Colostrum as a Therapeutic: A Meta Review

ABSTRACT

This meta-review is an examination of the therapeutic properties of colostrum. The scientific development and subsequent implementation of new therapeutics continues to influence researchers all over the globe today. Therefore, this review examines previously published research on colostrum and its effects on physiological functioning to determine its role as a potential therapeutic. Additionally, this review explores options for the potential therapeutic use of colostrum in immunology, IBS, diabetes and thyroid. There is abundant research supporting the immunomodulatory properties of colostrum, while also implicating its roles in alleviating IBS which is presented in this review. There is also evidence for the presence of IGF-1, T4, T3 and iodine in colostrum. Therefore, this review will also examine the current research examining the detection and respective physiological relevance for diabetes and thyroid functioning.

Keywords*: colostrum, immunology, IBS, diabetes, thyroid*.

1. INTRODUCTION

Colostrum serves as one of the first sources of conferred immunity to neonates post-partum. The benefits of colostrum, particularly its immunological properties have been known to the scientific community since the 19th century. In fact, the knowledge of the presence of colostral immune factors served as the basis for the current understanding and development of active and passive immunization [1]. Colostrum is the first form of maternal milk (2-5 days postpartum) and is crucial for providing passive immunity to neonates till their immune system is fully developed [2]. In addition to being rich in secretory immunoglobulins, colostrum also contains proteins (casein, albumin, lactoferrin) growth factors (EGF, IGFs, TGF-β),enzymes and immunomodulatory cytokines (interleukins, tumour necrosis factors, interferons). Gut permeability of neonates is highest immediately after birth, thereby allowing maximum absorption of colostral immunoglobulins within the first 24 hours [3]. Infants are at the highest risk of mortality in the first 28 days after birth and timely breastfeeding is crucial in reducing the risks of infant mortality [4], further implicating the role of colostrum towards neonatal development.

Extensive research throughout the years has already established the importance of colostrum for mammalian neonates. However, more recent research has also highlighted its potential applications as a therapeutic, particularly for intestinal inflammation and permeability. [5,6]. Colostrum (supplementation) has been shown to reduce bacterial translocation, NSAID-induced gut damage, while also improving mucosal barrier integrity [7,8]. Colostrum may also possess anti-cancer properties due to the presence of lactoferrins which have been shown to prevent cancer cell proliferation and metastasis [9]. With the increasing burden and mortality caused by non-communicable diseases such as diabetes, gastrointestinal diseases, autoimmunity and cancer [10], there is a mounting pressure for the development of newer and safer treatments and therapies. Many of the current treatment options available for these diseases tend to be expensive and possess higher toxicities, particularly cancer treatments. Therefore, colostrum could potentially prove to be an effective therapeutic for some of these diseases. Colostrum is easily accessible and can be processed and manufactured as supplements. Several RCTs have already indicated the effects of bovine colostrum supplements in improving immune function, mucosal integrity and reducing the risks of upper respiratory infections in athletes [11]. Additionally, colostrum also has a good safety profile and is generally well-tolerated [7].

Therefore, this review shall holistically examine the therapeutic properties of colostrum by analyzing its effects on four biological aspects including immunology, IBS, diabetes and thyroid. This review presents previously published research relevant to these four aspects to determine any clinical significance.

2. Physiological Effects of Colostrum:-

3.1.1 Table 1: <u>Interplay between colostrum and diabetes</u>

S. No.	Paper Title	Year Published
1	Preventive effect of ordinary and hyperimmune bovine colostrum on mice diabetes induced by alloxan	2008
2	Health-promoting effects of bovine colostrum in Type 2 diabetic patients can reduce blood glucose, cholesterol, triglyceride and ketones	2009
3	Oral administration of insulin-like growth factor-I from colostral whey reduces blood glucose in streptozotocin-induced diabetic mice	2011
4	The effectiveness of oral goat colostrum in the treatment of patients with type 2 diabetes mellitus: our preliminary experience	2013
5	Clinical applications of bovine colostrum therapy: a systematic review	2014
6	Bovine colostrum: an emerging nutraceutical	2015
7	Camel milk as a potential therapy for controlling diabetes and its complications: A review of in vivo studies	2015
8	Standardized bovine colostrum derivative impedes development of type 1 diabetes in rodents	2016
9	The effects of expressing antenatal colostrum in women with diabetes in pregnancy: A retrospective cohort study	2019
10	Bovine Colostrum: Its Constituents and Uses	2021

3.1.1.1 Normal and Hyperimmune Bovine Colostrum's preventive effects on alloxan induced diabetic mice[12]

The studied research paper focused on studying the anti-diabetic effects of normal and hyperimmune bovine colostrum on alloxan induced diabetic mice. To obtain hyperimmune colostrum, cows were vaccinated with specific pathogens as antigens. The result revealed how hyperimmune colostrum has more efficiency in reducing the blood glucose levels than the normal colostrum.

The results revealed that the alloxan induced diabetic mice experienced a gain, significantly lower than than normal mice group, in their body weights after administration of bovine colostrum for a period of 30 days. Weight gain was seen more in groups administered with a higher dosage capacity suggesting how diabetes inhibits gain of body weight in mice which can be improved with bovine colostrum in dosages dependent way.
Significant reduction in the blood glucose concentration was witnessed and recorded in diabetic mice after at the end of the clinical period with hyperimmune bovine colostrum administered group showing significantly more reduction in the levels as compared to ordinary colostrum suggesting the former's higher efficiency.
Glucose tolerance was strengthened as a result of colostrum administration in alloxan induced diabetic mice with Hyperimmune colostrum again proving to be more efficient.
At the end of the experimental period, it was clearly demonstrated that normal and Hyperimmune bovine colostrum, due to the presence of insulin like growth factors, reduce the glucose concentration in blood modifying the diabetic phenotype of the alloxan induced diabetic mice [12].

3.1.1.2 Reduction in blood glucose levels in type-2 diabetic patients due to health promoting benefits of bovine colostrum[13]

The studied paper used Accutrend GCT to monitor the glucose levels. The research revealed that obtaining Bovine colostrum in early stages of post-calving had more anti-diabetic benefits than later-stage obtainment.

Previous studies on Type-2 diabetes, caused by lifestyle changes, showed that its onset could be slowed down by dietary changes and exercise. This study focused on decrease in the blood glucose levels brought by including bovine colostrum

in diets of 8 men and 8 women aged 35-65 years who consumed 3 meals everyday without any diet experimentation in the past 3 months and had type-2 diabetes.
In this study 5 grams of bovine colostrum powder was ingested by the subjects 2 and 8 hours postprandial on empty stomach every morning and night for 4 weeks. Previous studies done on diabetic rats, using the same bovine colostrum sample showed significant reduction in blood glucose levels.
After the clinical period, it was tabulated that bovine colostrum induced decrease in blood glucose levels was seen to be highest in patients with higher glucose levels to start with. For women, the highest drop was recorded at 2 hours postprandial in contrast to men where it was recorded 8 hours postprandial.

Although a lot of research has been done on bovine colostrum, its anti-diabetic property was still relatively less studied, this research clearly demonstrated the reduction in blood glucose levels caused by ingestion of bovine colostrum in type-2 diabetic patients and how the earlier obtainment of bovine colostrum post-calving is important in the process. The decrease in the levels, seen to be highest in patients with higher glucose levels, however, can be argumented because this was not witnessed in the 2-hour postprandial study done on women [13].

3.1.1.3 Blood Glucose reduction in streptozotocin-induced diabetic rats, on oral administration with colostral whey[14]

Diabetes, caused by insulin deficiencies, cause increase in blood glucose concentration; therapeutic drug treatment have side-effects making use of natural products attractive as an alternative treatment option. Centrifugation and ultrafiltration techniques were utilized to separate IGF-I-RF and colostral whey from colostrum, these two and RH IGF-I was then orally administered to diabetic- induced mice for a period of 4 weeks. The results revealed that IGF-I-RF separated and obtained from Holstein colostrum has potential to treat diabetes in insulin resistant patients.

Significant reduction in glucose levels in blood was reported in IGF-I-RF and RH IGF-I groups in comparison to a slight decrease in colostral whey group for protein concentrations of less than 0.05. Streptozotocin (STZ) induced diabetic mice group experienced a steady decrease in body weight, whereas the weight increased slightly in groups with IGF-I-RF, RH IGF-I and colostral whey with less effective increase in weight the group fed with the later.
Kidney, liver and spleen weights were recorded to have been increased in STZ induced diabetic mice and a significant decrease kidney and spleen weight in groups administered with IGF-I-RF, RH IFG-I and whey colostral with protein concentration of less than 0.05. Liver weight, however, showed no considerable difference in whey group as opposed to a reduction in liver weight seen in IGF-I-RF and RH IGF-I groups.
The oral glucose tolerance test highlighted a decrease by 16.70 and 15.81 mmol/l in blood glucose in IGF-I-RF and RH IGF-I respectively at 60 minutes and by 13.93 and 13.17 at 120 minutes respectively.
There was recorded a significant increment blood insulin level in IGF-I-RF, RH IGF-I and colostrum whey groups than those with STZ.

The hypothesis here was that imitation of insulin like function is possible from IGF-I-RF obtained from colostrum. IGF-I-RF causes a reduction in the insulin resistance which is done by decreasing the bold glucose in STZ induced mice. Thus, this method is effective in treating and controlling level of blood glucose in diabetic patients [14].

3.1.1.4 Effectiveness in Type-2 diabetes treatment using oral goat colostrum: A review[15]

The studied review paper aimed at verifying with experimental data how insulin use is reduced in Type-2 diabetic patients who received goat colostrum treatment as 300 mg gastro-resistant tablets. A significant decrease was witnessed at the end of the research in insulin dosage and glucose levels were also restored to normal.

The study method was based on orally administering goat colostrum in 27 subjects out of which 14 were male and 13 females between 47 and 73 years of age with Type-2 diabetes. Gastro-resistant tablet were used to avoid destruction by gastric secretion. Under same nutritional habits of the studied groups after a period of two weeks there was seen a significant reduction on the reliance of taking insulin and glucose concentration in blood was also restored to normal after colostrum treatment. Along with this lower susceptibility to infection was also seen in the studied subjects.

The study revealed that without requiring a drastic change in the lifestyle of a diabetic patient, goat colostrum could restore normal blood glucose level and better insulin control. Colostrum, the first milk after birth, consists of several nutritionally rich ingredients like IGF-I is a good treatment against hyperglycemia thus helping diabetic patients [15]

3.1.1.5 Bovine colostrum treatment: A review on Clinical applications[16]

Bovine colostrum as a food supplement could have positive effects on an individual's health because of the high level of growth hormones present in it. Bovine colostrum, the first milk produced after parturition, has nutritional value to new born

calves and some of these effects seen in calves may also be beneficial to humans. However, further studies in this area should be conducted before clinically recommending them, for this purpose, animal models may prove to be helpful.

The literature search done initially identified 1,366 publications but only 789 papers remained eligible after the duplicates were removed. The process of screening identified 49 papers, reporting on 51 numbers of studies of the effect of bovine colostrum supplementation that met the eligibility criteria. A total of 2,326 patients were collectively enrolled.
Two double-blind, crossover, randomized trials were the type of trials identified of non-steroidal anti-inflammatory medication induced GI toxicity and five studies addressing HIV-associated diarrhea and immune-suppression were identified during the study. 24 studies looked at athletic performance, composition of the body, nutrition absorption, and endocrinological and immunological processes in healthy people during exercise.
Several studies not eligible were also identified during the survey, which included two of the trials which used lactoferrin from bovine colostrum; another study was on colostrum containing eye droplets for eye treatment, another on dental plaque and some other similar ones.

An effective reduction was seen in bacterial translocation in rats with carrageenan-induced intra-peritoneal inflammation after they were administered with bovine colostrum.
Administration of 10 g bovine colostrum concentrated for immunoglobulin to 27 adults and 2 children with HIV infection was done by Rump et al. Casein-precipitated, fat-free, spray-dried powder was the colostrum product. Transient or long-lasting normalization of stool frequency in the most of the patients was reached as a result of this treatment.
Consumption of porridge containing 32% bovine colostrum reduced HIV-associated diarrhea, with a significant decrease in the daily number of bowel evacuations.
The evidence suggested currently, however, are in the direction that bovine colostrum can effectively ameliorate HIV-associated diarrhea, probably due to the direct antimicrobial and endotoxin-neutralizing effects and the suppression of gut inflammation as well as to the promotion of mucosal integrity and tissue repair. These findings however must be confirmed in future placebo-controlled RTs.

Overall, exercise studies have not provided conclusive evidence for the effects of colostrum on immunity, but observations of humoral immunity are of potential interest and deserve further investigation and confirmation.
Bovine colostrum has been proposed to play a role in the treatment or prevention of chemotherapy-induced mucositis, and evidence suggests possible beneficial effects on the oral mucosa [16].

3.1.1.6 A review on Bovine colostrum as a prominent Nutraceutical[17]

The review reflected on the nutritional and pharmaceutical (nutraceutical) properties of bovine colostrum. Bovine colostrum being rich in growth, immunity and antimicrobial factors help promote tissue growth, build natural immunity with relatively fewer side effects, also showing less possible lactose intolerance than milk. The review focused on such and other therapeutic properties of colostrum while also addressing the future implications.

Bovine colostrum and derivatives were being intended to boost immunity in both healthy and ill people. The potency of colostrum constituents from cow was 100 to 1000 folds more than what is seen in human colostrum. Polio vaccine developer, Dr. Albert Sabin found bovine colostrum to contain antibodies against polio virus. Various synthetic colostrum using milk, egg yolk, etc. as temporary substitutes for young animals whose mother can't produce colostrum were being manufactured but their long-term use was highly discouraged as they lack antibodies which are present in natural colostrum.

Bovine colostrum contains nutritional components, immune factors like IgA-specific help factor, β-lactoglobulin, secretory IgA, lactalbumin, etc and growth factors. Proline-rich polypeptide (PRP) in colostrum helps in inhibiting allergy, autoimmune and cardiovascular diseases. The growth hormones in colostrum help in repairing damage to heart muscles. Hyperimmune Bovine colostrum has been reported to be effective against human rotavirus (HRV). Immunoglobulins, lactoferrins and cytokines in colostrum show strong antiviral activities. Leptine in colostrum induces feelings of fullness which reduces the desire to eat more thus helping in weight loss. Bovine colostrum and hyperimmune colostrum have been reported to work as an anti-diabetic because of IGF-I, BC-mediated beta-cell regeneration which led to insulin release.

Bovine colostrum, therefore, is effective against a wide variety of diseases and thus is an effective nutraceutical with relatively very less side effects with a good level of tolerance. More research needs to be conducted in this area and the future shows promise in use of colostrum in treating diseases like AIDS, GI and cardiovascular disorders, infectious diseases and certain types of cancers [17].

3.1.1.7 A Review on Camel milk's therapeutic use in controlling diabetes and the complications associated[18]

Diabetes, which has been prevalent for many years, and is expected to rise to 4.4% by 2030, is an increase in blood glucose concentration either due to inability to produce sufficient insulin (Type-1) or not responding to it properly (Type-2). This study was done with the purpose to review camel milk as an adjunct to therapy for diabetes and the complications that come with it.

Camel milk distinguishes itself from the milks of other ruminants because in an acidic environment it does not form coagulum. Even though lactose concentration of camel milk is 4.8%, the sugar still is easily metabolized by lactose intolerant people. Camel milk has around 52 micro unit/ml insulin like proteins in comparison to 16.32 micro unit/ml seen in cow milk.
Previous studies done showed a 55% decrease in blood glucose in diabetic patients receiving raw camel milk when compared to cattle milk (45%). Agrawal et al, after a series of clinical trials, in 2005 determined that camel milk had long term efficacy in insulin therapy in type-1 diabetes patients. Their studies conducted in various years all reflected towards decrease in mean blood glucose concentrations after receiving camel milk.
Studies done by Al-Numair et al reported around 30% reduction in STZ induced diabetic rats treated with camel milk for a clinical period of 6 weeks as compared to just 12 % and 10% for cow and buffalo milk treatment respectively. Similarly, another study demonstrated a reduction in total cholesterol with camel milk treatment as opposed to an increase seen in case of alloxan induced diabetic dogs treated with cow milk. The therapy is also effective in treating diabetes associated liver and kidney diseases as camel milk administration dramatically shifts liver enzymes to a normal level in STZ-induced diabetic rats (Khan et al) and can also control microalbumin levels in type-1 diabetic people with a study done by Mohamad et al reporting a decrease in microalbumin level from 92.08±15.18 to 75.75±3.17 after 24 hours in type-1 diabetic patients treated with camel milk. Camel milk is also effective against oxidative stress and wound healing in diabetic patients.

Camel Milk showed low degree of casein phosphorylation, produces less casomorphin and contains less amounts of beta-lactoglobulin and beta-casein, the latter factor contributes to camel milk having little or no allergic side effects. Camel milks' insulin-like proteins mimic insulin interaction with its receptor and the higher zinc content plays an important role in insulin secretory activity. Al Numair's studies showed that diabetes associated with hyperlipidemia risk could be reduced with camel milk. The review clearly pointed to camel milk being a therapeutic against treatment of diabetes and the complications that come with it. However, further studies are required to be conducted in the area [18].

3.1.1.8 Impedance of Type-1 diabetes in rodents through administration of standardized bovine colostrum derivative[19]

This research paper aimed to report health promoting benefits of bovine colostrum in Type-1 diabetes which have not been as reported as its effect in Type-2 diabetes and gastrointestinal tract diseases. Three models of Type-1 Diabetic mice, DP-BB rat and MLDS-induced diabetic C57BL/6 mice were prepared for the study.

Type-1 diabetic mice treated with standardized bovine colostrum derivative (SBCD) for a consecutive period of 12 weeks witnessed a 29% reduction in the disease onset for the first model. MLDS induced diabetes was also kept under normal glucose levels after SBCD treatment. These results suggested that oral administration of SBCD reduces pro-inflammatory Th 17 and Th1-mediated responses in MLNC, but also enhances Th2-mediated immunity thus shifting the balance towards an anti-inflammatory cytokine profile.

The research recorded data which clearly showed oral administration of standardized bovine colostrum derivative could prevent the development of type-1 diabetes in different mice models with no noted side-effects. This efficiency was attributed to reduced insulitis and in vivo modulation of mice immunity cell function. Cytokinine profile of diabetic mice was modulated due to apotransferrin while preventing disease development; SBCD effects Th cell differentiation which is crucial for preventing diabetes development [19].

3.1.1.9 Diabetic women expressing milk antenatally: A review on the effects[20]

The research aimed at analyzing the correlation between diabetic women expressing breast milk antenatally and store colostrum to prevent or treat hyperglycemia in infants after birth to those mothers who did not. Electronic maternity record examinations were used to collect data for the study done. No significant differences were seen in hyperglycemia rates in infants who received antenatally expressed milk and those who did not.

23% of the selected women expressed antenatally, around 62%, did not and for the rest it was unclear, thus they had to be excluded from the study. No significant differences were seen in hyperglycemia rates in infants who received antenatally expressed milk and those who did not. 81% babies whose mothers expressed and store antenatally received EBM in hospital, remaining did not, the inability to differentiate whether it was used for treating hyperglycemia between the

two led to the researchers of the paper to drop the exploration of correlation between antenatal expression and hyperglycemia rates in infants.

Diabetes leads to delay in lactogenesis in pregnant women due to which it is often advised to express mil antenatally and store the colostrum for the infant to reduce the reliance on formula feeding. Exclusive diabetes has often been associated with reducing diabetic risk development in already at-risk infants of diabetic mothers. Significant association between infant hyperglycemia rates or median neonatal BGL at 3, 12 and 24 hours postprandial and antenatal expression was not obtained; hence the researchers chose to rather study neonatal and maternal characteristics by whether the mother did or did not collect colostrum [20].

3.1.1.10 Constituents of bovine colostrum and its uses[21]

Bovine colostrum is the milk which is produced after the first few days of giving birth. It is rich in growth factors, immunoglobulins and antimicrobial peptides. It is essential for the development and growth of newborns. This paper was aimed at reviewing the effects of bovine colostrum and its various uses along with its constituents.

Bovine colostrum has many important constituents which have been discussed in this review; to start with it has micro and macro nutrients, immunoglobulins, peptides with antimicrobial activity. It has higher total protein content than what is found in mature milk. The concentration has been reported to decrease from a level of about 15% on the first day to about 3% in mature milk. 100 times higher concentration of bovine trypsin inhibitor is found in bovine colostrum as compared to mature milk.

Alpha-lactalbumin comprises 40% of the total protein content. The predominant saccharide in bovine colostrum is lactose, comprising about 2.5%, which is lower than what is seen in human milk or mature bovine milk. Bovine colostrum is also a rich source of glycosylated proteins with bovine glycomacropeptide (GMP) being the predominant one. Fat-soluble (A,D,E) and water soluble (B series) vitamins are also contained in bovine colostrum with most vitamin concentration, especially B2, B12, E, and D, being higher in bovine colostrum than the mature milk.
Major immunoglobulins in bovine colostrum are IgG contributing about 80-90% of the total IgGs and smaller amounts of IgA, IgD, IgE, IgM. Lactoferrin, however, is only about 10% of human values in bovine colostrum. Bovine colostrum has IGF-I concentrations much higher than found in human colostrum.

The higher level of protein content in bovine colostrum than mature milk is mainly because of the presence of immunoglobulin and casein, the latter of which has immune-regulatory, antibacterial and anti-inflammatory properties. Bovine trypsin inhibitors help in protection of growth factors and other biologically active proteins from proteolytic degradation. Alpha-lactalbumin has anti-microbial and anti-tumor properties. Bovine GMP has been shown to have bifidogenic abilities. IgG provides not only passive immunity but also modulates the adaptive and innate immunity systems of an individual. The bioactive saccharides in bovine colostrum act as prebiotics. Lactoferrin enhances iron absorption and has anti-microbial qualities. Cell-proliferation and differentiation is promoted by IGF-I and IGF-II. Multiple tests done against human and rodents intestinal cell lines showed bovine colostrum's stimulating effect towards cell migration and proliferation. Bovine colostrum has a healing effect for a range of GI conditions and non-steroidal anti-inflammatory drug (NSAID) gut injury.

Several studies done in animals and human have also suggested bovine colostrum to be effective against Type-2 diabetes by reducing the increased glucose levels in such patients. Thus, this study showed that bovine colostrum has many health benefits and is safe for a range of age groups. Hyperimmune bovine colostrum can help target individual conditions and the efficacy of bovine colostrum can also being increased if we use it along with other factors that can act synergistically with bovine colostrum [21].

3.1.2 Table 2 Immunomodulatory content of colostrum and its effects on the immune system

S. No.	Paper Title	Year Published
1	Human Colostrum T-lymphocytes and effector cytokines actively aid development of newborn immune system	2008

2	Premature Delivery Influences the Immunological Composition of Colostrum and Transitional and Mature Human Milk	2011
3	Human Colostrum and Breast Milk Contain High Levels of TNF-Related Apoptosis-Inducing Ligand (TRAIL)	2013
4	Presence of IL-9 in Paired Samples of Human Colostrum and Transitional Milk	2013
5	Early oral colostrum administration in preterm infants	2020
6	Extracellular Vesicles in Human Preterm Colostrum Inhibit Infection by Human Cytomegalovirus (HCMV) In Vitro	2020
7	Immunomodulatory Components of Human Colostrum and Milk	2020
8	Can Drinking Microfiltered Raw Immune Milk From Cows Immunized Against SARS-CoV-2 Provide Short-Term Protection Against COVID-19?	2020

3.1.2.1 Human Colostrum T-lymphocytes and their Effector Cytokines Actively Aid the Development of the Newborn Immune System[22]

T lymphocytes and their cytokines are some of the most important immunomodulatory factors present in colostrum that aid in the development of the immune system of an infant. Colostrum is rich in cellular components, about 4 x 10^9leukocytes/titre that consists of lymphocytes (5-10%) – mainly T cells, macrophages (40-50%) and neutrophils (55-60%).
Earlier animal studies have demonstrated that these milk leukocytes survive the infant's gastrointestinal tract where they adhere to the epithelium or cross the mucosa into the neonatal circulation and systemically influence the infant's immune response.
Ciardelli et. al, 2008 demonstrated that Colostrum T lymphocytes (CoTL) is mainly associated with memory subset as it has 100% memory phenotype by expanding CoTL in vitro. Due to this reason, CoTL has the potential to protect the newborn through the mother's previous immune experience. It was also reported that CoTL consists of both helper (CD3+CD4+) and cytotoxic cells (CD3+CD8+) equally. IL-2 and IL-4 were the major cytokines of all that were secreted by helper T-cells rather that cytotoxic T lymphocytes. IL-4 is one of the main type-2 T-cells cytokines which primarily induces B-cell differentiation. Cytotoxic cells majorly process IFN- γ that actively defend the offspring. CoTL also produces cytokine IL-10 that is crucial for maternal tolerance of the foetus and also exerts a protective action for the developing intestinal cells of the newborn. It also has an additive effect with IL-4 in activating B lymphocytes of newborn. Greater production of CoTL was represented by pro-inflammatory cytokines.
In addition, colostrum also helps in the postnatal development of both T type 1/ T type 2 responses [22].

3.1.2.2 Premature Delivery Influences the Immunological Composition of Colostrum and Transitional and Mature Human Milk[23]

Premature deliveries can influence the composition of immune-active components (IgA, growth factors like Epidermal growth factor(EGF), TGFβ1 and TGFβ2, cytokines such as IL-6, IL-8,IL-10,IL-13 and TNFα and its receptor, TNF-RI) in the colostrum and mature milk.
It was reported that preterm group deliveries were rich in the immune-active components as compared to term and very preterm group deliveries whereas very preterm groups had the least concentration of most of the immune factors which suggested that breast milk content is adapted to better collaborate in the immune defence and development of premature babies in preterm group deliveries but not in the very preterm group deliveries that occurs before 30 weeks of gestation.
Most of the immune-active component was highest in colostrum as compared to transitional and mature milk like IgA, Epidermal growth factor (EGF), TGFβ1 which were detected highest in colostrum and lowest in mature milk and some cytokines like IL-8, IL-6 and IL-10 were significantly lower in very preterm groups than the term and preterm groups. In Very preterm group, IL-13 concentration was so low that it was undetectable in milk samples.
Therefore, breast milk immune-active factors proportion varies with the length of lactation as well as gestational period [23].

3.1.2.3 Human Colostrum and Breast Milk Contain High Levels of TNF-Related Apoptosis-Inducing Ligand (TRAIL)[24]

Davanzo et al, 2013 demonstrated that colostrum contains soluble TRAIL (TNF- related apoptosis inducing ligand) that that is known to induce apoptosis and controls cell proliferation. Therefore, plays a crucial role in killing cancer cells both in vivo and in vitro and also regulates the immune and inflammatory responses. Colostrum contains highest level of TRAIL as compared to mature human milk, saliva and serum.
From this we conclude that TRAIL might be the potential substance in colostrum and human milk that has anticancer activity which can protect infants or newborn from cancer. We can study more on the biological effects of TRAIL as anticancer substance in colostrum and also in general [24].

3.1.2.4 Presence of IL-9 in Paired Samples of Human Colostrum and Transitional Milk [25]

Colostrum contains antibodies and many other immune factors like cytokines that plays an important role in development and regulation of a newborn's immune system and protect them from infection.
Marcuzzi et al, 2013 discovered the presence of IL-9 in the human colostrum for the first time that was significantly higher in the colostrum than transitional milk. IL-9 is a pleotropic cytokine that is secreted by CD4+ T cells. It gets elevated in allergic diseases like asthma and therefore, has been identified as a potential therapeutic target in asthma.
Twelve other cytokines and growth factors were also detected that were also significantly higher in human colostrum like L-1ra, IL-6, IL-7, IL-8, IL-12, IL-13, basic FGF, IFN-γ, MCP-1, MIP-1β, PDGF-BB, and RANTES but IL-10 and G-CSF were marginally higher in colostrum that in breast milk. Six out of 27 cytokines analyzed were only detected in colostrum which were below the detection limit in all samples of breast milk (IL-1β, IL-2, IL-4, IL-15, IL-17 and MIP-1α) whereas IL-5 was undetected in both the samples.
It would be interesting to further examine the role of IL-9 in both colostrum and milk in large samples as this study shows the analysis in a limited number of samples. Maybe, IL-5 can also be detected in the samples of colostrum and milk when we detect cytokines in large samples [25].

3.1.2.5 Early oral colostrum administration in preterm infants[26]

Oral Colostrum can influence the oral microbiome by stimulating lymphoid tissue and modulating bacterial adhesion and may alter the bacterial colonization in the trachea of intubated infants and decrease infections. Early oral colostrum may contribute to the development of more robust and protective microbiome as suggested by the deceased microbial diversity in the trachea with increased time to first oral colostrum.
It was reported that the immune proteins, i.e., lactoferrin and sIgA that are present in colostrum and human milk are absorbed after early oral colostrum administration and can be best administered by syringe into the buccal cavity and greater oral colostrum doses are associated with increased absorption of the selected immune proteins.
Like other immunomodulatory components they are also known to provide immunity and help in development of infants immune system through colostrum and play a key role in health and growth of the newborn by protecting them from infections and severe illness [26].

3.1.2.6 Extracellular Vesicles in Human Preterm Colostrum Inhibit Infection by Human Cytomegalovirus (HCMV) In Vitro[27]

Donalisio et al in 2020 reported that Human preterm colostrum and colostrum-derived extracellular vesicles (EVs) were reported to have anti-HCMV (Human Cytomegalovirus) activity which was demonstrated by an experimental study that revealed that colostrum derived extracellular vesicles were positive for the CD63, CD9, CD81 exosomes associated proteins. Interestingly, its high level of antiviral activity was also observed even when 10- fold greater viral inoculum was used.
Colostrum- derived EVs exert their antiviral activity by impairing the attachment of HCMV to the cell surface and the shaving experiment of extracellular vesicles indicated that the proteins on the surface of EVs plays a crucial role in antiviral mechanism of action of EVs. Many proteins were identified whose function were related to immune response, among which the most promising in terms of of antiviral properties are components of immune system like polymeric Ig receptor precursor, Ig κ-chain, C chain, Ig heavy constant alpha 1 and complement C9 and C3, caseins, lactoferrin, α lactalbumin, osteopontin, macrophage mannose receptor9, thrombospondin etc. The common feature in all these identified proteins is that their glycomoieties seems to play an important role in the interference mechanism between a virus and the host cells.
Naslund et al in 2014 also demonstrated similar antiviral activity of breast milk exosomes and showed that these exosomes significantly reduces the productive HIV- infection of monocyte-derived dendritic cells by approx. 50% and blocked its transfer to CD4+ cells.
Similarly, R. Francese et al, 2020 demonstrated the intrinsic antiviral activity of colostrum or human milk against flaviviruses like Zika virus and Usutu virus where colostrum does not inactivate viral particles, but it hampers the binding of the both flavivirus to the cells.

Therefore, anti-HCMV activity of human colostrum in vitro and extracellular vesicles was confirmed by this study together with previously well known non-specific immunoactive and immune components of human colostrum that protects preterm infant from the risk of congenital disease and severe illness [27].

3.1.2.7 Immunomodulatory Components of Human Colostrum and Milk [28]

Colostrum is the first form of milk that is produced by mammals and humans immediately after delivery of a newborn. Many earlier studies have shown the evidence that it contains many immunomodulatory components like IgA, cytokines, chemokines and growth factors that provides resistance to newborns from infections by microbes including viruses and also helps in the development of immature infants mucosal immune system to establish proper reactivity as the infant is suddenly exposed to the high load of antigenic stimuli.

Cytokines are secreted in the colostrum or milk by mammary gland epithelium and by resident leukocytes with a minor part being filtered from the mother's blood. For Eg - TGF-β, it is present in the form of TGF-β2 in the lacteal secretion whose concentration decreases after birth but it remains high due to the increase in lacteal secretion. It induces the differentiation and unresponsiveness to antigens which prevents the excessive reaction to gut microbiota and accelerated gut barrier closure and also stimulates local B cells to switch towards secretory IgA production, which enhances the immunity against infection and prevent development of inflammatory responses as they prevent binding and penetration of microbes into the mucosa and also play an important role in establishment and development of immature infant microbiota. Human milk contains antibodies to food antigens (including allergens), suggesting that SIgA antibodies prevent the penetration of these antigens into the circulation of the breastfed infant, which may be important for tolerance induction to food antigens.

In earlier studies it was also found that in piglets colostrum is the only source of antibodies because their maternal antibodies are unable to cross the 6 layered placenta to reach the newborn piglet.
Other cytokines like TNF-α, IL-17A, IL-1β, IL-6, IFN-γ and CCL18 and chemokines (IL-8 and MCP-1) together helps in establishing the mucosal immune responses without any tissue damage. Balance between pro- and anti-inflammatory cytokines is crucial for protecting the mammary gland from infection and dampening of inflammation.
Lactoferrin, the most abundant protein in whey, is also present in colostrum that has immunomodulatory effects. It is bactericidal to both gram positive and gram negative pathogens, inhibits virus and fungi and also modulates immune responses.

Besides these components maternal milk also contains live cells of maternal immune system(macrophages, neutrophils and lymphocytes) whose concentration is higher after delivery and decreases in mature milk. Generally, neonatal immune system should recognise cells of mother's milk as foreign but in real, it is not the case as it seems that breastfeeding induces regulatory T-cells that actively suppresses infants immune responses against non-inherited maternal antigens (NIMAs).

Therefore, breastfeeding is very essential as its immune-active components contribute to the adaption of the infant to the environment [28].

3.1.2.8 Can Drinking Microfiltered Raw Immune Milk from Cows Immunized Against SARS-CoV-2 Provide Short-Term Protection Against COVID-19? [29]

When the potential antiviral activity of bovine colostrum was investigated against SARS-COV-2, it was found that due to the presence of IgG antibody in colostrum it can boost the immune system and provide short term immunity in patients against the virus.

IgG is known to interact with different pathogens, including viruses from non-immunized cows. It is also involved in enhancing phagocytosis and the presentation of antigens to T-cells as IgG interacts with human Fcγ receptor and it has many other additional functions like agglutination of pathogens, complement fixation, inhibition of pathogen metabolism and neutralization of viruses.
Immunised cows can produce specific IgG antibodies against SARS CoV-2 glycoproteins in milk or colostrum against new pathogens and microfiltration of raw immune milk removes all pathogens from it without denaturing proteins and changes in nutrients.

Bovine IgG has been reported to also neutralize the respiratory syncytial virus (RSV) and can reduce its severity. With respect to influenza virus, bovine IgG and colostrum were reported to enhance natural killer cell activity and lower the viral burden in lungs after infection in mice. Scientists also reported earlier that bovine colostrum administration also reduces the severity of viral upper respiratory tract infections in children that are deficient in IgA.

Various clinical studies showed that oral Bovine IgG including IgG- derived hyperimmune colostrum can directly bind to the virus, preventing their adhesion to intestinal epithelial cells. Also, it is resistant to proteolysis that suggests the IgG – derived colostrum contains trypsin inhibitors that helps in their survival throughout the gastrointestinal tract. Therefore, helps in prevention and treatment of viral infections.

In conclusion, breastfeeding should always be encouraged especially for few days after birth during which colostrum is supplied to the newborn through breastfeeding, not only the nutrition but mainly because of its immunological components like T lymphocytes, cytokines, IgA, IgG etc. as they contribute to the adaption of the infant to the environment, protect them from infections by microbes including viruses and helps in development of immune system of newborns and colostrum can be further investigated to explore its applications against deadly pathogens [29].

3.1.3 Table 3 Effects of colostrum on thyroid gland, and interactions with thyroid hormones and iodine

S. No.	Paper Title	Year Published
1	Changes in the Plasma Level of Protein-bound Iodine in the Young Calf	1953
2	Butanol-Extractable Iodine in Human and Bovine Colostrum and Milk	1969
3	The presence of thyroxine in bovine pre-colostrum and colostrum.	1977
4	Neonatal levels of plasma thyroxine in male and female calves fed a colostrum or immunoglobulin diet or fasted for the first 28 hours of life	1985
5	Metabolic and endocrine traits of neonatal calves are influenced by feeding colostrum for different durations or only milk replacer	1998
6	Triiodothyronine (T3), insulin and characteristics of 5'-monodeiodinase (5'-MD) in mare's milk from parturition to 21 days post-partum	1998
7	Colostrum iodine and perchlorate concentrations in Boston-area women: a cross-sectional study	2009
8	Effect of bovine colostrum on the serum insulin-like growth factor-I (IGF-I), the IGF binding proteins-2 and -3 and the thyroid hormones in weaning piglets	2010
9	Effect of extended colostrum feeding on the plasma profile of insulin, thyroid hormones and blood glucose of crossbred pre-ruminant calves	2011
10	Oral Supplementation with Bovine Colostrum Decreases Intestinal Permeability and Stool Concentrations of Zonulin in Athletes	2017
11	A Field Study of Serum, Colostrum, Milk Iodine, and Thyroid Hormone Concentrations in Postpartum Draft Mares and Foals	2020

3.1.3.1 Colostral iodine and its relation to plasma iodine levels in neonatal calves[30]

Lewis et al. determined the trends in the PBI with age in calves and nursing and examine the potential sources and its effects on thyroid glands. The average PBI level were highest in the first 48h post-partum. The plasma PBI levels also increased after nursing as compared to baseline. The colostral total iodine and PBI levels were significantly higher than mature milk. Maternal PBI was lower at calving than the corresponding levels observed before and after calving. Thyroid gland histology also revealed deposition of colloids at thyroid follicles along with differentiation into secretory cells with age (between 6h to 6d postpartum). Therefore, colostrum is an important source of iodine in neonates which deposits at the thyroid glands.

The authors measured the plasma protein-bound iodine (PBI) in calves at different ages. The average PBI level were 14.8 γ % in the first 24h post-partum, 10.8 γ% 48h post-partum. The authors found that plasma PBI levels were significantly higher after nursing than before ((8.9 γ% vs 15.0 γ%; $p<0.05$, n=7). They found that the total iodine and PBI in colostrum was significantly higher as compared to mature milk. They observed that the plasma PBI levels at calving (2.5 γ%) (in cows) were significantly lower than the corresponding levels before and after (4.5 γ% and 4.6 γ% respectively; T=5.30).

Thyroid gland histology studies also revealed an increasing number of thyroid follicles and appearance of colloids at follicles with age observed among 12h,3d,4d and 6d calves. To conclude, colostrum is seemingly a significant source of iodine for calves and that this iodine is deposited and stored at the thyroid follicles [30].

3.1.3.2 Presence of iodine in human and bovine colostrum[31]

Man et al. detected and quantified the levels of thyroxine-like compounds (BEI and BII) in human and bovine colostrum and milk samples. The average BEI and BII in human colostrum and milk samples (2-5d postpartum) were 0.33µg/100 ml and 0.23µg/100 ml respectively (n=4). The average BEI and BII values in bovine colostrum and milk (between 1-10d postpartum) were 0.2µg/100 ml (with more sensitive techniques- 0.13µg/100 ml) and 2.8µg/100 ml (0.8 µg/100 ml with sensitive method) respectively. Total iodine concentrations in human and bovine samples were 6.93 and 8.1µg/100 ml respectively.

Butanol-extractable iodine (BEI) and Butanol insoluble iodine (BII) levels were measured in the subnatants of centrifuged human and bovine colostrum and milk samples. The average BEI and BII values from the human samples (2-5 days postpartum) were 0.33µg/100 ml and 0.23µg/100 ml respectively (n=4). The average BEI and BII in bovine samples was 0.2 µg/100 ml (0.13 µg/100 ml using sensitive methods) and 0.23 µg/100 ml (2.8 µg/100ml using sensitive methods) respectively. The total iodine concentrations in human and bovine samples were 6.93 µg/100 ml and 8.1 µg/100 ml respectively. While the levels of the thyroxine-like iodine compounds were not high enough to have physiological effects, the total iodine levels were much higher, and therefore could support the synthesis of thyroxine-like compounds in neonates [31].

3.1.3.3 Detection of thyroid hormones in bovine colostrum[32]

Grega et al. detected the presence of thyroid hormones in bovine pre-colostrum and colostrum (16d pre-partum to 16d postpartum). T3 levels were concluded to be less than 312pg/ml. T3 levels increased from 16d pre-partum, peaking at 4d pre-partum and declining towards 16d postpartum. The thyroxine levels range from 0.18 to 0.12µg/ 100ml in bovine pre-colostrum and colostrum. Therefore, from this paper it can be concluded that the thyroxine levels in cow's milk and colostrum are potentially too low to affect human metabolism.

10 Holstein, Red and White, and Polish Red cattle were used with milk and colostrum samples collected at 4-day intervals from 16d pre-partum till 16d postpartum. Only bound and diffusible thyroxine levels were measured (10ml samples) with competitive protein-binding analysis and RIA, and the highest sensitivity permissible through these methods for T3 detection was 6.25pg/20µl. Therefore, T3 levels in these samples were deduced to be lower than 312pg/ml. T3 levels increased from 16d pre-partum, peaking at 4d pre-partum and declining towards 16d postpartum. The thyroxine levels ranged between 0.18 to 0.12µg/ 100ml in bovine pre-colostrum and colostrum, compared to 4.56µg T4/100 ml found in human milk (Strbak*et al.,* 1974). Thyroxine levels in bovine samples were 10 times lower than human milk, hence could not have any effects on metabolic functioning [32].

3.1.3.4 Effects of diet on plasma thyroxine levels in neonatal calves[33]

The plasma T4 levels in neonatal calves were measured in response to three different types of diet. One group was fed colostrum diet till 28 hours post-partum, the second group was fed a solution containing only immunoglobulins from colostrum and the third group was fasted till 28 hours postpartum. The calves fed colostrum in the first 28 hours had higher plasma T4 levels than the latter two groups.

The calves were divided into 4 groups- A (n=40),B (n=16),C (n=11) and D (n=16). All calves in group A (n=40), 6 calves in group C (Cc) and 8 calves in group D (Dc) were fed colostrum at 4,10, 16 and 22 hours post-partum. Group B (n=16) and 8 calves from group D (Di) were fed immunoglobulins extracted from colostrum at the same intervals as colostrum-fed groups. 5 calves from group C (Cf) were fasted till 28h post-partum. The plasma T4 concentrations at birth were nearly identical in all the groups. The T4 concentrations in groups A and Dc reached peak levels at 22h postpartum, whereas B and Di reached peak levels at birth. Group Cf showed a weak increase in T4 concentrations, however Cc group showed maximal levels at 10h post-partum. Colostrum group showed the highest increases in plasma T4 levels followed by the colostral Ig only group. Fasted calves had the weakest increase in T4 levels, implicating the role of diet on thyroid functioning. Since the colostral Ig group only showed a weak plasma T4 increase compared to colostrum, this indicates the presence of important compounds within the colostrum (excluding Ig) which may affect the levels of thyroid hormones [33].

3.1.3.5 T3, insulin and 5'-MD levels in mare colostrum and milk[34]

Ślebodziński detected and measured T3, insulin and 5'-MD levels in mare colostrum and milk. T3 concentrations increased from day 0 to a peak value at day4, following which there was a decline till 21d postpartum. Insulin concentrations were highest at birth and decreased till day 2, till the levels increased from day 5 postpartum to day 21 postpartum. The 5'MD activity was found to be highest in colostrum at day 0, decreasing on day 1. There was a significant increase in 5'-MD value from day 1 to 4 ($p<0.05$). T3 concentrations from day 1 to 7 exhibited a linear correlation with 5'-MD activity. Therefore, T3 and insulin concentrations were higher in colostrum than milk and may have functions for intestinal enzyme metabolism.

Colostrum and milk samples were collected from 10 mares at days 0,2,7,14 and 21 postpartum and the concentrations of insulin and T3 were measured using RIA. T3 concentration in colostrum increased from day 0 (0.76±0.04nmol/L) to a peak value at day 4 (1.14 ± 0.08 nmol/L), and decreased from day 5 till day 21. T3 concentrations followed a linear relation with 5'-MD in the early stages (day 1-7). Insulin levels were high at birth ((401.0 ± 24.9 gU/mL), and decreased till day 2 (35.0 ± 2.3 pU/mL), and increasing from day 5 (25.5 ± 3.71 gU/mL) till day 21 (40.1±4.15 gU/mL). The 5'-MD activity on day 0 in colostrum was highest (7.3 ± 0.20 pmol I- released /mg protein/min) and decreased on day 1 (5.5±0.10). There was a significant increase in 5'-MD value from day 1 to 4 ($p<0.05$), with 5'-MD activity exhibiting a curvilinear relation with time from post-partum. T3 and 5'-MD activity showed a highly correlated and linear relationship.

5'MD activity in colostrum and milk can be suggestive of paracrine roles of T3, particularly in galactopoiesis. Moreover, the high T3 levels in colostrum may suggest its roles in intestinal digestion and gastric secretion in the neonates through its ingestion. Insulin was also present at higher levels in the colostrum than milk and can therefore also have physiological relevance for the intestinal tract [34].

3.1.3.6 Effects of colostrum feeding duration on metabolic and endocrine profiles[35]

Hammon et al. determined the effects of colostrum-feeding duration on the endocrine and metabolic parameters in neonatal calves. C6 group (colostrum twice daily for 3d+ milk replacer for 4d), C1 (colostrum once daily+ milk replacer 7d) and M (only milk replacer for 7d) groups. Serum IgG, plasma glucose and plasma γGT activity was higher in first week for colostrum-fed groups. Insulin concentrations on day 2 were also higher in colostrum-fed groups. Thyroid hormones were unaffected by group, but glucagon showed post-prandial increase in colostrum-fed groups on day 1. Therefore, colostrum administered twice daily for 3 days has positive effects on the systemic functions in neonatal calves.

18 calves were divided into 3 groups (6 calves/group)- C6 group (colostrum twice daily for 3d+ milk replacer for 4d), C1 (colostrum once daily+ milk replacer 7d) and M (only milk replacer for 7d) groups. Serum IgG concentrations increased on day 1 and day 2 ($p<0.001$) in C6 and C1 but declined from day 2-7. Serum levels of C1 and C6 were higher in week 1 ($p<0.01$).Plasma glucose levels on day 1, the postprandial increase was greater in the M group compared to C1 and C6.On day 7, glucose levels were higher in C1 and C6. Plasma lactic acid in all groups showed declines in lactic acid levels and no significant difference. Plasma triglyceride in the C6 group had significantly higher levels on day 2 compared to M group ($p<0.05$). Plasma phospholipid in C6 group had the highest level on day 7. Both C6 and C1 groups showed increasing phospholipid concentrations in the 1st week. Plasma cholesterol had basal concentrations on day 7 were highest in C6 compared to M group ($p<0.05$).γGT on day 1, both plasma γGT and postprandial activities were increased in C1 and C6 groups compared to M group. Serum AST showed postprandial activity increased in C1 and C6 groups on day 1 and remained the same in the M group, with C1 having a higher activity. Serum LDH and GLDH activity were increased post-colostrum intake (C1 and C6 groups) unlike post-milk replacer (M group). Plasma insulin concentration is higher in the C6 compared to M on day 2. C1 group showed increments in insulin concentration on day 1 and 2, whereas C6 showed increase on day 2.Plasma glucagon concentration in all three groups showed postprandial increments on day 1, with the increments being higher for C1 and C6 compared to M group. Plasma cortisol concentrations had declined in week 1 in all the groups. However, the mean and basal concentrations in the M group were higher than the C1 and C6 groups on day 2.Plasma T3 and T4 concentrations were relatively unaffected by treatments throughout the week, with T3 and T4 concentrations declining in this duration in all the groups. Serum PRL levels in the M group, the basal concentrations were higher on day 2 compared to day 1 and 7. Mean concentrations in the C6 group followed this similar trend.

Colostrum administered 6 times stimulated higher IgG concentrations than colostrum administered only once or only milk replacer. γGT, AST, LDH and GLDH activity was also relatively higher in colostrum-fed groups as compared to the milk replacer group. Colostrum intake also increased glucagon concentrations in C6 calves. Insulin concentrations were also higher in C6 calves correlated with increased energy intake through colostrum. Therefore, colostrum administration does improve metabolic and endocrine functioning. Thyroid hormone levels were not affected by treatment choice in this study [35].

3.1.3.7 Presence of iodine in colostrum and effects of its environmental inhibitors[36]

Leung et al. detected and measured the levels of colostral iodine and perchlorate in lactating women till 60h postpartum. Spot urine iodine, perchlorate, cotinine and creatinine levels were also measured and the relation between iodine concentrations and its environmental inhibitors was examined. The median iodine levels detectable in 61 samples was 51·4 μmol/l. Median urinary iodine level was 82·2 μmol/l. 43/46 colostral samples had detectable perchlorate traces with median 2·5 μmol/l. Median urinary perchlorate and cotinine concentrations were median 2·6 μmol/l and 6·4 nmol/l respectively. No significant correlation was found between colostral iodine and the environmental inhibitors. Therefore, colostrum is potentially an essential reservoir for iodine for neonatal utilization towards thyroid functioning and development.

Colostrum and urine samples were collected from 97 mothers who delivered vaginally (no iodophor usage or thyroid disease history). Spectrophotometry of colostrum and urine samples revealed median iodine concentrations to be 51·4 μmol/l (range 21·3–304·2 μmol/l; n=61) and 82·2 μmol/l (range, 10·3–417·1 μmol/l; n=97) respectively. Mass spectrometry of colostrum and urine samples revealed the median perchlorate concentrations to be 2·5 μmol/l (range, < 0·05–188·9 μmol/l; n=43) and 2·6 μmol/l (range, 0·2–160·6 μmol/l) respectively. Median urinary cotinine concentrations from 95 samples was 6·4 nmol/l (range, < 5·7–5481·2 nmol/l). Pearson's correlation coefficient and multiple linear regression models were used to analyse the relation between all of these parameters. No significant correlation was obtained between colostral iodine and colostral perchlorate, urinary iodine, urinary perchlorate and urinary iodine ($p>0.05$). Likewise, no significant correlation was observed between colostral perchlorate and either of the above-mentioned parameters ($p>0.05$). Urinary cotinine also showed no significant correlation with urinary iodine or urinary perchlorate concentrations ($p>0.05$).

Perchlorate and cotinine are two of the commonly found environmental inhibitors of iodide transport to the thyroid gland, and to the breast during lactation. An attempt to examine the effects of these inhibitors on the colostral iodine levels revealed no significant effects. Therefore, not only was iodine detectable in significant levels in the colostrum, but these levels were not affected by the presence of the iodide inhibitors. Therefore, colostrum is an important source of iodine for neonates and is necessary for their neurodevelopment [36].

3.1.3.8 Bovine colostrum improved feed intake, efficiency and hormonal levels in weaning piglets[37]

Boudry et al. determined the effects of bovine colostrum supplementation on feed intake and efficiency, IGF-I levels, thyroid hormone levels (T3 and T4) and TGFB2 and 3 levels in 96 post-weaning piglets. Piglets were either given a commercial diet with either bovine colostrum whey or bovine milk whey. The ADG, ADFI and G/F were found to be significantly higher in the colostrum-fed group in week 1 ($p<0.05$). Serum IGF-I levels also increased by 15% in the colostrum-fed group compared to the controls (day 7). At day 14 circulating T4 levels were higher in the colostrum-fed group, and while both groups showed post-weaning declines in T4 and T3 concentrations, T4 levels recovered faster in the colostrum-fed group. Therefore, colostrum improved hormonal levels through increased feed intake and efficiency.

96 post-weaning piglets were administered a commercial diet with 20g/kg of either bovine colostrum whey powder (experimental group) or bovine milk whey powder (control) for the first 2 weeks followed by 10g/kg for the remaining 2 weeks. Average daily gain (ADG), average daily feed intake (ADFI), feed efficiency (G/F), IGF-I, T3 and T4 levels were measured throughout the trial. ADG, ADFI, G/F were higher in the experimental group in the first week ($p<0.05$). ADG in the total trial period was also significantly higher in the experimental group ($p<0.05$). ADFI and G/F were not significantly different for the total trial duration between both groups ($p>0.05$). IGFB-2 and 3 did not differ with supplementation. However, serum IGF-I increased by 15% at day 7 in the colostrum-fed group compared to the control group, while circulating levels remained unaffected. IGF-I levels also correlated positively with ADG ($r=0.55;p<0.0001$) and bodyweight ($r=0.50;p<0.001$). Serum T4 levels at day 14 were significantly higher in the experimental group ($p<0.05$). While weaning resulted in decreased circulating T3 and T4 levels in both groups, T4 levels recovered to initial levels much faster in the experimental group compared to control (21-day vs 28-day). Serum T3 and T4 levels positively correlate with ADG (0.17 ($P<0.05$) and 0.27 ($P<0.001$) respectively) and bodyweight (0.26; $P<0.001$).

Colostrum supplementation increased the feed intake and efficiency, as evidenced by the week 1 increases in ADG, ADFI and G/F. Serum IGF-I levels were also increased, but circulating levels were unaffected. The authors deduced that colostral IGF-I (even though small quantities absorbed) could stimulate intestine functioning such as enhanced mucosal integrity, and therefore could explain the correlation with increased ADG. Post-weaning induced decreased feed ingestion which reduced T3 and T4 levels, however these levels recovered to their corresponding pre-weaning levels much faster in the experimental group, possibly due to enhanced feed intake and efficiency[37].

3.1.3.9 Prolonged colostrum feeding affects plasma insulin levels but not blood glucose levels and thyroid hormones[38]

Babitha et al. determined the effects of prolonged colostrum administration on the BGL (blood glucose levels), plasma insulin concentrations and thyroid hormone levels in calves. Calves were given either colostrum for 3 days followed by whole milk till 30 days of age (G-I) or colostrum for 30 days (G-II). BGL increased from birth in both groups, with there being no significant difference between both groups at any time point. Contrarily, the plasma insulin concentration was significantly lower in the G-I group compared to the G-II group. Plasma T3 and T4 levels showed a fluctuating trend, seemingly unaffected depending on either diet. Prolonged colostrum feeding did not have a significant impact on the BGL or thyroid hormone levels but did lead to a significant increase in the insulin levels.

Pre-ruminant calves were either fed colostrum for the first 3 days followed by whole milk($1/10^{th}$ B.W.) till 30 days of age (G-I group), or colostrum($1/10^{th}$ B.W.) till 30 days of age (G-II group). The blood glucose levels measured through GOD-POD in the G-I group was 102.001±15.99 mg/dl (day 0) and increased to 137.33±38.35 mg/dl on day 30. In G-II group, after birth BGL was 111.17±15.48 mg/dl and reached peak value of 140.67±24.15 mg/dl at day 24. Although, BGL values in G-II group were slightly higher than the G-I group no significant difference was observed in the values between both groups at any time point. Plasma insulin concentrations were significantly lower in G-I group on 12^{th}, 24^{th} and 30^{th} day (13.73±3.80 µU/ ml, 10.06±1.88 µU/ml and 13.20±2.59 µU/ml respectively) compared to the G-II group at the same days (18.43±2.90 µU/ml, 15.98±2.43 µU/ml and 24.04±2.84 µU/ml respectively). Plasma T4 concentrations showed no significant difference at any time point between both groups. Plasma T4 levels in G-I and G-II peaked at 18h after birth (9.12±9.65 ng/ml vs. 71.79±10.68 ng/ml respectively). T3 concentrations were significantly lower at day 12 and day 30 in the G-I group (0.99±0.17 ng/ml and 1.22±0.22 ng/ml) compared to the G-II group (1.54±0.20 ng/ml and 1.54±0.21 ng/ ml) but followed similar trends for the remaining period. T4:T3 ratio varied significantly different between both groups (47.07±8.35 vs 29.40±3.67) on day 12.

Prolonged colostrum feeding affected plasma insulin concentrations in the neonates which can support anabolic processes such as protein and triglyceride synthesis. However, no such effect was seen on thyroid hormones or glucose levels [38].

3.1.3.10 Bovine supplementation in athletes improves intestinal mucosal integrity[39]

Halasa et al. determined whether bovine supplementation improved intestinal permeability or not and measured on the basis of stool zonulin concentrations and differential sugar absorptions. 16 athletes were given either 500mg bovine supplementation or 500mg placebo. Double-blind (phase 1): L/M ratio was significantly lower in the colostrum group post-intervention, but no such change was seen in the placebo group. Stool zonulin concentrations also decreased post-intervention in the colostrum group but increased in the placebo group.

Open-label (phase 2): Colostrum supplementation in the placebo group (starting at the end of phase 1) also resulted in lowered significantly L/M ratio from baseline levels. Stool zonulin concentrations also followed similar trends. Therefore, colostrum supplementation can serve as a potential therapeutic due to its alleviating effects on intestinal permeability.

Double-blind phase (Phase 1): 16 athletes (20-43 years) received either 500mg colostrum bovinum (experimental) or 500mg desiccated banana (placebo). Baseline stool zonulin concentrations and lactulose/mannitol (L/M ratio) were recorded as a measure of intestinal permeability on day 0 and final recordings were made on day 22. Only post-colostrum supplementation L/M ratios were significantly lower than baseline ($p=0.01$; $n=8$). The change in the intestinal permeability due to intervention (Δ) was also significantly lower in the colostrum group compared to the placebo group ($p<0.05$; $n=16$). No significant difference in stool zonulin levels from baseline were obtained for both groups. However, zonulin levels increased in the placebo group but decreased for the colostrum group. Δ values were also significantly different between both groups ($p=0.03$).

Open-label phase (Phase 2): 7 participants from placebo group in phase 1 were given 500mg colostrum bovinum from day 23 for 20 days. L/M ratios at day 44 were significantly lower than at day 0 and day 22 ($p<0.05$). The Δ value (change due to intervention) also differed significantly between phase 1 and phase 2 of trial ($p=0.02$). Stool zonulin concentration lowered significantly at day 44 compared to day 0 and day 22 ($p<0.05$). Δ values for zonulin levels also differed significantly between phase 1 and phase 2 of the trial ($p<0.001$).

Colostrum supplementation improved L/M ratios to predetermined reference ranges. While zonulin concentrations did not improve till the reference ranges, they still decreased in the colostrum group. Therefore, colostrum improves intestinal permeability. Intestinal permeability can lead to auto-immune diseases such as celiac disease, diabetes and Hashimoto's thyroiditis. Hence, colostrum can potentially prevent auto-immune disease onset through improved mucosal integrity and reduced intestinal permeability [39].

3.1.3.11 Changes in serum iodine concentrations in foal and mare, and its relations to mare colostrum and milk[40]

Lopez-Rodriguez et al. determined the concentrations of iodine in colostrum and serum of mares and foals, and to determine its relation to thyroid hormone serum levels. Median colostral iodine concentrations were significantly higher than the corresponding levels in mare milk. Foal serum iodine, TT4 concentrations and TT4/TT3 ratios were significantly higher at day 0 (postpartum) than mares. TT4 and TT3 concentrations decreased significantly in foals from baseline till 10 days postpartum. Foal serum TT4 levels were also positively correlated with foal serum iodine levels at day 0 and 10. Hence, colostral iodine may be important for thyroid functioning.

Milk, serum and colostrum samples were taken from 10 mares, and serum samples from 10 foals. Median colostrum iodine (165±15.1 µg/l) concentrations were 3.4 times higher than in milk (48± 5.5µg/l; p=0.007). Foal serum iodine levels at day 0 (268.5± 7.5 µg/l) were significantly higher than those of mare (19± 0.5 µg/l; p=0.001). Foal serum iodine concentrations at day 10 (15.4±1.6 µg/l) were significantly lower than at day 0 (p=0.012). Serum TT4 levels positively correspond with foal serum iodine levels at days 0 and 10 (r= 0.930; p=0.001 and r=0.952; p=0.001 respectively). Median foal serum TT4 concentrations at day 0 were significantly higher than mares (1225±47.8nmol/l vs 18.6±0.6nmol/l; p=0.005). Median foal TT4 and TT3 serum levels decreased significantly from day 0 (1225±47.8nmol/l and 14.2±1.1nmol/l respectively) till day 10 (69.6±20.4nmol/l and 5.4±0.3nmol/l respectively; p=0.008 and p=0.011 respectively). Median foal TT4/TT3 ratio was significantly higher than mares at day 0 (85.9:1 vs 16.1 respectively; p=0.05) and compared to day 10 levels (15.4:1; p=0.008).

Mare colostrum obtained at day 0 had significantly higher concentration of iodine than milk. These findings point to colostrum as the potential significant source of iodine responsible for the higher levels in foal serum, although more work is needed for affirmation. The decreasing serum iodine concentrations were correlated with the decreasing TT4 concentration towards day 10, which can be explained through iodine utilization in TT4 synthesis. Moreover, the low serum iodine levels in mares at day 0 compared to foals might suggest that iodine levels are predominantly concentrated to the mammary tissues, and subsequently in colostrum and milk [40].

3.1.4. Table 4 Curative properties of colostrum for IBS and related gut permeability

S. No.	Paper Title	Year Published
1	Bovine colostrum is a health food supplement which prevents NSAID induced gut damage	1999
2	Reduction in heat-induced gastrointestinal hyperpermeability in rats by bovine colostrum and goat milk powders	2004
3	Effects of a bovine colostrum-supplemented diet on some gut parameters in weaned piglets	2006
4	The nutraceutical bovine colostrum truncates the increase in gut permeability caused by heavy exercise in athletes	2011
5	Randomized controlled trial of colostrum to improve intestinal function in patients with short bowel syndrome	2012
6	Evaluation of Serum-Derived Bovine Immunoglobulin Protein Isolate in Subjects with Diarrhea-Predominant Irritable Bowel Syndrome	2013
7	Effect of Colostrum on the Symptoms and Mucosal Permeability in Patients with Irritable Bowel Syndrome: A Randomized Placebo-controlled Study	2014
8	Zinc carnosine works with bovine colostrum in truncating heavy exercise–induced increase in gut permeability in healthy volunteers	2016
9	Pilot study of probiotic/colostrum supplementation on gut function in children with autism and gastrointestinal symptoms	2019

3.1.4.1 Bovine colostrum is a health food supplement which prevents NSAID-induced gut damage[41]

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective for arthritis but cause gastrointestinal injury. Bovine colostrum is a rich source of growth factors and is marketed as a health food supplement in the medical science. R J

Playford et al. tested Bovine colostrum as a food supplement for preventing NSAID-induced gut damage. Non-steroidal anti-inflammatory drugs or NSAIDs are effective for arthritis and are used for the treatment of musculoskeletal injury, but can cause gastrointestinal injury which includes peptic ulceration and injury to the small and large intestine causing increased permeability to protein leading to blood loss and stricture formation. This is because NSAID contains Indomethacin which causes damage to the gastrointestinal tract by several mechanisms including the reduction of mucosal prostaglandin levels, reduction of mucosal blood flow, stimulating neutrophil activation, and possibly also stimulating apoptosis. Bovine colostrum is a rich source of growth factors and is marketed as a health food supplement. Therefore, Playford et al. performed an examination utilising an indomethacin-restraint rat model of gastric damage and an indomethacin mouse model of small intestinal injury. Migration of the human colonic carcinoma cell line HT-29 and rat small intestinal cell line RIE-1 were assessed using a wounded monolayer assay system (used as an in vitro model of wound repair) with the effects on proliferation being determined through Thymidine incorporation.

Pretreatment with 0.5 or 1 ml colostral preparation reduced gastric injury by 30% and 60% respectively in rats. A milk preparation was much less efficacious. Recombinant transforming growth factor â added at a dose similar to that found in the colostrum preparation (12.5 ng/rat), reduced injury by about 60%. Addition of colostrum to drinking water (10% vol/vol) prevented villus shortening in the mouse model of small intestinal injury. Addition of milk preparation was ineffective. Colostrum increased proliferation and cell migration of RIE-1 and HT-29 cells. These effects were mainly due to constituents of the colostrum with molecular weights greater than 30 kDa. This *in vivo* and *in vitro* model study protocol revealed a reduction in NSAID-induced gastrointestinal damage. Animal models showed that gastric and small intestinal injury caused by indomethacin could be reduced by the potential value of defatted milk and colostrum. The *in vitro* studies showed that the colostrum preparation studied was able to stimulate both migration and proliferation. Size exclusion studies revealed that the majority of the biological activity was involved in stimulating cell migration and proliferation.

This study shows that this colostrum preparation has major beneficial effects in preventing NSAID induced gut injury in a variety of in vivo and in vitro models. Further studies are underway to determine its value in patients taking long term NSAIDs and in the treatment of other ulcerative conditions of the bowel, such as necrotising enterocolitis and inflammatory bowel disease, where therapy is suboptimal and novel approaches are required. Therefore, this paper supports the beneficial properties of colostrum in preventing NSAID-induced gut injury in a variety of *in vivo* and *in vitro* models [41]

3.1.4.2 Reduction in heat-induced gastrointestinal hyperpermeability in rats by bovine colostrum and goat milk powders[42]

Prosser et al. revealed the beneficial effects of bovine colostrum along with goat milk powder in reducing gastrointestinal hyperpermeability induced by heat in rats. Increased core body temperature of rats to 41.5°C due to transfer of 51Cr-EDTA from gut into blood 34-fold relative to the ambient temperature value (P= 0.05) in the control group of rats is indicative of increased gastrointestinal permeability. However, the degree of heating that induces gastrointestinal hyperpermeability in humans remains to be clarified, as does the potential protective benefits of either bovine colostrum or goat milk under these circumstances.

Twenty-four male Sprague-Dawley rats (200– 250 g) were randomly assigned to one of three dietary groups: standard diet supplemented with bovine colostrum powder (B-Colost; 1.7 g/kg, n =8), and standard diet supplemented with goat milk powder was given to them for 8 days to determine the ability of these supplements to reduce gastrointestinal hyperpermeability induced by heat and they were maintained in a regulated environment at a constant temperature of 22°C and relative humidity of 44%. Their gastrointestinal permeability was determined by measuring the amount of 51Cr-EDTA.

The result of this 8 day-study revealed that bovine colostrum powder partially alleviated the effects of hyperthermia on gastrointestinal permeability in the intact animal. Supplementation with bovine colostrum powder significantly reduced the amount of 51Cr-EDTA transferred from gut to blood in rats after heat exposure, also consistent with its ability to prevent gastrointestinal epithelial barrier dysfunction induced by indomethacin. However, the preliminary studies showed that the level of radioactivity in blood after 2 days did not differ from the background level, suggesting that 2 days were to allow clearance of any residual 51Cr-EDTA in the blood. In addition, this study has shown that supplementation with goat milk powder produces a protective outcome similar to that of bovine colostrum powder, at least with respect to increases in gastrointestinal permeability caused by heat stress.

The overall results support the hypothesis that bovine colostrum powder and goat milk powder help in the reduction of breakdown of gastrointestinal barrier function arising due to overheating, thereby implicating its potential use as a nutraceutical for reducing heat stress. Moreover, goat milk powder was as effective as bovine colostrum powder, also proving to be efficacious when gastrointestinal barrier function is compromised [42].

3.1.4.3 Effects of a bovine colostrum-supplemented diet on some gut parameters in weaned piglets[43]

This study investigated the effects of a bovine colostrum-supplemented diet on gut post-weaning adaptation and health in piglets. Huguet et al. tested bovine colostrum supplements on weaned piglets to investigate the effects on the gut, post-weaning adaptation and health in piglets. Weaning of piglets is characterized by a temporary anorexia inducing a growth check that is associated with a decline of sanitary status. Bovine colostrum-supplemented starter diet improves the growth performance and sanitary status of piglets during the early post-weaning period, possibly directly affecting gut health. In order to explain this effect, thirty-six 21-d-old piglets were allocated to one of the three following dietary treatments: sow-reared (SR), weaned on a control starter diet (WCtrl) or on a starter diet supplemented with bovine colostrum (WCol) until slaughter at 28 d or 35 d of age. Several analyses were done within this period including bacteriological analysis, wherein the duodenal contents of W piglets were collected for the evaluation of the antibacterial efficacy of the bovine colostrum-supplemented diet, structural analyses for measurements of villous height and crypt depth were made under blind conditions, enzyme activity assays to measure e protein content in mucosal homogenates, lactase, and aminopeptidase N, Fractional protein synthesis rate measurements, hormonal analysis determining Plasma insulin and IGF-I concentrations and many experimental analysis.

As a result, all analyses revealed BW of 12 piglets was significantly increased with age and affected by dietary treatment. Additionally, a significant age × dietary treatment interaction ($P = 0.002$) was found on gastric pH and duodenal bacterial counts, though there was no effect of the dietary treatment on coliform and lactobacilli counts expressed per total aerobia microflora (Tab. II), whereas the lactobacillicoliform ratio was 37% higher ($P = 0.05$) in WCol piglets compared to WCtrl piglets. A significant age × dietary treatment interaction was also found ($P = 0.004$) on plasma IGF-I concentrations, but there was no effect of dietary treatment and age × dietary treatment interaction on plasma insulin concentrations.

Therefore, the colostrum-supplemented diet significantly improved the lactobacillicoliform ratio in W piglets. The mechanism of action can be attributed to the local protective effects of the colostral immunoglobulins within the gut, which may then stimulate the SI immune system. In conclusion, a colostrum supplemented diet can induce variations within the gut parameters which then globally limits weaning-induced gut structural and microbial alterations [43].

3.1.4.4 The nutraceutical bovine colostrum truncates the increase in gut permeability caused by heavy exercise in athletes[44]

Marchbank et al. performed an experiment of bovine colostrum with athletes who do heavy exercise such as long-distance running, to stop heat stroke caused by increased intestinal permeability of luminal toxins after the heavy exercise. Heavy exercise causes gut symptoms such as increased blood lactate, heart rate, core temperature (mean 1.4°C rise) in similar amounts, and in extreme cases heat stroke. Heat stroke is a recognized hazard for people participating in vigorous sports, particularly in hot, humid conditions, and several authors have implicated gut injury in the pathogenesis of heatstroke. However, the degree of heating that induces gastrointestinal hyperpermeability in humans remains to be clarified, as does the potential protective benefits of either bovine colostrum under such circumstances. Additionally, severe cases of decompensation can result in the life-threatening condition of exertional heat stroke, associated with hyperthermia, multiorgan failure, and endotoxemia. Pharmacological options to reduce these problems are limited, particularly in competitive athletics, and hence there is great interest in the use of natural products. One such product that is already commercially available is bovine colostrum.

The 14-day experiment was performed with 12 volunteers through a double-blind, placebo-controlled, crossover protocol with bovine colostrum administration, a natural source of growth factors, as a potential moderator of such effects. The 12 volunteers were given supplements daily for 14 days before the main exercise trials began. Laboratory tests were conducted along with urine collection following overnight fasting, blood collection to measure hematocrit. Other parameters measured included blood glucose, lactate concentration and gut hormones concentrations such as plasma VIP, PYY, ghrelin, glucagon-like peptide (GLP-1) immunoreactivity and intestinal permeability.

Colostrum had minimal effects on the physiological responses to exercise. Mean plasma VIP levels increased slightly post-exercise in both arms of the study, however no additional effects were observed. A small but significant rise was observed for plasma GLP-1 concentration. There was also 2.5-fold increase in intestinal permeability in response to exercise for the placebo group, and this effect was truncated by colostrum. Colostrum also significantly truncated the rise in caspase-3 and -9 activity in both cell lines, thereby truncating the rise in temperature-induced apoptosis. The presence of the EGFR-blocking/neutralizing antibody reversed the changes in caspase-3 and 9 activities caused by colostrum. At 37°C, colostrum reduced Bax, and this effect was also reversed if the EGFR-neutralizing antibody was present. These effects were markedly truncated in the co-presence of colostrum. A similar effect was observed for temperature-induced transepithelial resistance in wells incubated at 37°C with medium alone, colostrum or placebo. In vitro studies have revealed the effects of core temperature increase on gut integrity in a controlled environment. Increased temperature also

increased apoptosis, and this response was effectively truncated by colostrum. The experiments performed with EGFR-neutralizing antibodies also revealed the presence of an EGFR ligand that was at least partially responsible.

These results show that in a physiologically relevant sports model, colostrum appears beneficial in maintaining gut stability. Mechanisms may include reduced apoptosis and paracellular permeability. Further studies involving more prolonged exercise protocols and colostrum's value in extreme heat stress situations appear justified to examine potential value in athletes and other subjects, such as members of armed forces, subjected to such stresses. [44].

3.1.4.5 Randomized controlled trial of colostrum to improve intestinal function in patients with short bowel syndrome[45]

Short bowel syndrome or SBS results from various surgical resections characterized by an inability of patients to maintain fluid, electrolyte, trace element, vitamin or nutrient balances when fed a conventional diet. Clinical treatments for this syndrome are very few and unknown, although there are some attempts aiming to improve health by maximizing intestinal absorption and reducing the extent of diarrhea and the need for parenteral support.

Another attempt was made by Lund et al. with bovine colostrum due to it being rich in immunoglobulins, antimicrobial peptides (lactoferrin and lacto-peroxidase) and various other bioactive molecules and growth factors. Lund et al. hypothesized that bovine colostrum supplementation would enhance intestinal adaptation and function in adult SBS patients compared to a standard milk-based protein control. This hypothesis was tested through a 4-week randomized, double-blind, controlled, cross-over study. 12 patients (five females, seven males; 55.7±10.7 years) were given either colostrum supplementation (250ml colostrum) or 250 ml control twice daily (morning and evening) along with their habitual diet to determine whether colostrum supplementation improved intestinal adaptation and function in SBS patients.

In this study, various analyses and physical examinations were performed including temperature analysis, statistical and forced spirometric analyses like- measuring hand grip strength, lung diffusion capacity for carbon monoxide (DLCO) evaluated by single breath test, respiratory muscle strength, wet weight and electrolytes balances. Body composition was finally measured using dual-energy X-ray absorptiometry and blood chemistry values (packed cell volume, hemoglobin, leukocytes, platelets, creatinine, glucose, potassium, magnesium, sodium, C-reactive protein, alanine transaminase, amylase, alkaline phosphatase, D-vitamin, parathyroid hormone). These experiments found that colostrum was not superior to its controls in its effects on intestinal absorption, body composition or functional tests. However, there was a significant effect of the high protein supplementation on handgrip strength which is a validated test to evaluate nutritional status and functional outcome in patients, although no effect was seen on lung function which is also a measure of nutritional status. Moreover, no improvements were detected in the respiratory muscle strength.

The final result of this study shows that Intake of high-protein milk supplements increased net nutrient absorption for adult SBS patients, but at the expense of increased diarrhea. Despite high contents of bioactive factors, colostrum did not significantly improve intestinal absorption, body composition or functional tests compared with the control.
Therefore, the high concentrations of bioactive factors within colostrum did not result in any observable effects [45].

3.1.4.6 Evaluation of Serum-Derived Bovine Immunoglobulin Protein Isolate in Subjects with Diarrhea-Predominant Irritable Bowel Syndrome[46]

Wilson et al. performed a randomized, double-blind, placebo-controlled study to evaluate the impact of oral serum-derived bovine immunoglobulin/protein isolate (SBI) on gastrointestinal symptom scores and the quality of life (QoL) in subjects with IBS-D.

A 6-week randomized, double-blind, placebo-controlled pilot study with nutritional therapy was performed with participants including adults between the ages of 18 and 65 years. All participants had to have received a diagnosis of IBS-D at least 6 months prior to enrolment into the study, and continued to experience symptoms according to the ROME II diagnostic criteria for IBS. The study protocol was followed as shown in below:

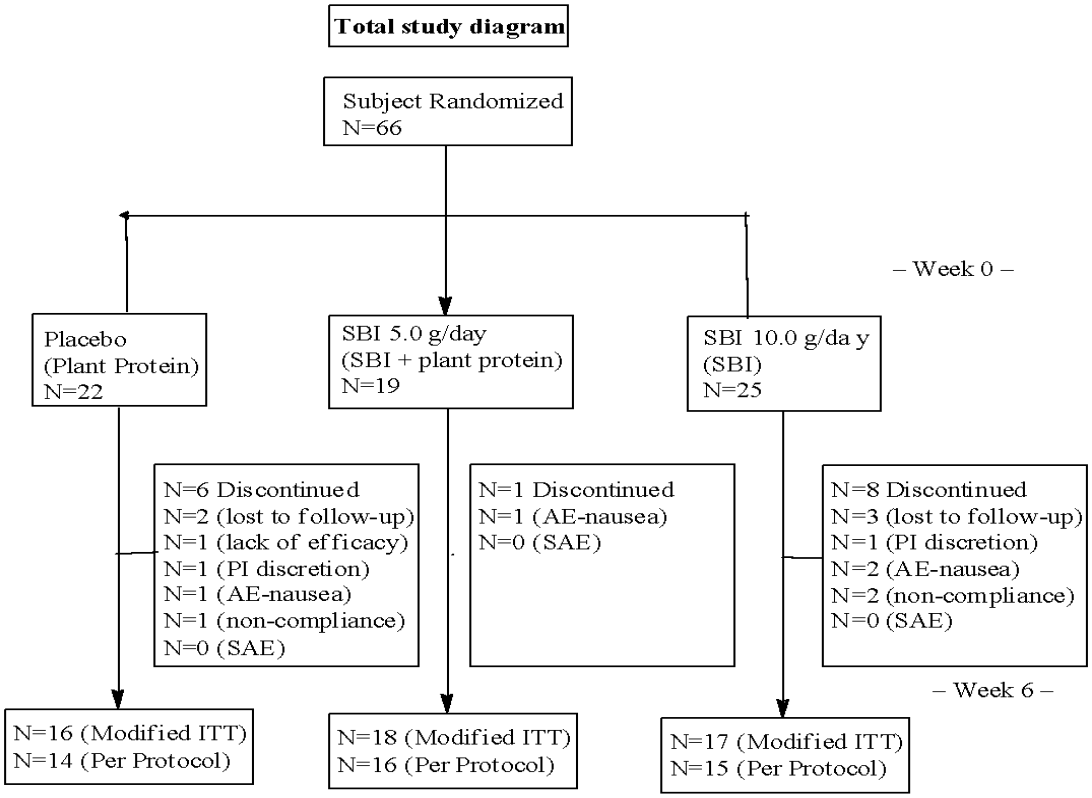

Figure 1. Flow chart depicting the study design of the 6-week randomised, placebo-controlled, double-blind study assessing the effects of oral serum-derived bovine immunoglobulin/protein isolate (SBI) on patients with IBS-D. SBI treatment was administered to determine its effects on the gastrointestinal symptom scores and quality of life in participants. 22 participants were assigned to receive placebo, 19 were assigned to receive 5g/day SBI and 25 were assigned to receive SBI 10g/day. Participants that were dropped during the study duration or those participants who experienced adverse effects or non-compliance issues were not considered in the intention-to-treat analysis to account for attrition bias.

The results of this study demonstrated an improvement in the frequency and severity of symptoms in subjects with diarrhea-predominant IBS.
Patients who ingested 10 g/day SBI for 6 weeks reported a significant decrease in the number of days with abdominal pain, flatulence, bloating, urgency, loose stools and total days with symptoms, from week two to end of study. Whereas, control patients ingesting an equivalent amount of soy protein showed no improvement. In addition, subjects reported improved symptom scores for loose stools, flatulence, urgency, nausea, hard stools and incomplete evacuation, suggesting an improvement in the quality of life of the subjects compared to the placebo group (artificial milk group). This study also revealed changes in intestinal structure and function in IBS due to inflammation, and that components within the SBI formulation may normalize gut bacteria that are beneficial to the intestinal mucosa.

Therefore, this study provides evidence that suggests SBI provides distinct nutrients in the form of a protein mixture containing immunoglobulins that accounts for management of various enteropathies when compared to other high protein controls [46].

3.1.4.7 Effect of Colostrum on the Symptoms and Mucosal Permeability in Patients with Irritable Bowel Syndrome: A Randomized Placebo-controlled Study[47]

Irritable bowel syndrome (IBS) is defined by the presence of abdominal discomfort or pain associated with altered bowel habits with symptoms of constipation and/or diarrhea. The pathogenesis of IBS appears to be multifactorial, involving altered gastrointestinal motor function, enhanced perception of visceral stimuli, and psychosocial factors. Yoon et al. performed an 8-week study which included a 4-week treatment period and a 4-week follow-up observation period without treatment with colostrum to find a standard treatment of IBS that primarily aims for symptom relief. Their main objective was to determine whether the administration of bovine colostrum could relieve symptoms of IBS and decrease endotoxin levels in patients. Colostrum is produced by female mammals immediately after birth and is a nutrient-rich fluid that contains immune, growth, and tissue repair factors.
Colostrum contains significant amounts of complement components that act as natural antimicrobial agents to actively stimulate the maturation of an infant's immune system. Bovine colostrum, a raw material for immune milk preparations, can be used to treat or prevent infections of the gastrointestinal tract. This double-blind, randomized, placebo-controlled

trial by Yoon et al. aimed to analyze the efficacy of bovine colostrum. A total of 18 (age 18-80 years) patients experiencing recurrent abdominal pain or discomfort for at least 3 days/month in the last 3 months were included in this study. The patients were randomly assigned to the colostrum group (n=9) and the placebo group (artificial milk group). However, no significant differences were observed between both groups.

The response rate of patients in the placebo group study is crucial in therapeutic trials conducted to evaluate IBS. The placebo response rates have ranged from 16.0−71.4% with a population-weighted average of 40.2% in randomized placebo-controlled trials of patients with IBS.

This high placebo response rate could also confirm the lack of any significant benefits of colostrum in patients with IBS. Therefore, this study did not find any beneficial effects of colostrum in relieving symptoms and improving mucosal immunity of patients with IBS [47].

3.1.4.8 Zinc carnosine works with bovine colostrum in truncating heavy exercise–induced increase in gut permeability in healthy volunteers[48]

Davison et al. performed an examination with bovine colostrum, adding zinc-carnosine which is also known as (Hamari–Xsto Solutions), as the key component with it. Zinc Carnosine is a health food supplement which stabilizes small bowel integrity and stimulates the gut repair process.
They performed a double-blind, placebo-controlled, crossover protocol to check whether these two mixtures of components can moderate the effects of heavy exercise such as gut symptoms and, in extreme cases, heat stroke.
The study included 8 volunteers who completed a 4-arm, double-blind, placebo-controlled crossover protocol before undertaking standardized exercise 2- and 14-d after the start of treatment. They followed the flow diagram given below-

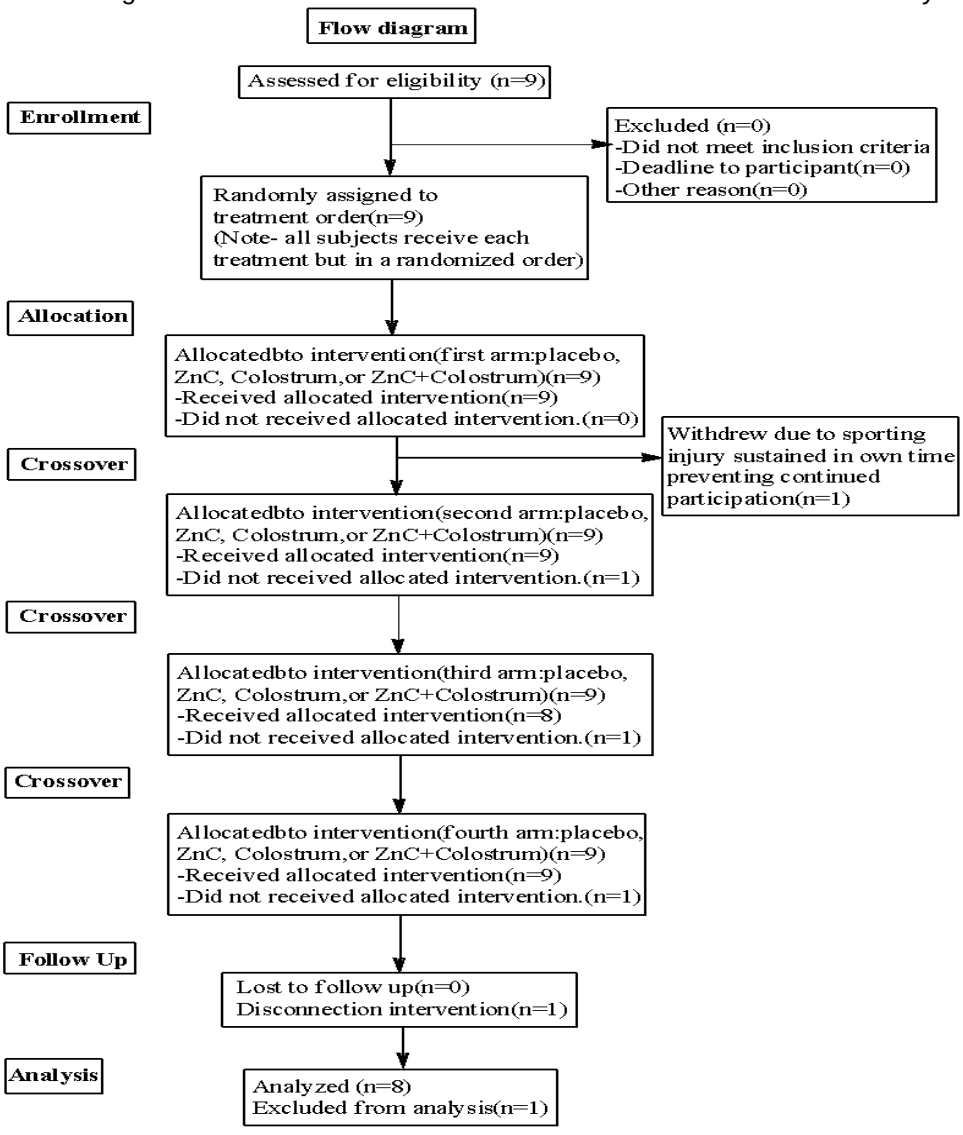

Figure 2. Flow diagram depicting the study design for the 4-arm double-blind, placebo-controlled, crossover protocol study (n=8) assessing the effects of zinc carnosine and bovine colostrum on exercise-induced gut permeability. 9 participants underwent randomization to receive placebo, Zinc carnosine-alone, colostrum-alone or zinc carnosine and colostrum in combination in crossover design. 1 participant was dropped from the study due to an unrelated sporting injury and was excluded from the final analysis.

The results were quite similar to the 1st experiment of Dr. Marchbank. As a result of this 4-arm, double-blind, placebo-controlled, randomized 14-day study, the body temperature of the volunteers increased 2 degrees. Additionally, *in vitro* studies also showed doubling of apoptosis and reduced epithelial resistance by 3–4-fold, and also 3-fold increase in gut permeability (5-h urinary lactulose:rhamnose ratios) after exercise. ZnC or Colostrum truncated this rise by 70% after 14 days of treatment. It was observed that an increasing heat shock protein 70, preventing heat stroke in military personnel and truncating temperature-induced changes in B cell leukemia/ lymphoma-2 associated X protein a and B cell lymphoma 2. This combination also increased total occludin and reduced phosphorylated tyrosine claudin, phosphorylated tyrosine occludin, and phosphorylated serine occludin, thereby enhancing the TJ formation and stabilization.

In conclusion, this particular study focusing on temperature changes builds on previous work that showed ZnC prevents NSAID gut damage [48].

3.1.4.9 Pilot study of probiotic/colostrum supplementation on gut function in children with autism and gastrointestinal symptoms[49]

Children having autism spectrum disorder (ASD) also suffer from gastrointestinal (GI) comorbidities, including chronic constipation, diarrhea, and irritable bowel syndrome, and about half of the children having ASD show severity of these symptoms. A 12-week randomized, double blind pilot study, including 5 weeks of probiotic-prebiotic supplementation, followed by a two-week washout period, and 5 weeks of prebiotic only supplementation, was performed with the children with ASD (2-11 years) and GI co-morbidities (n = 8).

The whole study protocol and participants are described in the following figures-

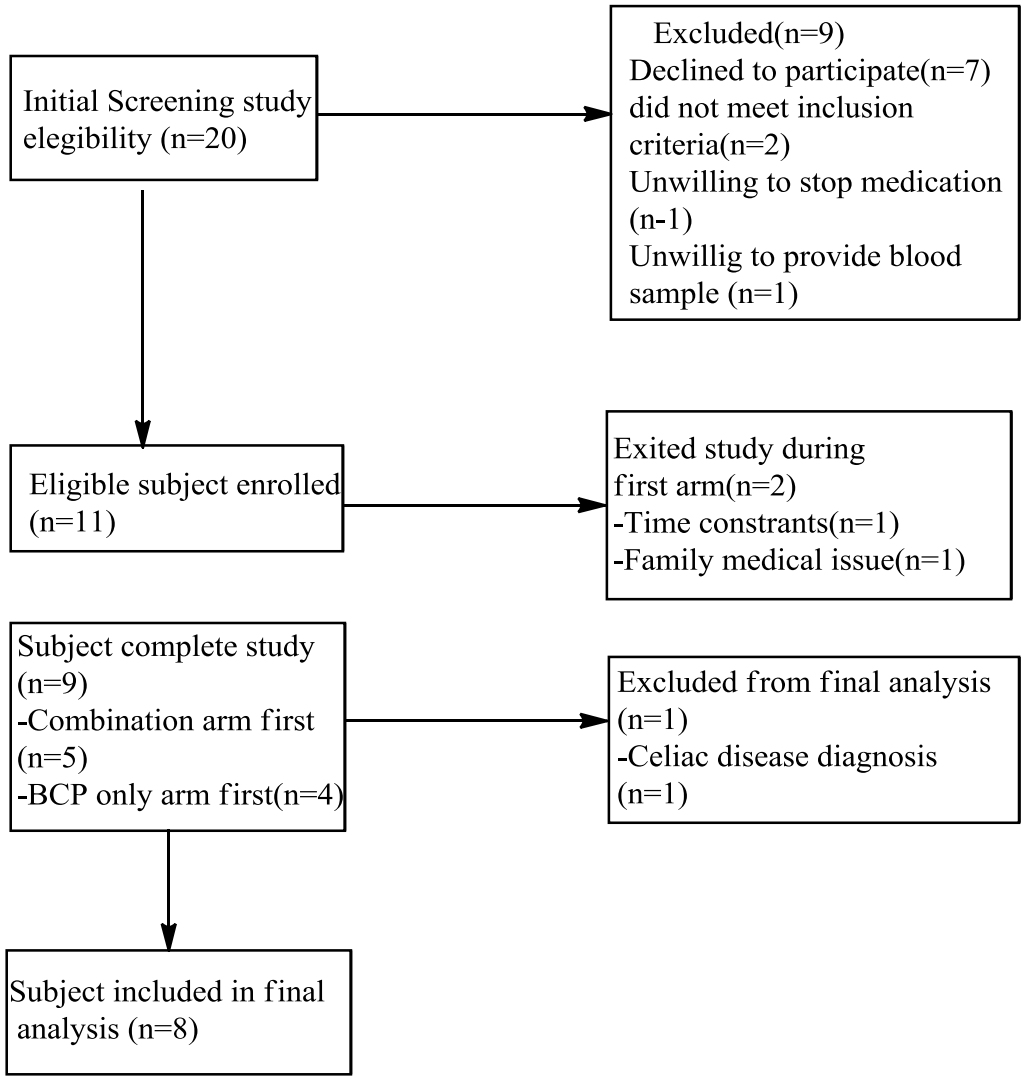

Figure 3. Flow diagram depicting study design for the 12-week randomized, double-blind pilot study assessing the effects of probiotic/bovine colostrum on gastrointestinal co-morbidities in children with autism spectrum disorder (ASD). 20 subjects were included in the initial screening process with 11 eligible subjects being enrolled into the study. Due to non-compliance issues, 3 subjects were excluded from the final analysis (n=8).

A 12-week study program included children with average ages ranging between 3.9 to 10.9 years with a male to female ratio of 7:1. The study protocols like questionnaires and logs, faecal DNA extraction, microbiota analysis was also performed.

As a result of this randomized clinical trial, study participants experienced functional constipation, functional diarrhea with several of them experiencing irritable bowel syndrome as well. 7 of the participants experienced gassiness and bloating during the study period. Although not statistically significant, weight gain was also experienced by two participants during the study. The reason for this may be due in part to the presence of an abnormal microbiota as well as aberrant immune function in the GI tracts of these children. Additionally, some parents also reported an increased appetite and willingness to consume novel foods, mostly fruit and meat, by their child during the study. This may be due to the reduction of abdominal pain or improved stool evacuation, thereby partially explaining the weight gain experienced. Overall, most of the participants experienced reduced gastrointestinal symptoms to some extent. Further changes in adaptive, repetitive and aberrant behavior with supplementation were also assessed among the participants in order to assess their tolerability, and it was found out that there was a significant reduction of certain aberrant behaviors, including irritability, lethargy, stereotypy and hyperactivity, with supplementation, mostly in the BCP only group.

Bovine colostrum not only contains a limited amount of milk oligosaccharides that may promote the growth of this particular bacteria, but it also contains an abundance of immune proteins, including immunoglobulins, lactoferrin and a range of cytokines, that can further modulate the microbiota and the immune system. The results of this study show that bovine colostrum product is well-tolerated by children with ASD and GI symptoms when administered alone or in

combination with probiotic B. infantis. There were some mild side effects coupled with reduced frequency of some GI symptoms in children supplemented with BCP with and without B. Infantis [49].

4. CONCLUSION

This research review's purpose is to help the reader understand the effects of colostrum on different biological aspects. This is significant because it gives insights about the physiological effects of colostrum on the immune system, IBS, diabetes and thyroid functioning. While the beneficial properties of colostrum have been known for decades, particularly towards neonatal development, it is only recently that the notion of colostrum as a nutraceutical has been gaining traction. Our review has explored some of the beneficial properties of colostrum such as the reduction in blood glucose levels and the presence of IGFs which may have implications for diabetes treatment. Colostrum was also characterized by the presence of immunomodulatory factors which help in the development and maturity of the neonatal immune system. Colostrum particularly showed efficacy in the alleviation of intestinal permeability and associated gastrointestinal disorders. Colostrum was also found to contain thyroid hormones, although their physiological relevance is still unclear. However, this review has revealed it to be a significant source of iodine with implications for proper thyroid functioning and neurodevelopment in neonates. Therefore, this review provides a basis for understanding the curative properties of colostrum. However, many of the current studies examining colostrum as therapeutic target for disorders involve *in vivo* animal studies, and therefore more clinical trials are needed to strengthen these findings. More research and testing are also required to gain a better understanding on the implications of these properties and how these would apply within clinical settings.

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5. ETHICAL APPROVAL

Not applicable.

6. HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

7. CONSENT FOR PUBLICATION

Not applicable.

8.AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

COMPETING INTERESTS DISCLAIMER:

AUTHORS HAVE DECLARED THAT NO COMPETING INTERESTS EXIST. THE PRODUCTS USED FOR THIS RESEARCH ARE COMMONLY AND PREDOMINANTLY USE PRODUCTS IN OUR AREA OF RESEARCH AND COUNTRY. THERE IS ABSOLUTELY NO CONFLICT OF INTEREST BETWEEN THE AUTHORS AND PRODUCERS OF THE PRODUCTS BECAUSE WE DO NOT INTEND TO USE THESE PRODUCTS AS AN AVENUE FOR ANY LITIGATION BUT FOR THE ADVANCEMENT OF KNOWLEDGE. ALSO, THE RESEARCH WAS NOT FUNDED BY THE PRODUCING COMPANY RATHER IT WAS FUNDED BY PERSONAL EFFORTS OF THE AUTHORS.

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