EFFECTS OF BOVINE COLOSTRUM SUPPLEMENT INTAKE TO HEALTH: A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

Introduction: Bovine colostrum has been widely consumed as it is claimed to provide immunity to adults and also beneficial to the gastrointestinal tract for children. **Aim:** This study aimed 1) to identify the dosage of bovine supplement needed to improve health outcome in human, 2) to assess the duration for bovine supplement intake to produce positive health outcome in human, 3) to identify the outcome of bovine supplement intake to human. **Methods:** Four databases (Scopus, PubMed, ProQuest and Semantics) were used to search for relevant journal articles. The PRISMA checklist was used for this systematic review with inclusion and exclusion criteria. Search terms were determined to identify relevant journal article. Cochrane Risk of Bias Tool and Robins-I Tool were used to assess the risk of bias. **Results:** Ten articles were included for review. The dosage and duration of bovine colostrum intake depended on the age groups and condition. The dosage of bovine colostrum for children was between 0.5 g to 3 g per day while for adults and older adults, the dosage was 3.2 g to 60 g per day. The duration of bovine colostrum intake identified in this review was from 4.5 hours to 5 months. The results showed that bovine colostrum intake has positive effects for children with diseases, hospitalized ICU adults, and athletes. Not all effects were observed in certain groups especially among healthy adults and older adults. However, there was no negative effect reported. **Conclusions:** The intake of bovine colostrum supplementation provided positive outcomes and could be one of the treatments for certain diseases but further research is warranted. Researchers can broaden their studies in human with different age range and with different conditions and diseases related to immune system.

KEYWORDS: Bovine Colostrum Supplementation, Effects, Health

INTRODUCTION

Today, dietary supplements become one of the most trending items that have been included in people's eating habits. Based on the prevalence, there is an increasing trend of the intake of supplements. From the Malaysian Adult Nutrition Survey (MANS) 2014, the prevalence of vitamin/mineral supplements intake among Malaysian adults was 28.1 % while food supplements intake was 34.0 % (Mohd Zaki et al., 2014). Bovine colostrum is believed to have the same nutritional content as human colostrum due to high content of immune factor such as immunoglobulin A and immunoglobulin G, nutritional factors and growth factors (McGrath, Fox, McSweeney, Kelly, 2015). The intake of this supplement has been questioned whether it can bring benefits to human's health or not. Nevertheless, effectiveness of bovine colostrum warrants further investigation. In current trend, bovine colostrum has become one of the supplements that have been known due to its benefits. Godhia and Patel (2013) reported that bovine colostrum supplementation intake has risen significantly over 10 years. Many studies have been done to find out whether bovine colostrum supplement is effective towards human's health. The beneficial effects of bovine colostrum intake based on its amount and duration to various health conditions can be identified through findings of previous conducted studies. It is therefore important to systematically review the effective amount and duration for each particular condition to identify the new findings of the intake of bovine colostrum supplementation among different population such as children, adults and older adults or in specific conditions such healthy or hospitalized population.

METHODS

Study design

This study reviewed journal articles that studied about bovine colostrum by using Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Moher, Liberati, Tetzlaff, and Altman, 2009).

Eligibility criteria

The eligibility criteria were based on PICOS elements which are Population, Intervention, Comparator, Outcome and Study Design. The details of criteria according to PICOS are shown below:

Population: human

Intervention: Bovine colostrum supplement

Comparator: placebo/other products

Outcome: health outcomes such as results of blood, saliva, body weight, body mass index, CD4+ count, stool frequency and others.

Study design: randomized controlled trial (RCT), non-randomised control trial, cross-sectional studies, case control studies and cohort studies

Information sources

Four databases were used which are Scopus, Pub Med, Semantics and ProQuest Health & Medical Complete. The years of published journals articles included and selected were from 2014 until 2020 as the last review about bovine colostrum therapy was published in 2014.

Search strategy

The search strategy for this review was: ("bovine colostrum") AND (effect* OR benefit*) AND (people OR human OR adult OR children). The search was limited to journals on human studies in English language from 2014-2020 in the databases.

Study selection

The study selection was based on PRISMA flow diagram (Moher, Liberati, Tetzlaff, and Altman, 2009) which consists of identification, screening, eligibility and included. The eligibility was assessed based on the inclusion and exclusion criteria. The inclusion criteria were human study, randomized controlled trial (RCT), non-randomised control trial, cross-sectional studies, case control studies, cohort studies, English journal and journal articles from 2014-2020 while the exclusion criteria were animal study, cell study, review study, case report study and non-English journal.

Risk of bias

To assess the risk of bias in the individual studies in this review, Cochrane Risk of Bias Tool was used for randomized controlled trials (Higgins et al, 2019). The bias was assessed as a judgment on risk of bias from five domains which are selection, performance, attrition, reporting and others. This was then judged as high, low, or unclear of risk of bias. As for non-randomized studies, the Risk of Bias in Non-randomized Studies-of intervention (ROBINS-I) tool was used (Sterne et al., 2016). The tools provide signalling questions to flag the potential for bias.

Synthesis of results

First, certain number of records were identified through database searching and additional records were identified through other sources. Next, the screening process removed the duplicate of the same journals from the databases. After duplicates were removed, the records were screened through the inclusion and exclusion criteria. The excluded records stated the reason on why they were excluded. The last step was the included journals which were analysed in qualitative synthesis.

Data analysis

The results were tabulated in a table adapted from Cochrane Review and adjusted based on the objectives of this review.

RESULTS

Study selection

A total of 134 records were identified through database searching (Scopus: n=69, Semantics: n=19, PubMed: n=36, ProQuest: n= 10) and no additional records identified through other sources.

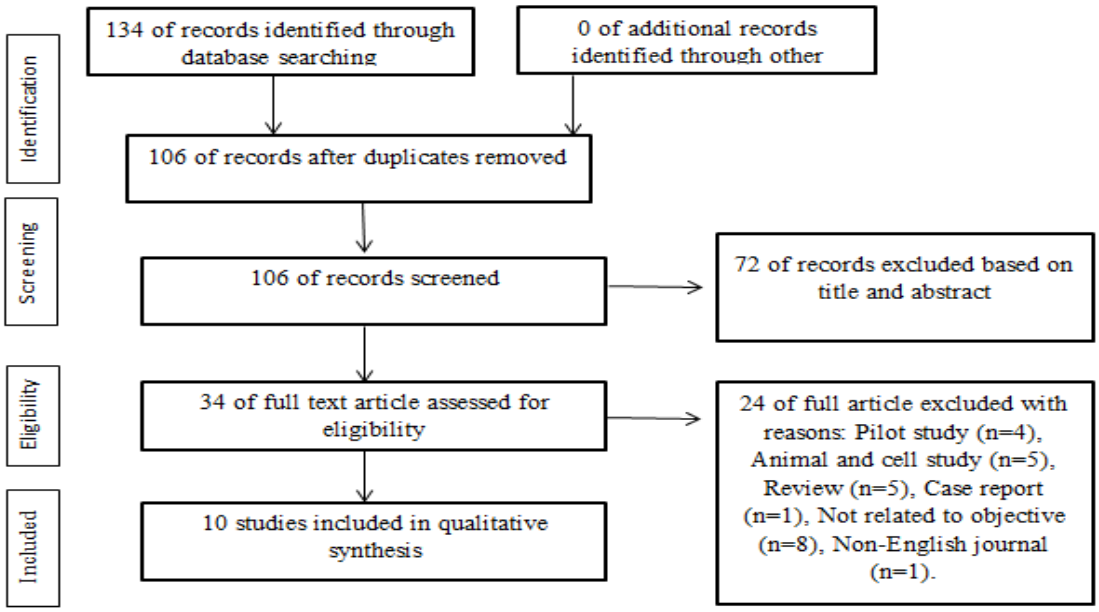

Figure 1: The flow of study selection based on PRISMA flow diagram

From 134 of records identified through database searching, 106 duplicate records were removed. In the screening stage, 72 records were excluded based on the title and abstract. Thirty-four full text articles were assessed for eligibility and 10 studies were included in qualitative synthesis. There were 24 full articles that were excluded at eligibility stage. Among the 24 excluded studies, four pilot studies were excluded due to unpublished data. These studies were excluded based on the inclusion and exclusion criteria.

Study characteristics

Table 1 shows the details of the included studies. The study design for nine studies were randomized control trials with eight placebo and double-blind studies (Barakat, Meheissen,Omar & Elbana, 2019; Davison, Jones, Marchbank & Playford, 2019; Duff et. al, 2014; Eslamian, Ardehali, Baghestani, & Vahdat Shariatpanahi, 2019; Jones et al, 2019; Jones, Thatcher, March, & Davison, 2015; Jones, Cameron, Thatcher, Beecroft, Mur, & Davison, 2014; Kotsis et. al, 2018; Rathe et. al, 2019), one study used parallel trial, while another one study used retrospective observational study design (Nigro, Nicastro, & Trodella, 2014).

The dosage of bovine colostrum and the duration of studies differed based on the objectives of each study. As for children, the dosage of bovine colostrum which ranged from 0.5 to 3.0 g/day (Barakat, Meheissen,Omar & Elbana, 2019; Nigro, Nicastro, & Trodella, 2014; Rathe et. al, 2019) were lower than adults, (3.2 to 40 g per day) (Davison, Jones, Marchbank & Playford, 2019; Eslamian, Ardehali, Baghestani, & Vahdat Shariatpanahi, 2019; Jones et al, 2019; Jones, Thatcher, March, & Davison, 2015; Jones, Cameron, Thatcher, Beecroft, Mur, & Davison, 2014; Kotsis et. al, 2018) and for the older adults, since only one study focused on elderly, the dosage of bovine colostrum given were 60 g per day (Duff et. al, 2014).

The duration of the studies also differed in every study. In children, the duration of the bovine colostrum supplementation was one week to five months (Barakat, Meheissen, Omar & Elbana, 2019; Nigro, Nicastro, & Trodella, 2014; Rathe et. al, 2019). For healthy adults, the duration of the supplementation were 4.5 hours to 12 weeks (Davison, Jones, Marchbank & Playford, 2019; Eslamian, Ardehali, Baghestani, & Vahdat Shariatpanahi, 2019; Jones et al, 2019; Jones, Thatcher, March, & Davison, 2015; Jones, Cameron, Thatcher, Beecroft, Mur, & Davison, 2014; Kotsis et. al, 2018). As for the elderly, the duration of the supplementation was one week (Duff et. al, 2014).

Table 1: Results of the reviewed studies (N=10).

Author	Study design	Participants	Type of instrument	Dosage	Duration	Key findings
Barakat, S. H., Meheissen, M. A., Omar, O. M., & Elbana, D. A. (2019).	Double blind, Randomized control trial, Placebo	Children with diarrhea, n=160, colostrum group: n=80, control group (placebo): n=80, male and female, 6 months-2 years old	Frequency and duration of diarrhea and vomiting, Vesikari scoring	3 g/sachet per day	1 week	• After 48 hours, presence and frequency of vomiting and diarrhea significantly lower in colostrum group (p=0.000). • Median time of disappearance of vomiting, diarrhea and fever in colostrum group is earlier in colostrum group compared to control group (p=0.000). • Vesikari scoring after 48 h in Rota Ag positive and E,coli positive significantly lower in colostrum group (p=0.000). • Median time of disappearance of diarrhea in Rota Ag positive and E.coli positive significantly earlier in colostrum group than control group (p=0.000).

Davison, G., Jones, A. W., Marchbank, T., & Playford, R. J. (2019).	Double blind, Placebo controlled, Randomized trial.	Adult, Study 1: n=16 Colostrum group: n=8 Placebo: n=8, Male, 25± 6 years old. Study 2: n=20 Colostrum group: n=10 Placebo: n=10, Male, 28± 8 years old Study 3: n=53 Colostrum group: n=25 Placebo group: n=28, Male, 30.8 ± 13.8 years old.	Plasma samples from blood.	Study 1: 40g/day (30g for resting activities, 5g before 2.5 h cycling and 5g for another 1.25 h cycling Study 2: 20 g/day Study 3: 20g/day (10g in the morning and 10g in the evening)	Study 1:4.5 hours Study 2:4 weeks Study 3:12 weeks	• No effects on IGF 1 level.
Duff, W. R. D. W. R. D., Chilibeck, P. D. P. D., Rooke, J. J. J., Kaviani, M., Krentz, J. R. J. R., & Haines, D. M. D. M. (2014).	Double blind, Randomized, Placebo	Older adults, n=40 bovine colostrum: n=19 placebo: n=21, male and female, Mean age: male=59.1 ± 5.4 years old, female= 59.0 ± 6.7 years old.	Muscle thickness of the elbow flexor and knee extensor, IGF-1 and C-reactive protein, composition by dual energy x-ray absorptiometry (DXA), strength by determination of 1-repitition maximum (1-	60 g/day (3 doses per day)	1 week	• Significant increase in lean tissue mass, bone mineral content and fat percentage decrease in both groups. • Strength increase more in bovine colostrum group. (p=0.026) • No difference in muscle size between both groups.

			RM), strength by determination of 1-repitition maximum (1-RM) on bench press and leg press, and Telephone Interview of Cognitive Status (TICS)			• No difference between groups in cognitive functions. • No effects in IGF-1 and C-reactive protein. • Significant increase in leg press strength in colostrum group. (p=0.045) • Decrease bone resorption in older adults in colostrum group.
Eslamian, G., Ardehali, S. H., Baghestani, A. R., & Vahdat Shariatpanahi, Z. (2019).	Randomized, Double-blind, placebo-controlled trial.	ICU hospitalized adult, n=70, colostrum group: n=35, control group: n=35, male and female, >18 years old (no mean age)	Plasma endotoxin and zonulin concentrations.	20 g/day	48 hours after admission to discharge from the ICU or 10 days	• Significant decrease in plasma endotoxin concentration in colostrum group. (p=0.007) • Significant decrease in zonulin concentration in colostrum group. (p<0.001) • Incidence of diarrhea significant lower in colostrum group (p=0.02)

Jones, A. W., March, D. S., Thatcher, R., Diment, B., Walsh, N. P., & Davison, G. (2019).	Double blind Randomized Control Trial, Placebo	Adult, n= 34 Bovine colostrum: n=17, placebo: n=17, male, Mean age: colostrum=30.5±13.8 years old Placebo=31.5± 13.2 years old	Main exercise trial, novel antigen diphenylcyclopropenone (DPCP), leucocyte counts, and IGF-1 concentrations.	20 g/day (2 doses per day)	58 days	• Sensitivity of in vivo immune responsiveness is the same in both groups. • No effects on physiological responses to exercise. • No difference in total leukocyte counts. • No difference for effect on plasma IGF-1.
Jones, A. W. W., Thatcher, R., March, D. S. S., & Davison, G. (2015).	Randomized, Double blind, Parallel group design	Adult, n=20 Bovine colostrum: n=10, placebo: n=10, Male, Mean age: 28 ±8 years old	Gas exchange threshold (GET), maximal oxygen uptake (VO2 max), saliva	20 g/day (2 doses per day)	4 weeks	• No effects on leukocyte trafficking, phorbol-12-myristate-13- acetate-stimulated oxidative burst, bacterial-stimulated neutrophil degranulation, salivary secretory IgA, lactoferrin or lysozyme. • Significant effects of formyl-methionyl-leucyl phenylalanine-stimulated oxidative burst in colostrum group (p=0.049)

Jones, A. W., Cameron, S. J. S., Thatcher, R., Beecroft, M. S., Mur, L. A. J., & Davison, G. (2014).	Double blind, Placebo	Adult,n=57 Bovine colostrum: n=28 placebo: n=29, male, 30-43 years old (no mean age)	Health questionnaire, blood sample, serum metabolomics, saliva	20 g/day (2 doses per day)	12 weeks	• Significantly low on mean number of URI episodes in the colostrum group. (p=0.033) • No difference number of URI episodes in both groups. • No effects on in vitro neutrophil oxidative burst, salivary secretory IgA or salivary antimicrobial peptide.
Kotsis, Y., Mikellidi, A., Aresti, C., Persia, E., Sotiropoulos, A., Panagiotakos, D. B., … Nomikos, T. (2018).	Double blind, Randomized, Placebo-controlled, Parallel group	Soccer player, n=22 Bovine colostrum: n=11, placebo: n=11, Male, age not mentioned	Loughborough Intermit- tent Shuttle Test (LIST), jump performance, perceived muscle soreness, activity of creatine kinase, High-sensitivity C-reactive protein and IL-6.	3.2 g/day	6 weeks	• Subjects recover faster from exercise in colostrum group • Low creatine kinase in colostrum group • Significant intervention x time interaction for C-reactive protein (CRP) in colostrum group (p=0.038)

Nigro, A., Nicastro, A., & Trodella, R. (2014).	Retrospective observational, Cohort study	Children with Recurrent Respiratory Infections (IRR), n=167 Treatment with Sinerga (nutritional product containing bovine colostrum): n=67 Treatment with bacterial extracts: n=100, male and female, Mean age: 4.5 years old	The frequency of episodes of respiratory infection.	1 sachet contains 3g of bovine colostrum For month 1, 1 sachet/ day for 20 consecutive days For month 2 to 4, 1 sachet/day for 10 consecutive days	5 months	• Significant reduction in frequency of respiratory infections with antibiotic therapy in colostrum group • No more than two episodes of respiratory infection in colostrum group.
Rathe, M., De Pietri, S., Wehner, P. S.,Frandsen, T. L., Grell, K., Schmiegelow, K., … Müller, K. (2019).	Randomized, Double-Blind and Placebo Controlled Trial	Children with acute lymphoblastic leukemia, n=62 Colostrum: n=30 Placebo: n=32, male and female, 1-18 years old	Days of fever, plasma C-reactive protein, neutrophil count, data on bacteremia or fungaemia episodes.	0.5-1.0 g/kg/d	4 weeks	• No effects for days of fever. • No effects were observed for neutropenic fever, intravenous antibiotics or incidence of bacteremia. • Significant decrease of severity of oral mucositis in colostrum group (p=0.009).

DISCUSSION

This review aimed to assess the effects of bovine colostrum supplement intake to human's health.

In children, bovine colostrum is used to treat acute diarrhea. Children with diarrhea, aged from 6 months to two years old were randomly treated by using bovine colostrum and placebo. The results showed that after 48 hours, the presence and frequency of vomiting and diarrhea significantly lower in colostrum group (Barakat, Meheissen, Omar and Elbana, 2009). In the restrospective observational and cohort study by Kotsis et al (2018), children with RRI were divided into two groups in which one group was given Sinerga, the nutritional product that contains bovine colostrum while the other group was treated with bacterial extracts. After five months, there was a significant reduction in frequency of respiratory infections with antibiotic therapy and there were no more than two episodes of infection in the colostrum group. Rathe et al (2019) conducted a study to identify the effects of bovine colostrum against chemotherapy-induced gastrointestinal toxicity in children with acute lymphoblastic leukemia. The results showed that there was a major decrease in severity of oral mucositis in colostrum group but there is no effect for days of fever and neutropenic fever, intravenous antibiotic or bacteremia incidence.

A study by Davison, Jones, Marchbank and Playford in 2019 showed that oral bovine colostrum supplementation did not give any effect to IGF-1 level in healthy adults. The study was conducted for 4.5 hours for short term study; while one and four weeks for long term study administration. There was also no effect on IGF-1 plasma level in another study by Jones et al (2019) that carried out research on the effects of bovine colostrum supplementation on in vivo immunity following prolonged exercise. There was no effect on the sensitivity of in vivo immune responsiveness, physiological responses to exercise and differences in total leucocytes counts. As for the effects of bovine colostrum intake on neutrophil and mucosal immune responses to prolonged cycling, the outcomes were significant effects of formyl-methionyl-leucylphenylalanine-stimulated oxidative burst in colostrum group but there was no effect on leucocytes trafficking, phorbol-12-mysristate-13-acetate-stimulated neutrophil degranulation, salivary IgA, lactofferin and lysozyme (Jones, Thatcher, March & Davison, 2015). Jones, Cameron, Thatcher and Beecroft (2014) conducted a research to examine the effects of bovine colostrum intake on upper respiratory illness in active males. The outcomes demonstrated that the mean number of upper respiratory illness (URI) was significantly low while there was no difference of URI episodes in both groups. No effects detected on in vitro neutrophil oxidative burst, salivary secretory IgA or salivary antimicrobial peptide.

One research was conducted on soccer players in which low dose of bovine colostrum dosage was assigned to assess the performance and reduce inflammation in the subjects (Kotsis et. al, 2018). The results showed that the subjects that were assigned with bovine colostrum supplementation recovered faster from exercise and the level of protein kinase were lower in the colostrum group.

One study was conducted on ICU hospitalized adults to investigate the effects of early enteral bovine colostrum supplementation on intestinal permeability in critically ill patients. There was a significant decrease in plasma endotoxin and zonulin concentration in colostrum group. The incidence of diarrhea was also lower in bovine colostrum group compared to the placebo group (Eslamian, Ardehali, Baghestani & Vahdat, 2019).

Only one study in the included article identified the effects of bovine colostrum in the elderly. There was a significant increase in leg press strength and decrease bone resorption in bovine colostrum group while there was no effect in muscle size, no difference in cognitive functions between both groups, no effects in IGF-1 and C-reactive protein (Duff et al, 2014).

CONCLUSION

In conclusion, bovine colostrum has shown positive effects for children with diseases as well as for hospitalized ICU adults. However, mixed effects were observed in healthy adults. As for the athletes, the intake showed positive effects on C-reactive protein while for older adults the results have mixed effects which were either positive and no effects in some measure outcomes. However, no negative effects were reported. The dosage and duration of bovine colostrum intake also depends on the age groups and the health conditions as well as the types of the population (whether normal adult or athletes). Since bovine colostrum showed many positive effects towards immunity especially in children with certain diseases and also for hospitalized ICU adults and athletes, it can be consumed within recommended dosage range for each particular group which were 0.5 gram per day per kilogram body weight to 3 gram per day for children, 3.2 -60 gram per day for adults. More research is warranted as it could help to further identify alternative treatments for specific diseases.

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REFERENCES

Mohd Zaki, N. A., Rasidi, M. N., Awaluddin, S. M., Hiong, T. G., Ismail, H., & Mohamad Nor, N. S. (2018). Prevalence and Characteristic of Dietary Supplement Users in Malaysia: Data from the Malaysian Adult Nutrition Survey (MANS) 2014. Global Journal of Health Science, 10(12), 127. https://doi.org/10.5539/gjhs.v10n12p127

McGrath, B. A., Fox, P. F., McSweeney, P. L. H., & Kelly, A. L. (2016). Composition and properties of bovine colostrum: a review. Dairy Science and Technology, 96(2), 133–158. https://doi.org/10.1007/s13594-015-0258-x

Godhia, M. L., & Patel, N. (2013). Colostrum - Its composition, benefits as a nutraceutical: A review. Current Research in Nutrition and Food Science, 1(1), 37–47. https://doi.org/10.12944/CRNFSJ.1.1.04

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. https://doi.org/10.1371/journal.pmed.1000097

Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A. (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Barakat, S. H., Meheissen, M. A., Omar, O. M., & Elbana, D. A. (2019). Bovine colostrum in the treatment of acute diarrhea in children: A double-blinded randomized controlled trial. *Journal of Tropical Pediatrics*, *66*(1), 46–55. https://doi.org/10.1093/tropej/fmz029

Davison, G., Jones, A. W., Marchbank, T., & Playford, R. J. (2019). Oral bovine colostrum supplementation does not increase circulating insulin-like growth factor-1 concentration in healthy adults: results from short- and long-term administration studies. *European Journal of Nutrition*. https://doi.org/10.1007/s00394-019-02004-6

Duff, W. R. D. W. R. D., Chilibeck, P. D. P. D., Rooke, J. J. J., Kaviani, M., Krentz, J. R. J. R., & Haines, D. M. D. M. (2014). The effect of bovine colostrum supplementation in older adults during resistance training. *International Journal of Sport Nutrition and Exercise Metabolism*, *24*(3), 276–285. https://doi.org/10.1123/ijsnem.2013-0182

Eslamian, G., Ardehali, S. H., Baghestani, A. R., & Vahdat Shariatpanahi, Z. (2019).
Effects of early enteral bovine colostrum supplementation on intestinal permeability in critically ill patients: A randomized, double-blind, placebo-controlled study. *Nutrition*, *60*, 106–111. https://doi.org/10.1016/j.nut.2018.10.013

Jones, A. W., March, D. S., Thatcher, R., Diment, B., Walsh, N. P., & Davison, G. (2019). The effects of bovine colostrum supplementation on in vivo immunity following prolonged exercise: a randomised controlled trial. *European Journal of Nutrition*, *58*(1), 335–344. https://doi.org/10.1007/s00394-017-1597-6

Jones, A. W. W., Thatcher, R., March, D. S. S., & Davison, G. (2015). Influence of 4 weeks of bovine colostrum supplementation on neutrophil and mucosal immune responses to prolonged cycling. *Scandinavian Journal of Medicine and Science in Sports*, *25*(6), 788–796. https://doi.org/10.1111/sms.12433

Jones, A. W., Cameron, S. J. S., Thatcher, R., Beecroft, M. S., Mur, L. A. J., & Davison, G. (2014). Effects of bovine colostrum supplementation on upper respiratory illness in active males. *Brain, Behavior, and Immunity*, *39*, 194–203. https://doi.org/10.1016/j.bbi.2013.10.032

Kotsis, Y., Mikellidi, A., Aresti, C., Persia, E., Sotiropoulos, A., Panagiotakos, D. B., … Nomikos, T. (2018). A low-dose, 6-week bovine colostrum supplementation maintains performance and attenuates inflammatory indices following a Loughborough Intermittent Shuttle Test in soccer players. *European Journal of Nutrition*, *57*(3), 1181–1195. https://doi.org/10.1007/s00394-017-1401-7

Nigro, A., Nicastro, A., & Trodella, R. (2014). Retrospective observational study to investigate Sinerga, a multifactorial nutritional product, and bacterial extracts in the prevention of recurrent respiratory infections in children. *International Journal of Immunopathology and Pharmacology*, *27*(3), 455–460. https://doi.org/10.1177/039463201402700318

Rathe, M., De Pietri, S., Wehner, P. S., Frandsen, T. L., Grell, K., Schmiegelow, K., … Müller, K. (2019). Bovine Colostrum Against Chemotherapy-Induced Gastrointestinal Toxicity in Children with Acute Lymphoblastic Leukemia: A Randomized, Double-Blind, Placebo-Controlled Trial. *Journal of Parenteral and Enteral Nutrition*. https://doi.org/10.1002/jpen.1528