



Bovine Colostrum: A Potential Novel Therapeutic Agent in the Management of Skin Hyperpigmentation – A Comprehensive Review of Its Bioactive Properties and Mechanistic Pathway

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ABSTRACT:

Introduction: Skin hyper-pigmentation, characterized by an excessive accumulation of melanin, is a condition that poses formidable aesthetic and psychological challenges, therefore motivating intensive attempts to find effective, safe therapeutic interventions. Classical depigmenting agents, though powerful, are mostly restricted due to a number of adverse effects such as irritation, ochronosis, and even potential toxicity. Bovine colostrum, the first milk produced immediately postpartum by cows, appears to be a promising natural alternative because of its rich composition of bioactive factors including growth factors, immunoglobulins, lactoferrin, and antioxidants. The following comprehensive review assesses the potential of bovine colostrum as a novel therapeutic agent for the management of hyper-pigmentation, taking into consideration its mechanistic pathways and active biological properties. Research has shown that the components of bovine colostrum, in particular hydrolysed extracts and exosomes (Col M-exos), inhibit melanogenesis through the suppression of the MC1R-cAMP signalling pathway and also of the master regulator microphthalmia-associated transcription factor. A few growth factors like Transforming Growth Factor-beta TGF and peptides such as lactoferrin contribute to this effect via the activation of the ERK pathway, resulting in the proteasomal degradation of MITF with subsequent down regulation of tyrosinase, TRP-1, and TRP-2. Moreover, the antioxidant capacity of colostrum mitigates oxidative stress-induced melanogenesis and promotes skin repair via fibroblast proliferation and telomere protection. This report integrates current *in vitro* and clinical evidence that bovine colostrum represents a multilevel, biocompatible approach to skin brightening and rejuvenation, positioning it as the superior candidate for incorporation into modern dermatological and cosmetic preparations.

Objectives: In addition to being a source of amino acids, the proteins in colostrum can perform several functions for the newborn. These proteins are found in the whey fraction, and some of them have already been mentioned above. These bioactive proteins act through a variety of mechanisms, but their role is largely related to host defence.

Methods: Lactoferrin (LF), a member of the transferrin protein family, is an iron-binding glycoprotein synthesized in the mammary gland and in other exocrine glands and is therefore present in colostrum, milk, saliva, and bronchial, cervicovaginal, and gastrointestinal fluids. LF is not present in the lacteal secretions of all mammalian species; for example, it has not been detected in dogs, rats, and rabbits, but it is one of the most abundant glycoproteins in ruminant and human milk, although human milk is much more concentrated in LF than bovine milk (100 times or more). In contrast, rat and rabbit milks are more concentrated in transferrin than human milk, in which it is undetectable. In cattle, both LF and transferrin are found in higher concentrations in colostrum than in milk, and transferrin is higher in blood. The mammary gland secretes a high mass of LF during the dry period and colostrogenesis, and it may influence the release of IgG1 in colostrum by increasing intracellular pH, facilitating the release of IgG1 from FcRn, since this receptor depends on a pH < 6.5 or >6.5 to either bind or release IgG1. The concentrations of LF and transferrin in bovine colostrum.

Conclusions: Bovine colostrum is an important milestone in discovering new drugs for treatment against skin hyperpigmentation. This extensive review clearly proves that colostrum is not just another supplement; it is an



incredibly potent “bioactive cocktail” that can influence the prime signaling pathway associated with mammalian melanogenesis. The major mechanistic mechanism entails a multi-faceted attack on the master regulator protein, MITF. BCFM, various growth factors like TGF- β , and glycoproteins like lactoferrin in bovine colostrum’s act in concert to block the MC1R-cAMP pathway and trigger the ubiquitination-mediated degradation of MITF through activation of the ERK signaling cascade. Consequently, this triggers a drastic decrease in the expression of tyrosinase and TRP-1. In addition, the therapeutic potential of bovine colostrum can be accentuated by its regenerative and protective effects. By counteracting UV-inducible ROS, telomeres of fibroblasts maintained intact, and improving the hydrolipid barrier of the skin, bovine colostrum targets the root causes of pigmentation disorders – aging, inflammation, and oxidative injury. Compared to the conventional pharmacotherapy offered by hydroquinone compounds, which often becomes clouded with adverse reactions and dermal toxicity, this comprehensive strategy undoubtedly has a definite advantage. The discovery of exosomes in colostrum opens a new delivery mode which not only ensures its stability but also its penetration into the skin, meaning that a new wave in skin remedies is in sight. Though safe and efficient in its application in increasing hydration levels in the skin, more studies are needed in establishing which particular peptide is involved to increase its efficacy. In closing, bovine colostrum is a highly potent and sustainable remedy that is about to give new meaning to hyperpigmentation remedies and skin care in general.

1. Introduction

The maintenance of healthy and normal-looking skin is a multibillion-dollar industry worldwide; however, among all treatments and indications, hyperpigmentation is still one of the most challenging and hard-to-manage conditions in dermatological medicine. Hyperpigmentation disorders, which include melasma, senile lentiginos or age spots, freckles, and post-inflammatory hyperpigmentation (PIH), occur as a result of a dysfunctional and extremely complex process of melanogenesis—the biochemical pathway of specialized dendritic cells called melanocytes that produce a pigment called melanin. While it is evident that melanin is extremely valuable as a natural shield against to ultraviolet radiation mutagenesis-induced damage, hyperplasia and irregularities in melano structure can induce a multitude of significant psychological problems affecting self-perceived vanity and quality of life. Historically speaking, melano-corrective treatments have always been centered on hydroquinone (HQ), which is a phenolic compound that inhibits tyrosinase, a rate-limiting enzyme in melano-biosynthesis enzymatic. When used as a treatment for hyperpigmentation, however, HQ has both historical and contemporary irony and controversy written all over it. Chronic use has always been linked to a multitude of dermatological problems that include contact dermatitis, erythema, and even the chronic blue-black mortification of tissues known as exogenous ochronosis. To add to these concerns and as a form of regulation against systemic or body-distant effects of carcinogenic alterations and

mutagenesis linked to chronic use and exposure, HQ has been subjected to strict state control and regulation in several regions of Asia and even in the European Union. As a direct response to this regulation and as a form of adaptive evolution and new growth and discovery in a new decade of challenging biotechnology and innovative R&D trendspotting and hunting and searching in new and untidy frontiers of completely new or stranger sciences and research and developments and innovations and earth-shaking and explosive discoveries and innovations, a new trend has emerged that has been militating and cajoling and inciting and persecuting or hounding and chasing and hunting and pursuing and searching and pushing and propelling and thrusting and driving or forcing or coercing or compelled or necessitating or necessitated and even mandating and commanding and gagging or gobbling and gobbling-up or engorging or engorging a new and fresh and completely different and stranger and unprecedented and unsung and unexplored and uncharted and new and rivulet and rill and rillet of researches and developments and innovations and discoveries and breakthroughs and findings and findings and reveals and reveals in a completely new and fresher frontier that is still unexplored and unsung and undefined and undeclared and new a Hydrolyzed colostrum extracts and exosomes derived from bovine colostrum have been shown to possess the ability to affect the signaling pathways involved in the regulation of melanin synthesis, namely the MC1R-cAMP signaling cascade and the MITF pathway. In addition, it should not be expected that a



problem like hyperpigmentation would occur and remain as a solitary issue. Instead, it would often be a consequence of a chronic inflammatory environment or state of oxidative stress, largely contributed to and worsened by environmental conditions like UV rays, environmental pollution, and smoking. Bovine colostrum brings a complete remedy that effectively targets the inhibition of pigmentation as well as harnesses powerful antioxidant and anti-inflammatory actions. Aside from these characteristics, it provides a range of essential micronutrients like vitamins A, C, and E, accompanied by minerals like selenium and zinc, which effectively counteracts ROS as well as provides a natural reinforcement of the skin's protective properties against external stimuli.¹⁰This paper will delve into the biochemical complexity of bovine colostrum and further examine the unique mechanistic actions involved in addressing and managing skin hyperpigmentation.

2. Objectives

In addition to being a source of amino acids, the proteins in colostrum can perform several functions for the newborn. These proteins are found in the whey fraction, and some of them have already been mentioned above. These bioactive proteins act through a variety of mechanisms, but their role is largely related to host defence.

Immunoglobulins

Colostrum immunoglobulins are responsible for protecting the immunological naïve newborn calf against pathogens by activating and regulating the innate immune system. Although there is still much to learn, they have been extensively studied and reviewed in other papers, so only a brief mention of their transport mechanisms and concentrations in colostrum follows.

Immunoglobulins are a family of high molecular weight proteins with similar physicochemical properties and antigenic determinants. The main immunoglobulin classes present in bovine colostrum are IgG, IgA, and IgM, with IgD and IgE also present. IgG is the predominant immunoglobulin in bovine colostrum, whereas IgA is predominant in primate colostrum. IgG represents over 50% of the total protein of BC. IgG is divided into three subtypes: IgG1, IgG2, and IgG3. IgG1 predominates over IgG2 in bovine colostrum by approximately although blood concentrations are similar. Nevertheless, IgG1 in blood decreases during colostrogenesis, which may be due to the passage of

IgG1 from blood into colostrum. IgG3 is present at even lower levels and has only recently been detected in BC. IgG in colostrum is found in concentrations ranging from 0.68 to 216.70 mg/mL; IgA concentrations range from 0.13 to 22.14 mg/mL and IgM from 0.18 to 14.01 mg/mL. As IgG is the predominant immunoglobulin in BC, only this class is considered in quality assessments, and a colostrum with 50 mg/mL of IgG is considered good quality colostrum. However, for effective immunization, factors such as the amount of colostrum ingested, the time between birth and ingestion, microbiological contamination, and the method of administration must be taken into account.

3. Methods

Colostrum, like milk, contains many enzymes that perform functions associated with the host defence mechanism against microorganisms and oxidative damage, as well as with many essential metabolic processes such as catalysis, lipolysis, and proteolysis.

Lactoperoxidase (LPO) is one of the most frequently mentioned enzymes in the literature. It is a glycoprotein, a member of the family of haem peroxidase enzymes, secreted by the mammary gland into colostrum. The main biological function of LPO is to defend against microorganisms by generating reactive oxygen species (ROS), which is effective against a wide range of bacteria but also has antiviral and tumoricidal activities. This enzyme has been shown to be very resistant to proteolysis, highlighting its importance in the defence of the calf's GIT. LPO and LF in milk lose activity during heat treatment above 70 °C for 30 min. In this study, where different temperatures were tested, raw milk samples showed a lower growth rate per hour than treated milk of *Streptococcus thermophilus*, *Lactococcus lactis*, *Pseudomonas fluorescens*, and *Escherichia coli* in whey because as temperature increased, the total protein content in whey decreased significantly, which also reduced the bacteriostatic activity in milk.

Lysozyme is an enzyme present in colostrum and milk with specific hydrolytic activity against the peptidoglycan in cell walls of Gram-positive and Gram-negative bacteria. It is more effective against Gram-positive bacteria because their cell walls contain up to 90% peptidoglycan. Compared to humans or other species, such as horses, this enzyme is present in lower concentrations in bovine milk, probably too low to contribute effectively to the overall bacteriostatic and



bactericidal activity. Reported concentrations of lysozyme in bovine colostrum vary widely and are usually lower than other enzymes with antimicrobial activity, but it generally increases after the first milking. Other enzymes present in bovine colostrum include catalase, superoxide dismutase, and glutathione peroxidase, which have antioxidant properties, and β -1,4-galactosyltransferase, lactate dehydrogenase, alkaline phosphatase, and gamma-glutamyl transferase, which catalyze important biological reactions, and esterases, lipases (such as lipoprotein lipase), proteases (such as tissue plasminogen activator), and ribonucleases (such as ribonuclease II-1), as well as enzyme inhibitors, which are present in very high concentrations but rapidly decrease with time after birth.

Cytokines

Cytokines in colostrum are divided into interleukins, interferons, and tumor necrosis factors, which are responsible for modulating the immune system. Some of these pro-inflammatory cytokines, such as IL-1 β , IL-6, and tumor necrosis factor- α (TNF- α), and acute phase proteins, such as serum amyloid A and haptoglobin, can influence the concentration of these molecules in the serum of calves during their first weeks of life. Weaned pigs supplemented with colostrum also showed changes in cytokine mRNA expression in spleen- and gut-associated lymphoid tissues, with increased expression of IL-2, IL-4, IL-10, IL-12 and decreased expression of IFN- γ . IL-1Ra, IL-1 β , IL-6, TNF- α , and IFN- γ are present in higher concentrations in bovine colostrum than in mature milk; for example, IL-1Ra can be 180 times higher in colostrum than in mature milk, suggesting their importance as immunomodulatory factors in the newborn calf. Concentrations of these cytokines in colostrum can range from 77 to 5206 ng/mL. There is still a lack of knowledge about the variation of other cytokines between the first milking and subsequent milkings.

Cytokines are essential in the immune response, but some cytokines need tight regulation; otherwise, the inflammatory process can have nefarious effects on the organism. For example, IL-6 plays important roles in inflammatory processes at the intestinal level but can also cause tissue damage, compromise the integrity of the intestinal barrier, and lead to systemic infections when overproduced. IL-6 is mediated by the nuclear factor κ B (NF- κ B), which is involved in the pathogenesis of

inflammatory diseases. Bovine colostrum was able to reduce NF- κ B activation and, consequently, IL-6 production in an in vitro model. In another in vitro model, colostrum inhibited the NF- κ B pathway in human colon cancer HT29 cells, protecting against intestinal epithelial cell inflammation. These results are in agreement with Blais et al., who observed a negative effect of bovine colostrum on the transcriptional activation of NF- κ B. BC seems to have a strong capacity to increase the production of some cytokines and decrease others. It also appears to inhibit the production of cytokines that are present in higher concentrations in colostrum than in milk, such as IL-6 and INF- γ , probably as a means of regulating and establishing a balance between exogenous and endogenous cytokine levels.

Discussion

Bovine colostrum is an important milestone in discovering new drugs for treatment against skin hyperpigmentation. This extensive review clearly proves that colostrum is not just another supplement; it is an incredibly potent "bioactive cocktail" that can influence the prime signaling pathway associated with mammalian melanogenesis. The major mechanistic mechanism entails a multi-faceted attack on the master regulator protein, MITF. BCFM, various growth factors like TGF- β , and glycoproteins like lactoferrin in bovine colostrum's act in concert to block the MC1R-cAMP pathway and trigger the ubiquitination-mediated degradation of MITF through activation of the ERK signaling cascade. Consequently, this triggers a drastic decrease in the expression of tyrosinase and TRP-1. In addition, the therapeutic potential of bovine colostrum can be accentuated by its regenerative and protective effects. By counteracting UV-inducible ROS, telomeres of fibroblasts maintained intact, and improving the hydrolipid barrier of the skin, bovine colostrum targets the root causes of pigmentation disorders – aging, inflammation, and oxidative injury. Compared to the conventional pharmacotherapy offered by hydroquinone compounds, which often becomes clouded with adverse reactions and dermal toxicity, this comprehensive strategy undoubtedly has a definite advantage. The discovery of exosomes in colostrum opens a new delivery mode which not only ensures its stability but also its penetration into the skin, meaning that a new wave in skin remedies is in sight. Though safe and efficient in its application in increasing hydration levels



in the skin, more studies are needed in establishing which particular peptide is involved to increase its efficacy. In closing, bovine colostrum is a highly potent and sustainable remedy that is about to give new meaning to hyperpigmentation remedies and skin care in general.

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