thesis was to investigate the effects of bovine colostrum in different aspects of human medicine, highlighting the nutritious value of BC, and its rich profile of bioactive molecules that are superior to that in mature milk, as almost all its compounds are at a higher level. These include immunoglobulins, growth factors, cytokines, macro- and micronutrients, all of which contribute to the development of the immune system, the maturation of the microbiome within the GIT and the growth and development of the newborn calf.

The review was compiled using a variety of specific word terms which were formulated and entered into numerous search engines of the scientific platforms used throughout this thesis. Many studies that surfaced, had ample information and research on the specific constituents of BC and how vital its impact is to the newborn calf, sparking the ongoing investigations for its use in human therapeutic approaches. The majority of the scientific literature and trials, which supported this thesis review, concluded their findings of BC having potential beneficial impacts in human medicine.

The main findings involved substantial evidence to support a range of conditions within the GIT, emphasising its potential to reduced hyperpermeability in the intestinal lining, reducing the effects of Leaky Gut Syndrome, reduced GI damage in association with NSAID therapy and decreasing symptoms, frequency and pain associated with diarrhoea. Volume, frequency and symptoms were also seen to be alleviated by BC in patients with infectious pathogen-induced diarrhoea such as HIV, rotavirus, ETEC and *Cl. difficile*.

Respiratory tract infections were seen to reduce in episodes as well as symptoms in patients suffering from infections, stress or influenza. Athletes was a major topic of discussion, some studies suggested increased performance, recovery and lean muscle mass; however, it was not without some discrepancies. Some studies, which have been studied to a lesser extent, such as BC in infants, wound healing and diabetes, have suggested some positive outcomes with compelling results.

Overall, the literature review for the purpose of this thesis has been positive, with a lot of potential, moving forward within the scientific community.

## 8. REFERENCES


1. Hammon HM, Liermann W, Frieten D, Koch C (2020) Review: Importance of colostrum supply and milk feeding intensity on gastrointestinal and systemic development in calves. Animal 14:s133–s143. https://doi.org/10.1017/S1751731119003148

2. Playford RJ, Weiser MJ (2021) Bovine colostrum: Its constituents and uses. Nutrients 13:265. https://doi.org/10.3390/nu13010265

3. Moore M, Tyler JW, Chigerwe M, Dawes ME, Middleton JR (2005) Effect of delayed colostrum collection on colostral IgG concentration in dairy cows. J Am Vet Med Assoc 226:1375–1377. https://doi.org/10.2460/javma.2005.226.1375

4. Virtala AM, Gröhn YT, Mechor GD, Erb HN (1999) The effect of maternally derived immunoglobulin G on the risk of respiratory disease in heifers during the first 3 months of life. Prev Vet Med 39:25–37. https://doi.org/10.1016/s0167-5877(98)00140-8

5. Hagiwara K, Kataoka S, Yamanaka H, Kirisawa R, Iwai H (2000) Detection of cytokines in bovine colostrum. Veterinary Immunology and Immunopathology 76:183–190. https://doi.org/10.1016/S0165-2427(00)00213-0

6. Boudry C, Dehoux J-P, Wavreille J, Portetelle D, Théwis A, Buldgen A (2008) Effect of a bovine colostrum whey supplementation on growth performance, faecal Escherichia coli population and systemic immune response of piglets at weaning. Animal 2:730–737. https://doi.org/10.1017/S175173110800164X

7. McGrath BA, Fox PF, McSweeney PLH, Kelly AL (2016) Composition and properties of bovine colostrum: a review. Dairy Sci & Technol 96:133–158. https://doi.org/10.1007/s13594-015-0258-x

8. Bleck GT, Wheeler MB, Hansen LB, Chester-Jones H, Miller DJ (2009) Lactose synthase components in milk: Concentrations of α-Lactalbumin and β1,4-Galactosyltransferase in milk of cows from several breeds at various stages of lactation - Bleck - 2009 - Reproduction in Domestic Animals https://onlinelibrary.wiley.com/doi/10.1111/j.1439-0531.2007.01047.x.

9. Zivkovic AM, Barile D (2011) Bovine milk as a source of functional oligosaccharides for improving human health. Adv Nutr 2:284–289. https://doi.org/10.3945/an.111.000455

10. Arslan A, Kaplan M, Duman H, Bayraktar A, Ertürk M, Henrick BM, Frese SA, Karav S (2021) Bovine colostrum and its potential for human health and nutrition. Front Nutr 8:651721. https://doi.org/10.3389/fnut.2021.651721

11. Liu H, Radlowski EC, Conrad MS, Li Y, Dilger RN, Johnson RW (2014) Early supplementation of phospholipids and gangliosides affects brain and cognitive development in neonatal piglets. The Journal of Nutrition 144:1903–1909. https://doi.org/10.3945/jn.114.199828

12. Küllenberg D, Taylor LA, Schneider M, Massing U (2012) Health effects of dietary phospholipids. Lipids in Health and Disease 11:3. https://doi.org/10.1186/1476-511X-11-3

13. Debier C, Pottier J, Goffe Ch, Larondelle Y (2005) Present knowledge and unexpected behaviours of vitamins A and E in colostrum and milk. Livestock Production Science 98:135–147. https://doi.org/10.1016/j.livprodsci.2005.10.008

14. DeLuca HF (1986) The metabolism and functions of vitamin D. Adv Exp Med Biol 196:361–375. https://doi.org/10.1007/978-1-4684-5101-6_24

15. Bikle DD (2012) Vitamin D and bone. Curr Osteoporos Rep 10:151–159. https://doi.org/10.1007/s11914-012-0098-z

16. Jahnen-Dechent W, Ketteler M (2012) Magnesium basics. Clin Kidney J 5:i3–i14. https://doi.org/10.1093/ndtplus/sfr163

17. Galland L (1988) Magnesium and immune function: An overview. Magnesium 7:290–299

18. Godden SM, Lombard JE, Woolums AR (2019) Colostrum management for dairy calves. Vet Clin North Am Food Anim Pract 35:535–556. https://doi.org/10.1016/j.cvfa.2019.07.005

19. Puppel K, Gołębiewski M, Grodkowski G, Slósarz J, Kunowska-Slósarz M, Solarczyk P, Łukasiewicz M, Balcerak M, Przysucha T (2019) Composition and factors affecting quality of bovine colostrum: A review. Animals (Basel) 9:1070. https://doi.org/10.3390/ani9121070

20. Maunsell FP, Morin DE, Constable PD, Hurley WL, McCoy GC, Kakoma I, Isaacson RE (1998) Effects of mastitis on the volume and composition of colostrum produced by holstein cows. Journal of Dairy Science 81:1291–1299. https://doi.org/10.3168/jds.S0022-0302(98)75691-7

21. Chauhan A, Semwal DK, Mishra SP, Semwal RB (2015) Ayurvedic research and methodology: Present status and future strategies. Ayu 36:364–369. https://doi.org/10.4103/0974-8520.190699

22. Godhia DML, Patel N (2013) Colostrum – its composition, benefits as a nutraceutical – A review. Current Research in Nutrition and Food Science Journal 1:37–47

23. Rocha JM (2016) On the historical background of bovine colostrum

24. Antonio J. Gonzaga, Robert J. Warren, Frederick C. Robbins; Attenuated poliovirus infection in infants fed colostrum from poliomyelitis immune cows. *Pediatrics* December 1963; 32 (6): 1039–1043. 10.1542/peds.32.6.1039

25. Thapa BR (2005) Therapeutic potentials of bovine colostrums. Indian J Pediatr 72:849–852. https://doi.org/10.1007/BF02731112

26. Davis PF, Greenhill NS, Rowan AM, Schollum LM (2007) The safety of New Zealand bovine colostrum: Nutritional and physiological evaluation in rats. Food and Chemical Toxicology 45:229–236. https://doi.org/10.1016/j.fct.2006.07.034

27. Dziewiecka H, Buttar HS, Kasperska A, Ostapiuk-Karolczuk J, Domagalska M, Cichoń J, Skarpańska-Stejnborn A (2022) A systematic review of the influence of bovine colostrum supplementation on leaky gut syndrome in Athletes: Diagnostic biomarkers and future directions. Nutrients 14:2512. https://doi.org/10.3390/nu14122512

28. Kinashi Y, Hase K (2021) Frontiers | Partners in leaky gut syndrome: Intestinal dysbiosis and autoimmunity. In: Frontiers. https://www.frontiersin.org/articles/10.3389/fimmu.2021.673708/full. Accessed 5 Nov 2023

29. Ribeiro FM, Petriz B, Marques G, Kamilla LH, Franco OL (2021) Frontiers | Is there an exercise-intensity threshold capable of avoiding the leaky gut? In: Frontiers in Nutrition. https://www.frontiersin.org/articles/10.3389/fnut.2021.627289/full. Accessed 5 Nov 2023

30. Siqueiros-Cendón T, Arévalo-Gallegos S, Iglesias-Figueroa BF, García-Montoya IA, Salazar-Martínez J, Rascón-Cruz Q (2014) Immunomodulatory effects of lactoferrin. Acta Pharmacol Sin 35:557–566. https://doi.org/10.1038/aps.2013.200

31. Hałasa M, Maciejewska D, Baśkiewicz-Hałasa M, Machaliński B, Safranow K, Stachowska E (2017) Oral supplementation with bovine colostrum decreases intestinal permeability and stool concentrations of zonulin in athletes. Nutrients 9:370. https://doi.org/10.3390/nu9040370

32. March DS, Jones AW, Thatcher R, Davison G (2019) The effect of bovine colostrum supplementation on intestinal injury and circulating intestinal bacterial DNA following exercise in the heat. Eur J Nutr 58:1441–1451. https://doi.org/10.1007/s00394-018-1670-9

33. Playford RJ, Macdonald CE, Johnson WS (2000) Colostrum and milk-derived peptide growth factors for the treatment of gastrointestinal disorders1234. The American Journal of Clinical Nutrition 72:5–14. https://doi.org/10.1093/ajcn/72.1.5

34. McDowell C, Farooq U, Haseeb M (2023) Inflammatory bowel disease. In: StatPearls. StatPearls Publishing, Treasure Island (FL)

35. Sienkiewicz M, Szymańska P, Fichna J (2021) Supplementation of bovine colostrum in inflammatory bowel disease: Benefits and contraindications. Advances in Nutrition 12:533–545. https://doi.org/10.1093/advances/nmaa120

36. Detzel CJ, Horgan A, Henderson AL, Petschow BW, Warner CD, Maas KJ, Weaver EM (2015) Bovine immunoglobulin/protein isolate binds pro-inflammatory bacterial compounds and prevents immune activation in an intestinal co-culture model. PLOS ONE 10:e0120278. https://doi.org/10.1371/journal.pone.0120278

37. Bindu S, Mazumder S, Bandyopadhyay U (2020) Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochemical Pharmacology 180:114147. https://doi.org/10.1016/j.bcp.2020.114147

38. Sinha M, Gautam L, Shukla PK, Kaur P, Sharma S, Singh TP (2013) Current perspectives in NSAID-induced gastropathy. Mediators of Inflammation 2013:e258209. https://doi.org/10.1155/2013/258209

39. Playford RJ, MacDonald CE, Calnan DP, Floyd DN, Podas T, Johnson W, Wicks AC, Bashir O, Marchbank T (2001) Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability. Clin Sci (Lond) 100:627–633

40. Hosny Barakat S, Ahmed Meheissen M, Magdy Omar O, Ali Elbana D (2020) Bovine colostrum in the treatment of acute diarrhea in children: A double-blinded randomized controlled trial | Journal of Tropical Pediatrics | Oxford Academic. In: Oxford Academic. https://academic.oup.com/tropej/article/66/1/46/5511643. Accessed 5 Nov 2023

41. Sanctuary MR, Kain JN, Chen SY, Kalanetra K, Lemay DG, Rose DR, Yang HT, Tancredi DJ, German JB, Slupsky CM, Ashwood P, Mills DA, Smilowitz JT, Angkustsiri K (2019) Pilot study of probiotic/colostrum supplementation on gut function in children with autism and gastrointestinal symptoms. PLOS ONE 14:e0210064. https://doi.org/10.1371/journal.pone.0210064

42. Kaducu FO, Okia SA, Upenytho G, Elfstrand L, Florén C-H (2011) Effect of bovine colostrum-based food supplement in the treatment of HIV-associated diarrhea in Northern Uganda: a randomized controlled trial. Indian J Gastroenterol 30:270–276. https://doi.org/10.1007/s12664-011-0146-0

43. Parreño V, Béjar C, Vagnozzi A, Barrandeguy M, Costantini V, Craig MI, Yuan L, Hodgins D, Saif L, Fernández F (2004) Modulation by colostrum-acquired maternal antibodies of systemic and mucosal antibody responses to rotavirus in calves experimentally challenged with bovine rotavirus. Veterinary Immunology and Immunopathology 100:7–24. https://doi.org/10.1016/j.vetimm.2004.02.007

44. Hurley WL, Theil PK (2011) Perspectives on immunoglobulins in colostrum and milk. Nutrients 3:442–474. https://doi.org/10.3390/nu3040442

45. Ebina T, Sato A, Umezu K, Ishida N, Ohyama S, Oizumi A, Aikawa K, Katagiri S, Katsushima N, Imai A, Kitaoka S, Suzuki H, Konno T (1985) Prevention of rotavirus infection by oral administration of cow colostrum containing antihumanrotavirus antibody. Med Microbiol Immunol 174:177–185. https://doi.org/10.1007/BF02123694

46. Mitra A, Mahalanabis D, Ashraf H, Unicomb L, Eeckels R, Tzipori S (1995) Hyperimmune cow colostrum reduces diarrhoea due to rotavirus: a double-blind, controlled clinical trial. Acta Paediatrica 84:996–1001. https://doi.org/10.1111/j.1651-2227.1995.tb13814.x

47. Davidson GP, Daniels E, Nunan H, Moore AG, Whyte PBD, Franklin K, Mccloud PI, Moore DJ (1989) Passive immunisation of children with bovine colostrum containing antibodies to human rotavirus. The Lancet 334:709–712. https://doi.org/10.1016/S0140-6736(89)90771-X

48. Sarker SA, Casswall TH, Mahalanabis D, Alam NH, Albert MJ, Brüssow H, Fuchs GJ, Hammerström L (1998) Successful treatment of rotavirus diarrhea in children with immunoglobulin from immunized bovine colostrum. The Pediatric Infectious Disease Journal 17:1149

49. Hilpert H, Briissow H, Mietens C, Sidoti J, Lerner L, Werchau H (1987) Use of bovine milk concentrate containing antibody to rotavirus to treat rotavirus gastroenteritis in infants. The Journal of Infectious Diseases 156:158–166. https://doi.org/10.1093/infdis/156.1.158

50. Sears KT, Tennant SM, Reymann MK, Simon R, Konstantopoulos N, Blackwelder WC, Barry EM, Pasetti MF (2017) Bioactive immune components of anti-diarrheagenic enterotoxigenic Escherichia coli hyperimmune bovine colostrum products | Clinical and Vaccine Immunology. In: American Society For Microbiology. https://journals.asm.org/doi/10.1128/cvi.00186-16. Accessed 5 Nov 2023

51. Kean BH (1986) Travelers' diarrhea: An overview | Clinical Infectious Diseases | Oxford Academic. In: Oxford Academic. https://academic.oup.com/cid/article-abstract/8/Supplement_2/S111/323829?redirectedFrom=fulltext. Accessed 5 Nov 2023

52. Otto W, Najnigier B, Stelmasiak T, Robins-Browne RM (2011) Randomized control trials using a tablet formulation of hyperimmune bovine colostrum to prevent diarrhea caused by enterotoxigenic Escherichia coli in volunteers. Scandinavian Journal of Gastroenterology 46:862–868. https://doi.org/10.3109/00365521.2011.574726

53. Huppertz H-I, Rutkowski S, Busch DH, Eisebit R, Lissner R, Karch H (1999) Bovine colostrum ameliorates diarrhea in infection with diarrheagenic Escherichia coli, shiga toxin-producing E. coli, and E. coli expressing intimin and hemolysin. Journal of Pediatric Gastroenterology and Nutrition 29:452

54. Mietens C, Keinhorst H, Hilpert H, Gerber H, Amster H, Pahud JJ (1979) Treatment of infantile E. coli gastroenteritis with specific bovine anti-E. coli milk immunoglobulins. Eur J Pediatr 132:239–252. https://doi.org/10.1007/BF00496847

55. Steele J, Sponseller J, Schmidt D, Cohen O, Tzipori S (2013) Hyperimmune bovine colostrum for treatment of GI infections. Human Vaccines & Immunotherapeutics 9:1565–1568. https://doi.org/10.4161/hv.24078

56. Rodríguez L, Cervantes E, Ortiz R (2011) Malnutrition and gastrointestinal and respiratory infections in children: A public health problem. International Journal of Environmental Research and Public Health 8:1174–1205. https://doi.org/10.3390/ijerph8041174

57. Cashat-Cruz M, Morales-Aguirre JJ, Mendoza-Azpiri M (2005) Respiratory tract infections in children in developing countries. Seminars in Pediatric Infectious Diseases 16:84–92. https://doi.org/10.1053/j.spid.2005.12.005

58. Alsayed A, Al-Doori A, Al-Dulaimi A, Alnaseri A, Abuhashish J, Aliasin K, Alfayoumi I (2020) Influences of bovine colostrum on nasal swab microbiome and viral upper respiratory tract infections – A case report. Respiratory Medicine Case Reports 31:101189. https://doi.org/10.1016/j.rmcr.2020.101189

59. Patıroğlu T, Kondolot M (2013) The effect of bovine colostrum on viral upper respiratory tract infections in children with immunoglobulin A deficiency. The Clinical Respiratory Journal 7:21–26. https://doi.org/10.1111/j.1752-699X.2011.00268.x

60. Brinkworth GD, Buckley JD (2003) Concentrated bovine colostrum proteinsupplementation reduces the incidenceof self-reported symptoms of upperrespiratory tract infection in adult males. Eur J Nutr 42:228–232. https://doi.org/10.1007/s00394-003-0410-x

61. Crooks C, Cross ML, Wall C, Ali A (2010) Effect of bovine colostrum supplementation on respiratory tract mucosal defenses in swimmers. International Journal of Sport Nutrition and Exercise Metabolism 20:224–235. https://doi.org/10.1123/ijsnem.20.3.224

62. Ramesh Menon P, Lodha R, Kabra SK (2010) Bovine colostrum in pediatric respiratory diseases: A systematic review. Indian J Pediatr 77:108–109. https://doi.org/10.1007/s12098-009-0257-0

63. Jones AW, March DS, Curtis F, Bridle C (2016) Bovine colostrum supplementation and upper respiratory symptoms during exercise training: a systematic review and meta-analysis of randomised controlled trials. BMC Sports Science, Medicine and Rehabilitation 8:21. https://doi.org/10.1186/s13102-016-0047-8

64. Baśkiewicz-Hałasa M, Stachowska E, Grochans E, Maciejewska-Markiewicz D, Bühner L, Skonieczna-Żydecka K, Hałasa M (2023) Moderate dose bovine colostrum supplementation in prevention of upper respiratory tract infections in medical university students: A randomized, triple blind, placebo-controlled trial. Nutrients 15:1925. https://doi.org/10.3390/nu15081925

65. Tregoning JS, Russell RF, Kinnear E (2018) Full article: Adjuvanted influenza vaccines. In: Taylor & Francis Online. https://www.tandfonline.com/doi/full/10.1080/21645515.2017.1415684. Accessed 5 Nov 2023

66. Luo M (2011) Influenza virus entry. Viral Molecular Machines 726:201–221. https://doi.org/10.1007/978-1-4614-0980-9_9

67. Cesarone MR, Belcaro G, Di Renzo A, Dugall M, Cacchio M, Ruffini I, Pellegrini L, Del Boccio G, Fano F, Ledda A, Bottari A, Ricci A, Stuard S, Vinciguerra G (2007) Prevention of influenza episodes with colostrum compared with vaccination in healthy and high-risk cardiovascular subjects: The epidemiologic study in San

Valentino. Clin Appl Thromb Hemost 13:130–136. https://doi.org/10.1177/1076029606295957

68. Uchida K, Hiruta N, Yamaguchi H, Yamashita K, Fujimura K, Yasui H (2012) Augmentation of cellular immunity and protection against influenza virus infection by bovine late colostrum in mice. Nutrition 28:442–446. https://doi.org/10.1016/j.nut.2011.07.021

69. Batista Da Silva Galdino A, Do Nascimento Rangel AH, Buttar HS, Sales Lima Nascimento M, Cristina Gavioli E, Oliveira RDP, Cavalcanti Sales D, Urbano SA, Anaya K (2021) Bovine colostrum: benefits for the human respiratory system and potential contributions for clinical management of COVID-19. Food and Agricultural Immunology 32:143–162. https://doi.org/10.1080/09540105.2021.1892594

70. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP (2020) The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 20:363–374. https://doi.org/10.1038/s41577-020-0311-8

71. Kell DB, Heyden EL, Pretorius E (2020) The biology of lactoferrin, an iron-binding protein that can help defend against viruses and bacteria. Front Immunol 11:1221. https://doi.org/10.3389/fimmu.2020.01221

72. Fox A, Marino J, Amanat F, Krammer F, Hahn-Holbrook J, Zolla-Pazner S, Powell RL (2020) Evidence of a significant secretory-IgA-dominant SARS-CoV-2 immune response in human milk following recovery from COVID-19. Infectious Diseases (except HIV/AIDS)

73. Mero A, Miikkulainen H, Riski J, Pakkanen R, Aalto J, Takala T (1997) Effects of bovine colostrum supplementation on serum IGF-I, IgG, hormone, and saliva IgA during training. Journal of Applied Physiology 83:1144–1151. https://doi.org/10.1152/jappl.1997.83.4.1144

74. Brinkworth GD, Buckley JD, Slavotinek JP, Kurmis AP (2004) Effect of bovine colostrum supplementation on the composition of resistance trained and untrained limbs in healthy young men. Eur J Appl Physiol 91:53–60. https://doi.org/10.1007/s00421-003-0944-x

75. Antonio J, Sanders MS, Van Gammeren D (2001) The effects of bovine colostrum supplementation on body composition and exercise performance in active men and women11This study was funded by Symbiotics, Sedona, CA (www.symbiotics.com). This experiment is in compliance with the current laws of the United States, the state of Nebraska, and the University of Nebraska system. Nutrition 17:243–247. https://doi.org/10.1016/S0899-9007(00)00552-9

76. Kotsis Y, Mikellidi A, Aresti C, Persia E, Sotiropoulos A, Panagiotakos DB, Antonopoulou S, Nomikos T (2018) A low-dose, 6-week bovine colostrum supplementation maintains performance and attenuates inflammatory indices following a Loughborough Intermittent Shuttle Test in soccer players. Eur J Nutr 57:1181–1195. https://doi.org/10.1007/s00394-017-1401-7

77. Buckley JD, Abbott MJ, Brinkworth GD, Whyte PBD (2002) Bovine colostrum supplementation during endurance running training improves recovery, but not performance. Journal of Science and Medicine in Sport 5:65–79. https://doi.org/10.1016/S1440-2440(02)80028-7

78. Mero A, Nykänen T, Keinänen O, Knuutinen J, Lahti K, Alen M, Rasi S, Leppäluoto J (2005) Protein metabolism and strength performance after bovine colostrum supplementation. Amino Acids 28:327–335. https://doi.org/10.1007/s00726-005-0179-8

79. Shimomura Y, Yamamoto Y, Bajotto G, Sato J, Murakami T, Shimomura N, Kobayashi H, Mawatari K (2006) Nutraceutical effects of branched-chain amino acids on skeletal muscle123. The Journal of Nutrition 136:529S-532S. https://doi.org/10.1093/jn/136.2.529S

80. Heibel AB, Perim PHL, Oliveira LF, McNaughton LR, Saunders B (2018) Time to optimize supplementation: Modifying factors influencing the individual responses to extracellular buffering agents. Frontiers in Nutrition 5:

81. Nanang M, Fuad N, Didik R, Topo S, Panuwun J (2018) Effect of alkaline fluids to blood pH and lactic acid changes on sub maximal physical exercise. IOP Conf Ser: Earth Environ Sci 197:012049. https://doi.org/10.1088/1755-1315/197/1/012049

82. Lancha Junior AH, de Salles Painelli V, Saunders B, Artioli GG (2015) Nutritional strategies to modulate intracellular and extracellular buffering capacity during high-intensity exercise. Sports Med 45:71–81. https://doi.org/10.1007/s40279-015-0397-5

83. Brinkworth GD, Buckley JD, Bourdon PC, Gulbin JP, David AZ (2002) Oral bovine colostrum supplementation enhances buffer capacity but not rowing performance in elite female rowers. International Journal of Sport Nutrition and Exercise Metabolism 12:349–363. https://doi.org/10.1123/ijsnem.12.3.349

84. Davison G (2021) The use of bovine colostrum in sport and exercise. Nutrients 13:1789. https://doi.org/10.3390/nu13061789

85. Brinkworth GD, Buckley JD (2004) Bovine colostrum supplementation does not affect plasma buffer capacity or haemoglobin content in elite female rowers. Eur J Appl Physiol 91:353–356. https://doi.org/10.1007/s00421-003-1023-z

86. Davison G (2012) Bovine colostrum and immune function after exercise. https://doi.org/10.1159/000341966

87. Główka N, Durkalec-Michalski K, Woźniewicz M (2020) Immunological outcomes of bovine colostrum supplementation in trained and physically active people: A systematic review and meta-analysis. Nutrients 12:1023. https://doi.org/10.3390/nu12041023

88. Shing CM, Hunter DC, Stevenson LM (2009) Bovine colostrum supplementation and exercise performance. Sports Med 39:1033–1054. https://doi.org/10.2165/11317860-000000000-00000

89. Kaplan M, Arslan A, Duman H, Karyelioğlu M, Baydemir B, Günar BB, Alkan M, Bayraktar A, Tosun Hİ, Ertürk M, Eskici G, Duar RM, Henrick BM, Frese SA, Karav S (2022) Production of bovine colostrum for human consumption to improve health. Frontiers in Pharmacology 12:

90. Crooks CV, Wall CR, Cross ML, Rutherfurd-Markwick KJ (2006) The effect of bovine colostrum supplementation on aalivary IgA in distance runners. International Journal of Sport Nutrition and Exercise Metabolism 16:47–64. https://doi.org/10.1123/ijsnem.16.1.47

91. Korhonen H, Pihlanto A (2007) Technological options for the production of health-promoting proteins and peptides derived from milk and colostrum. CPD 13:829–843. https://doi.org/10.2174/138161207780363112

92. Mehra R, Garhwal R, Sangwan K, Guiné RPF, Lemos ET, Buttar HS, Visen PKS, Kumar N, Bhardwaj A, Kumar H (2022) Insights into the research trends on bovine colostrum: Beneficial health perspectives with special reference to manufacturing of functional foods and feed supplements. Nutrients 14:659. https://doi.org/10.3390/nu14030659

93. Bagwe S, Tharappel LJP, Kaur G, Buttar HS (2015) Bovine colostrum: an emerging nutraceutical. Journal of Complementary and Integrative Medicine 12:175–185. https://doi.org/10.1515/jcim-2014-0039

94. Guberti M, Botti S, Capuzzo MT, Nardozi S, Fusco A, Cera A, Dugo L, Piredda M, De Marinis MG (2021) Bovine colostrum applications in sick and healthy people: A systematic review. Nutrients 13:2194. https://doi.org/10.3390/nu13072194

95. Juhl SM, Ye X, Zhou P, Li Y, Iyore EO, Zhang L, Jiang P, Van Goudoever JB, Greisen G, Sangild PT (2018) Bovine colostrum for preterm infants in the first days of life: A randomized controlled pilot trial. Journal of Pediatric Gastroenterology & Nutrition 66:471–478. https://doi.org/10.1097/MPG.0000000000001774

96. Staak C (1992) [Bovine colostrum and protection of young animals]. Berl Munch Tierarztl Wochenschr 105:219–224

97. Satyaraj E, Reynolds A, Pelker R, Labuda J, Zhang P, Sun P (2013) Supplementation of diets with bovine colostrum influences immune function in dogs. Br J Nutr 110:2216–2221. https://doi.org/10.1017/S000711451300175X

98. Sangild PT, Vonderohe C, Melendez Hebib V, Burrin DG (2021) Potential benefits of bovine colostrum in pediatric nutrition and health. Nutrients 13:2551. https://doi.org/10.3390/nu13082551

99. Ulfman LH, Leusen JHW, Savelkoul HFJ, Warner JO, Van Neerven RJJ (2018) Effects of bovine immunoglobulins on immune function, allergy, and infection. Front Nutr 5:52. https://doi.org/10.3389/fnut.2018.00052

100. Brunse A, Worsøe P, Pors SE, Skovgaard K, Sangild PT (2019) Oral supplementation with bovine colostrum prevents septic shock and brain barrier disruption during bloodstream infection in preterm newborn pigs. Shock 51:337–347. https://doi.org/10.1097/SHK.0000000000001131

101. Wang P-H, Huang B-S, Horng H-C, Yeh C-C, Chen Y-J (2018) Wound healing. Journal of the Chinese Medical Association 81:94–101. https://doi.org/10.1016/j.jcma.2017.11.002

102. Kim H, Kim DE, Han G, Lim NR, Kim EH, Jang Y, Cho H, Jang H, Kim KH, Kim SH, Yang Y (2022) Harnessing the natural healing power of colostrum: Bovine milk-derived extracellular vesicles from colostrum facilitating the transition from inflammation to tissue regeneration for accelerating cutaneous wound healing. Adv Healthcare Materials 11:2102027. https://doi.org/10.1002/adhm.202102027

103. Blais M, Pouliot Y, Gauthier S, Boutin Y, Lessard M (2014) A gene expression programme induced by bovine colostrum whey promotes growth and wound-healing processes in intestinal epithelial cells. J nutr sci 3:e57. https://doi.org/10.1017/jns.2014.56

104. Doillon CJ, Lehance F, Bordeleau L, Laplante-Campbell M, Drouin R (2011) Modulatory effect of a complex fraction derived from colostrum on fibroblast contractibility and consequences on repair tissue. International Wound Journal 8:280–290. https://doi.org/10.1111/j.1742-481X.2011.00783.x

105. Tanideh N, Abdordideh E, Yousefabad SLA, Daneshi S, Hosseinabadi OK, Samani SM, Derakhshan Far A (2017) Evaluation of the healing effect of honey and colostrum in treatment of cutaneous wound in rat. Comp Clin Pathol 26:71–77. https://doi.org/10.1007/s00580-016-2347-5

106. Nikolic I, Stojanovic I, Vujicic M, Fagone P, Mangano K, Stosic-Grujicic S, Nicoletti F, Saksida T (2017) Standardized bovine colostrum derivative impedes development of type 1 diabetes in rodents. Immunobiology 222:272–279. https://doi.org/10.1016/j.imbio.2016.09.013

107. Aunsholt L, Jeppesen PB, Lund P, Sangild PT, Ifaoui IBR, Qvist N, Husby S (2014) Bovine colostrum to children with short bowel syndrome: A randomized, double-blind, crossover pilot study. J Parenter Enteral Nutr 38:99–106. https://doi.org/10.1177/0148607112469630

108. Ashraf H, Mahalanabis D, Mitra A, Tzipori S, Fuchs G (2007) Hyperimmune bovine colostrum in the treatment of shigellosis in children: a double-blind, randomized, controlled trial. Acta Paediatrica 90:1373–1378. https://doi.org/10.1111/j.1651-2227.2001.tb01598.x

109. Soyer P, Tekgöz M, Tunali Y (2023) Determination of potential probiotic properties of lactic acid bacteria isolated from colostrum milk. Eur J Life Sci 2:31-38. https://doi.org/10.55971/EJLS.1263343

## ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr. Szenci Otto for his support and guidance throughout the writing of my thesis, and providing a topic in which I have a keen interest. I would also like to express my gratitude to the professors who taught me throughout the course of my studies at the University of Veterinary Medicine, Budapest. Finally, I would like to thank my family and friends for their heartfelt encouragement and continuous support.

# Thesis progress report for veterinary students

Name of student: Cassandra Traynor Muñoz

Neptun code of the student: HXAMKX

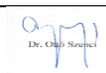
Name and title of the supervisor: Dr. Szenci Ottó PhD, DSc, Dipl. ECBHM

Department: Obstetrics and Food Animal Medicine Clinic

Thesis title: *The effects of bovine colostrum in human medicine*

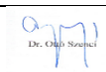
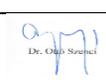
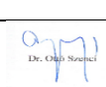
……

## Consultation – 1st semester

| Timing | | | | Topic / Remarks of the supervisor | Signature of the supervisor |
|---|---|---|---|---|---|
| | year | month | day | | |
| 1. | 2022 | 09 | 12 | Selection of the topic for the thesis |  |
| 2. | 2023 | 03 | 13 | Discussing the progress of the thesis |  |
| 3. | 2023 | 06 | 21 | Discussing the progress of the thesis |  |
| 4. | | | | | |

**Grade achieved at the end of the first semester: 5 (five)**

## Consultation – 2nd semester

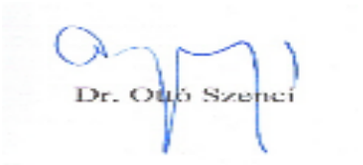
| Timing | | | | Topic / Remarks of the supervisor | Signature of the supervisor |
|---|---|---|---|---|---|
| | year | month | day | | |
| 1. | 2023 | 06. | 24-25. | Discussing the progress of the thesis |  |
| 2. | 2023 | 11. | 05-07. | Discussing the final version of the thesis |  |
| 3. | 2023 | 11. | 11-13. | Discussing the final version of the thesis |  |
| 4. | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 5. | | | | | |

**Grade achieved at the end of the second semester: 5 (five)**

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,




……...
signature of the supervisor

Signature of the student: …Cassandra Grayson Muñoz

Signature of the secretary of the department: ……..……

Date of handing the thesis in…… ……..…....