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Review article

# Current and emerging methods for treatment of hemoglobin related cutaneous discoloration: A literature review

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ABSTRACT

*Background:* Currently, there is no available medication for immediate correction of bruise discoloration. Instead, makeup, cosmetic powders, concealers, and various traditional herbal remedies are used to mask discoloration. These approaches have no influence on the pathology behind the discoloration. The purpose of this study was to explore existing methods and current trends in correction of hemoglobin related cutaneous discoloration.

*Methods:* This paper describes the treatment methodologies available for proposed correction of hemoglobin related cutaneous discoloration. A thorough literature review was conducted to assess current knowledge of available treatments for bruise discoloration.

*Results:* current cosmetics being marketed under the names "Bleacher bruises," "Bleaching agents" and "Blood bleachers" addressing bruise related discoloration do not offer targeted pathological treatment. Several methods for immediate discoloration of the skin and nail plate in the area of bruising and hematoma were found, yet no method offered sufficient clinical data in support of its efficacy and safety. The intricate mechanisms of discoloration associated with hemoglobin extravascular deterioration are not targeted by any treatment method. Only one paper outlining the clinical application of bleaching agents was found.

*Conclusion:* The primary blood pigments responsible for the discoloration in bruises include methemoglobin, oxyhemoglobin, carbohymoglobin, verdoglobin, biliverdin, and bilirubin. No existing method targets the degradation of hemoglobin in the area of ecchymosis. The efficacy of existing patented methods remains questionable and unsupported clinically. Future research should focus on developing a drug targeting hemoglobin derivatives, preventing discoloration at an early stage.

## 1. Introduction

Bruising refers to cutaneous discoloration due to erythrocyte and hemoglobin degradation outside the vascular system, particularly in the cutaneous and subcutaneous layers. Bruising is a common complication of medical procedures such as injections, as well as domestic trauma, sport, tourism, combat injuries, abrasions. Bruising causes aesthetic discoloration of the skin and mucous membranes [1, 2, 3]. Topical agents have most commonly been used to correct aesthetical aspects of the bruise, yet there is no method of correcting bruise pathology by acting upon the mechanisms behind discoloration.

Cutaneous discoloration is caused by displaced blood, which permeates the tissue after escaping damaged vessels [4, 5, 6]. Hemoglobin changes color depending on connection with oxygen or carbon dioxide, though all hemoglobin adducts retain a reddish color. Oxyhemoglobin is vividly red, deoxyhemoglobin is dark red, methemoglobin is dark-brown-red, carboxyhemoglobin cherry-red, carbohemoglobin is pale-red, sulfhemoglobin is greenish-red. The blue appearance of bruises is due to the higher reflection of the blue light component, whereas the red component penetrates through tissues more deeply and is therefore significantly absorbed (by hemoglobin as well). The human eye receives reflected light, which is why deoxygenated venous blood seems bluer,

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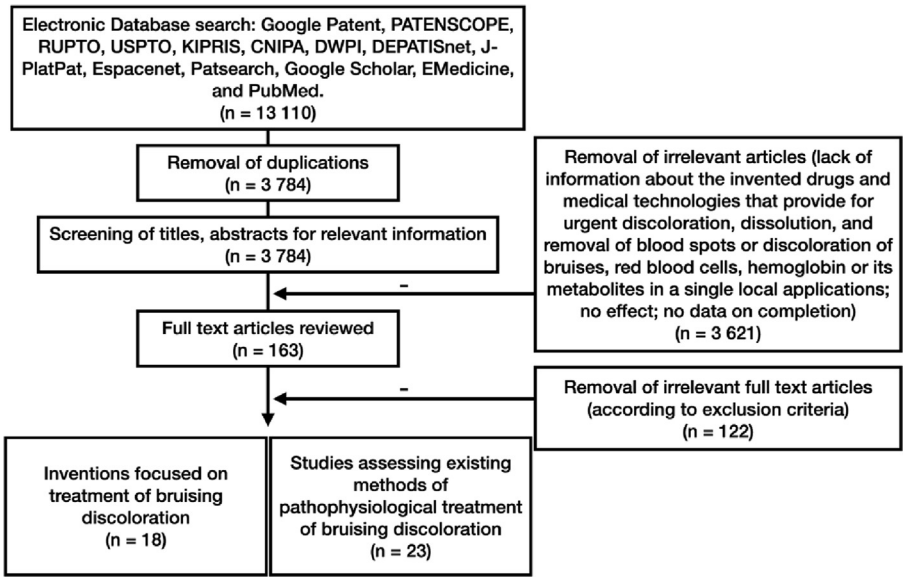


**Figure 1.** Research methodology.

due to the higher absorption coefficient in the red spectral region, compared to oxygenated arterial blood [7, 8, 9].

Hemoglobin in erythrocytes can reversibly bind to oxygen, so after the flow of blood from the damaged blood vessels into the surrounding tissues, hemoglobin inside the erythrocytes carries oxygen and along the way gives it to the tissues, capturing carbon dioxide from them [10, 11]. At average body temperature in the portion of the blood flowing from the damaged vessel, oxyhemoglobin content rapidly decreases and carbohemoglobin content increases in red blood cells. This leads to a rapid change in bruise coloration [12, 13, 14]. The primary coloring of the bruise is determined by the active lysis of erythrocytes outside the vascularture, which is associated with the release of hemoglobin and its oxidation to methemoglobin creating a dark-brown reddish color. The later eventually undergoes metabolic changes and is broken down into yellow pigments (biliverdin/bilirubin).

Historically, conventional medicine does not recognize bruising as an independent disease, amd bruises are not considered to be specific symptoms of any particular disease. Consequently, modern standards of examination of patients do not require physicians to identify, photograph, and monitor the dynamics of size, shape, and color of the skin in places of bruises [15, 16, 17]. In this regard, there is little information in recent reports of medical institutions on this subject [18]. Additionally, existing literature does not offer a means for etiopathological correction of bruise discoloration [19]. Modern medical guidelines do not contain abundant information about medicines that provide dissolution and amelioration of bruises [16]. Besides, there are no set standards for urgent care for skin and nail bruising. No cosmetics offer etiopathological treatment for cutaneous discoloration in the area of bruising. However, patients pay increased attention to their physical appearance and tend to use skin paint, foundation or homeopathic remedies with limited effectiveness in an attempt to correct bruise related discoloration [20, 21].

Chemical industrial bleachers are used for removal of blood staining from fabrics, paper, wood and certain foods [22, 23, 24] yet have not been analyzed for their physico-chemical potential in cosmetology. Thick pus can be dissolved with a warm alkaline solution of hydrogen peroxide [25, 26]. However, there are no studies on the possibility of bleaching bloodstains and bruises using cosmetics that contain hydrogen peroxide. Well-known industrial bleaches can be potentially used as a basis for the creation of a new group of medicines that provide immediate treatment for bruising related discoloration. In order to assess the existing methods for correction of hemoglobin related cutaneous discoloration, we performed a systematic review of existing literature covering methods and materials used for correction of bruising discoloration. It is important to assess new methods of treatment in all areas of medicine, including aesthetic medicine. Bruise discoloration by itself is not only an aesthetic deficiency, but a risk factor for infection, skin necrosis and scar tissue formation. Therefore, acting upon the pathophysiological mechanisms behind bruise progression can help reduce related complications.

## 2. Materials and methods

A thorough literature search for information on existing drugs and methods for correction of bruising with help of certain physical and chemical factors of local interaction was carried out, using the databases of the Google Patent, PATENSCOPE, RUPTO, USPTO, KIPRIS, CNIPA, DWPI, DEPATISnet, J-PlatPat, Espacenet, Patsearch, Google Scholar, EMedicine, and PubMed. We studied the references and conducted a citation search. A systematic review was conducted according the quality standards described in the AMSTAR measurement tool [27] and the PRISMA 2009 checklist [28]. The PICO model forms the basis of the search strategy [29, 30]. Two co-authors independently selected, evaluated, and extracted data. The flowchart for selecting articles was a spiral in which each spiral turn was an iteration [31, 32]. Keywords of the strategy of the search were the following: bruising, hematoma, ecchymosis, blood, red blood cells, hemoglobin, bleaching, whitening products, whitening methods, patent, discoloration. The criteria for inclusion of the scientific source were limited to the presence in it of information about the invented drugs and methods of their use, which allow due to physical and chemical factors of local interaction to urgently discolor erythrocytes and hemoglobin, or bloodstains on the surface of textiles or skin, or discolor bruises, a portion of liquid blood or dry blood crust. The criterion for the exclusion of the article was the lack of information about the invented drugs and medical technologies that provide for urgent discoloration, dissolution, and removal of blood spots or discoloration of bruises, red blood cells, hemoglobin or its metabolites in a single local application. Reduction in the risk of individual bias in judgments done by relying on the essence of the invention as a generally accepted criterion of novelty.

## 3. Results

A total of 13,110 information sources were studied, of which only 18 inventions and 23 studies were used to form a hypothesis (Figure 1). Cutaneous discoloration due to bruising is a result of a complex biochemical and pathophysiological chain of events resulting from blood exiting the vessels into surrounding tissue [4, 5, 7]. Individual isolated red blood cells typically have a yellow-green color, but in their mass, they acquire a darker hue, due to a greater coefficient of absorbed red light and reflected blue light [10, 11]. A group of red blood cells studied in reflected light are often described as scarlet, red, dark red, and sometimes cherry blue in color [8, 9, 10]. The appearance of a mass of red blood cells can depend on the stage of their development and the color of the respiratory pigment hemoglobin [12, 13, 14]. Thus, erythroblasts in the early stages of their development have a blue appearance; later, erythroblast cells become grayer, and become red only after fully maturing [33]. The respiratory pigment hemoglobin has been described as having a red color [10, 11, 12, 13, 14]. Inside the skin and other tissues, oxyhemoglobin is easily and quickly released from oxygen, binds to carbon dioxide, and turns into carbohemoglobin, which results in a greater absorbance of the red light spectrum and a higher reflection of blue light, causing all bruises to appear blue [8, 9, 11]. A few hours following the action of enzymes, hemoglobin begins to break down and turns into verdoglobin, which has a high red light absorbtion, therefore appearing blue in color. After 4–5 days, verdoglobin turns into biliverdin, which appears greenish. After another 1–2 h under the action of enzymes, biliverdin is metabolized into bilirubin, which has a yellow color. So at the end of its existence, the bruise becomes yellow. Then gradually, the bilirubin is absorbed into the blood from the site of the injury, and the bruise disappears [31, 32, 33, 34]. Therefore, in normal conditions, spanning from hours to several days, the primary source of cutaneous discoloration in bruises are hemoglobin adducts and the products of their metabolsim. A point of future research is into the possibility of discovering a drug targeting hemoglobin adducts and inducing enzymatic breakdown to increase the speed of its metabolism, and that is fast-acting against the skin discoloration formed in bruises.

### 3.1. Bleaching products

All liquids recommended for removal of blood stains are aqueous solutions of several groups of substances soluble in water. Therefore, the main ingredient is water. The second bleaching component is hydrogen peroxide. Hydrogen peroxide has numerous non-medical uses because of these properties. As an example, consider the compositions of industrial hair bleaches specified in the Modern Guide to Industrial Dies [23, 24]. In addition to industrial bleaching of various household items, hydrogen peroxide is used to bleach food products [35]. Over-the-counter products used for human use are typically sold at 3 percent active ingredient [35, 36]. Bleaching of textile products for removal of bloodstains has been thoroughly described in literature [37, 38, 39, 40]. Most solutions used for bloodstain removal represent aqueous solutions of hydrogen peroxide or its water-soluble source of from 0.01 to 15% in combination with agents maintaining a pH of more than 7.0 at the level of its osmotic activity below 140 mosmol/l and with a local temperature in the range from +26 to +42 °C. Due to alkalinity, temperature characteristics, and hypo-osmotic activity, these solutions influence the removal of blood stains due to erythrocyte hemolysis [41, 42, 43]. The described bleaching agents exclude the coagulation of blood proteins. Insight into the mechanisms behind physicochemical aspects of forced hemoglobin degradation provide valuable understanding of the factors leading to reversal of cutaneous discoloration due to bruising [44].

The mechanism of action of bleachers used for bruises is that they cause alkaline saponification, oxidation and degradation of colored proteins and protein-lipid complexes (in particular, plasma, blood cells, hemoglobin, and its metabolites) [45, 46, 47]. Saponification is provided by sodium hydrogen carbonate, and oxidation is provided by hydrogen peroxide. Sodium hydrogen carbonate is a sufficient alkaline buffer and hydrogen peroxide is a "battery" of oxygen, which is released from the bound state under the action of blood catalases [48]. It was found that the intensity of the formation of molecular oxygen and bleaching depends on the activity of catalases, the concentration of hydrogen peroxide, and the local temperature of the medium. Therefore, in case of excessive concentration increase of hydrogen peroxide can cause formation of foam and gas embols [49]. It should be noted that to date, no formal studies have been conducted on the safety of aqueous solutions of hydrogen peroxide and peroxide gels for bruises in clinics. More so, FDA guidelines permit the use of topical low concentration (3%) hydrogen peroxide, but no higher concentrations or injections have been approved for human use. This is seen in clinical practice, as a 3% solution of hydrogen peroxide is sold in pharmacies without a required prescription as a local antiseptic. Non-medical uses include a solution of 5% hydrogen peroxide used to bleach hair, a solution of 6.5% carbamide peroxide used as an over-the-counter softener of earwax, and a solution of carbamide peroxide at a concentration of 5–20% is widely used in dentistry for teeth whitening [50, 51, 52].

### 3.2. Bleaching agents for correction of bruising

In 2009 a patent "Methods of diagnostics and treatment of clotted hemothorax" by A.Y. Malchikov (RU Patent 2368333) reported that a heated 37 °C solution of 5% sodium bicarbonate and 1.5% hydrogen peroxide successfully dissolved clotted blood in the lungs. In 2010 a report emerged about applying 15% hydrogen peroxide carbamide gel for minimization of discomfort associated with bruising [44]. In 2015, a method of intradermal injection using a unique solution - "Bruise bleacher" (RU Patent 2539380) was proposed for bruise treatment. The "Bruise bleacher" consisted of an alkaline solution of hydrogen peroxide (0.03–0.01% hydrogen peroxide and 1.8% sodium bicarbonate). The sodium hydrogen carbonate in the proposed concentration creates a physiological analog of "hydrogen carbonate" buffer providing the solution with a stable alkaline pH of 8.4, with the ability to dissolve fat, blood, intercellular fluid, lymph, and improve the diffusion of the aqueous solution into the skin and the subcutaneous adipose tissue. In this case, the alkaline solution does not cause alkaline burns. Hydrogen peroxide in the proposed concentration gives the solution sufficient oxidative activity but excludes the formation of oxygen gas bubbles during injection of the solution into the skin and subcutaneous fat in the area of bruising, that is, excludes cold boiling in the tissues when injected into them. Immediately after the demonstration of this new method, several modifications of the formula of the first clinical bleaching agent and the development of its application for discoloration of the skin in the area of bruising were initiated.

Several patents, such as "Bleaching agent " (RU Patent 2589682), "Agent for intradermal bruise whitening" (RU Patent 2573382), "Method of skin discoloration in the area of bruising" (RU Patent 2582215) "Method for skin discoloration in the bruising area" (RU Patent 2586278) were presented. Essentially, all new bleaching solutions for bruises remained an aqueous solution for injection in which the main ingredients were 0.01–0.03% hydrogen peroxide, 1.7 or 1.8% sodium hydrogen carbonate, and 0.125–0.250% lidocaine hydrochloride. Additionally, it was proposed to use a solution heated to a temperature of 37–42 °C. Secondly, it was recommended to introduce a warm solution into the skin by injection until the formation of the entire area of the bruising effect of a colorless lemon crust. At the end of the procedure of bleaching the bruise, it is recommended to use a vibrational high-temperature massage of the skin until complete resorption of the infiltrate. In 2016, a patent "Method of removing cutaneous discoloration" (RU Patent 2600504) emerged. The essence of this patent was that for to remove discoloration from the skin by method of repeatedly piercing injections introducing a metal scaler with an antiseptic solution at a pH of 7.4–8.5 and a temperature of +37 - +42 °C and consequent administration of longitudinal oscillations with a frequency of 25–43 kHz. However, intradermal

**Table 1.** Existing patents for targeted correction of hemoglobin related staining.

| Patent | Method | Limitations |
|---|---|---|
| "Emergency bleaching and blood crust removal following acne treatment" (RU Patent 2631593) | The essence of these inventions is that for discoloration of traces of blood on the skin and inside the skin, it is proposed to use a warm solution of bleachers externally using a warm compress. At the same time, a solution of hydrogen peroxide and sodium bicarbonate was supplemented with a local anesthetic that quickly penetrates through intact skin. In particular, lidocaine hydrochloride was proposed as such a local anesthetic. A local anesthetic that quickly penetrates the skin gave the bleach solution of bruises a local anti-inflammatory effect. | External application does not influence pathological transformation of hemoglobin and has irritative side effects. |
| «Intravital skin whitening near blue eyes" (RU Patent 2639485) | | Ophthalmological application only, does not affect blood stains. |
| "Bleaching removal of dried blood for wrapping bandages adhered to a wound" (RU Patent 2653465). | An aqueous solution that containing 0.75–1% hydrogen peroxide, 1.2% sodium hydrogen carbonate, and 0.5% lidocaine hydrochloride used for dried blood and stain removal. It is shown that the solution of this agent has optimal osmotic, alkaline, buffer, foaming, washing, analgesic, and bleaching activity. The proposed method provides effective and safe sanitation of wounds, softening of blood crusts on the bandage, bloodless, and painless removal of the bandage from the wound. | Only external application, no evidence of possibility for internal use. No applicable on bruises. |
| "Decolorant of blood" (RU Patent 2647371). | It is an aqueous solution that contains hydrogen peroxide - 3 ± 0.3% and sodium hydrogen carbonate - in an amount that provides saturation of the liquid and the preservation of the precipitate at a temperature of 42 °C. With local interaction with the blood and/or blood residues, the invented tool very quickly completely dissolves, discolors and removes them. This blood bleach is intended for urgent bleaching and removal of a portion of fresh blood on the surface of laboratory utensils, old and dry blood stains on clothes, gloves, medical instruments, bandages, as well as on hair, skin and mucous membranes in places of injuries, bruises, abrasions, and surgical incisions. It is shown that this blood bleach provides complete discoloration of blood spots 30 s after the start of local interaction. | This method is intended for external use only. |
| "Method for whitening of sore under nail" (RU Patent 2631592). | A solution of 3% hydrogen peroxide and 10% sodium hydrogen carbonate is used as a blood bleach, which at a temperature of 37–42 °C is first used inside the hematoma, and then externally (almost immediately after the bleaching of the hematoma cavity) [45]. The drug is used in a dose that provides complete discoloration of the tissues inside the hematoma cavity. After complete bleaching of the hematoma immediately, the same solution is used externally with a warm compress. The compress is superimposed on 10–15 min. It is shown that usually, a single application of this technology provides rapid and complete discoloration of the hematoma under the nail and in the skin. | Limited applicability. Cannot be applied externally, intervention is needed. |
| "Method for blue nail treatment" (RU Patent 2641386). | | |
| "Method of emergency bleaching of the skin hematoma under the eye" (RU Patent 2679334). | | |
| "Bruise amelioration composition and method of use" (US patent 8673278B2) | A bruise amelioration composition that can be applied for one hour to an affected site, such as a bruise in the form of a gel, liquid or adhesive bandage. The composition includes at least 40% by weight of glycerin and at least 2% by weight of primrose oil. Preferably, the composition includes a fragrance, such as peach oil and marjoram and 1%–10% by weight of vitamins A, C, D, E and K. | No evidence to support the main hypotheses of the patent, that bruising discoloration is prevented with glycerin. Only theoretical potential. |
| "Topical arnica treatment for reducing bruising" (US patent 20090104292A1) | A method of treatment for post-traumatic bruising of the skin by applying topically to the affected area of the skin a treatment comprising of at least 15% by weight *Arnica Montana* (preferably 30–40% by weight *Arnica Montana)*. | Topical application only. |
| "Composition and method for treatment of bruising" (US patent 8309081B2) | Topical application of onintment consisting of *Arnica montana* extract, a helating agent (phytic acid 70% unbound), protease (bromelin or serrapaptidase), rutin, zinc, pine tree bark, vitamin K, C, E, Coenzyme Q10 | Homeopathic method. No specific target. |

injections are themselves invasive procedures with a risk of bruising. Therefore, injection-free procedures (Table 1) are more favorable.

### 3.3. Non-bleaching agents

Topical ointments are often discussed for bruising discoloration treatment and are applied directly to the skin in the area of ecchymosis. As a rule, it is recommended to apply a solution of corticosteroids, or a solution of adrenaline with local anesthesia to the area of the bruise with ice, as well as solutions, infusions, and decoctions of medicinal plants, such as arnica, Montana or melilotus gels, ointments and creams with vitamin K [41, 42, 43]. The efficacy of topical vitamin K application is questionable, and requires further experimental evaluation. Most existing ointments and topical creams are composed of homeopathic remedies and cannot be regarded as a substrate for correction of hemoglobin related discoloration.

As a result of the performed patent analysis, it can be seen that no method offers targeted etiopathological treatment. All currently available bleaching agents consist mainly of an aqueous solution of hydrogen peroxide, and sodium hydrogen carbonate, are mild alkaline, osmotic, oxygen-forming, and high temperature agents [48]. These features of the composition and activity give the bleaching agents a unique pharmacological activity: they have a pronounced nonspecific local effect on protein and protein-lipid complexes, which contain hemoglobin and its metabolites, as well as the enzyme catalase. Potentially, the correct combination of sodium bicarbonate and hydrogen peroxide with each

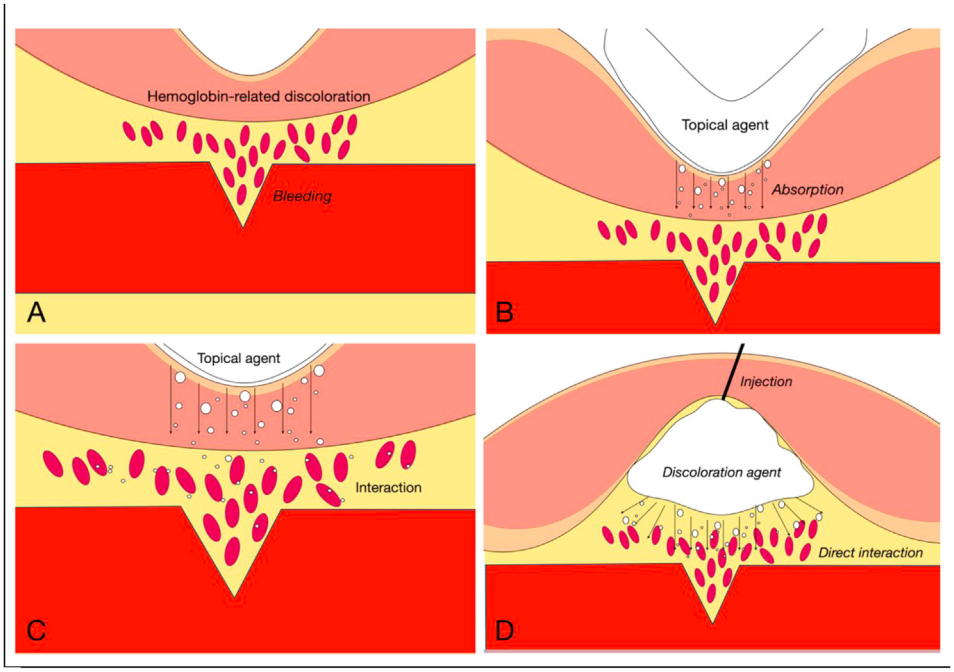


**Figure 2.** Potential treatment modalities (A – mechanism of hemoglobin related cutaneous discoloration; B – Application of topical discoloration agent, transcutaneous absorption; C – Interaction of topical discoloration agent with red blood cells, responsible for cutaneous discoloration; D – Subcutaneous injection of discoloration agent with direct interaction with red blood cells).

other may well lead shortly to the formation of a new group of cosmetics that provide rapid bleaching of the skin and nail plates in the area of bruises and bruises without the need for intradermal injection.

## 4. Discussion

Currently there are no existing FDA approved treatment methods that act upon the early stages of bruise development, halting further deterioration and progression. More often, anti-inflammatory drugs, vitamins and topical homeopathic remedies are used for symptomatic bruise treatment. Industrial bleaches, which are aqueous solutions of hydrogen peroxide, used for bleaching hair, skin, paper, wood, and seafood offer insight into the physico-chemical properties required for a potentially novel treatment method for bruise correction. The bleaching effect of hydrogen peroxide can be enhanced by increasing its concentration in the solution, increasing the temperature and pH of the solution, increasing the interaction time, as well as by combining it with other peroxides. Yet these aspects of bruise treatment undoubtably have potentially hazardous effect on healthy tissue. Existing methods for bruise bleaching have been found in Russia, and are characterized by a low (<5%) concentration of hydrogen peroxide, which is injected into the area of bruising. These efficacy and necessity of these methods remains highly questionable.

Generally, for skin discoloration, intracutaneous injections of a solution of a bleaching agent with 0.01–0.03% hydrogen peroxide and 2–4% sodium hydrogen carbonate are proposed interventions. For discoloration of the nail plates, injection for subungual hematomas containing 3% hydrogen peroxide and 10% sodium hydrogen carbonate can be used. Moreover, in all cases, it is recommended to combine injections with local hyperthermia at a temperature of + 42 °C. Yet the need for invasive procedures in these methods is a significant drawback, due to the risk of infection and other complications related to tissue penetration. Clinical application of these methods was seen in an article published in 2015 “Bleach bruising: a new group of medicines”. The author performed an evaluation of the effect of local injection of bleaches into volunteers with bruises formed by autoinjection of own venous blood into the dorsal forearm subcutaneous adipose tissue. The author successfully discolored bruises in two volunteers by local injection of 1.8% sodium hydrocarbonate and 0.03% hydrogen peroxide injection [53].

Additional experimental and clinical studies are needed to assess the safety and effectiveness of treating bruises with injectable bleaching agents and hydrogen peroxide gels. Additional tests may include a biopsy of the treated and untreated plots bruises; placebo-controlled, blind studies; measurement of hemoglobin before and after treatment of large bruises to demonstrate safety; the evaluation of changes in pigmentation and the skin's integrity; the assessment of the depth of penetration; and other applications for local peroxide gels under occlusion. Currently no evidence based studies have been performed regrading a large number of bleaching agents and their effect on cutaneous hemoglobin related discoloration.

According to existing literature, the two main setbacks in development of a targeted treatment for bruising discoloration are toxicity of discoloration agents and lack of efficacy. Potential substances can be applied topically and via injection (Figure 2). Topical application is simple, yet includes transcutaneous transfer of the topical agent, which complicates and prolongs the interaction of the substance with the blood stain. Injection of a discoloration agent can provide a direct interaction with the extravascular blood, but requires cutaneous puncturing, which undermines the efficacy of this procedure. Therefore, the limitations in forming the hypothesis are due to our outline of inventions based on physical and chemical factors of local interaction, which do not act upon the pathophysiological changes associated with bleeding. The found methods of bruise discoloration were sparse and were not accompanied by significant clinical data. Therefore it is necessary to conclude, that currently no existing method offers targeted treatment of bruise related discoloration. Despite this, several methods offer interesting conclusions regarding potential applicability of hematoma dissolution agents.

## 5. Conclusion

The primary blood pigments responsible for the discoloration in bruises include carbohemoglobin, oxyhemoglobin, verdoglobin, biliverdin, and bilirubin. In the first hours and days after the formation of a

bruise, the primary cause for discoloration is the result of erythrocyte degradation and hemoglobin metabolism. Current research does not offer a treatment method for the pathological mechanisms behind cutaneous discoloration due to hemoglobin staining. Future research should focus on developing a drug targeting hemoglobin derivatives, preventing further discoloration at an early stage. Affecting temperature, acidity, oxidation in the bruise can help reverse the staining of skin by effectively dissolving the proteins responsible for discoloration. Patented bleaching agents for bruising discoloration are not backed by significant clinical data and the safety and efficacy of their clinical application is questionable. Though an interesting topic, clinical application still remains only a theory, as no effective methods have been studied thoroughly.

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### *Additional information*

No additional information is available for this paper.

## References

[1] S.J. McPhee, M.A. Papadakis, M.W. Rabow (Eds.), Current Medical Diagnosis and Treatment, 2012, fifty-first ed., San Lange Medical Book, New York, Chicago, San Francisco, Lisbon, London, Madrid, Mexico City, Milan, New Delhi, Juan, Seoul, Singapore, Sydney, Toronto, 2012.
[2] M.S. Hamman, M.P. Goldman, Minimizing complications following bruising fillers and other cosmetic injectables, J. Clin. Aesthet. Dermatol. 6 (8) (2013) 16–18.
[3] M. King, The management of bruising following nonsurgical cosmetic treatment, J. Clin. Aesthet. Dermatol. 10 (2) (2017) E1–E4.
[4] R.W. Duggal, N.J. Harger, The safe and appropriate use of thrombolytics in the emergency department, U.S. Pharmacist 36 (2) (2011) HS11–HS16.
[5] C.P. Hayward, Diagnosis and management of mild bleeding disorders, in: ASH Education Program Book 2005(1), 2005, pp. 423–428.
[6] S. Leu, J. Havey, L.E. White, et al., Accelerated resolution of laser-induced bruising with topical 20% arnica: a rater-blinded randomized controlled trial, Br. J. Dermatol. 163 (3) (2010) 557–563.
[7] A. Kienle, L. Lilge, I.A. Vitkin, M.S. Patterson, B.C. Wilson, R. Hibst, R. Steiner, Why do veins appear blue? A new look at an old question, Appl. Optic. 35 (7) (1996) 1151–1160.
[8] R.N. Pittman, Regulation of Tissue Oxygenation, Morgan & Claypool Life Sciences, San Rafael (CA), 2011.
[9] J.W. Severinghaus, Blood gas calculator, J. Appl. Physiol. 21 (1966) 1108–1116.
[10] Erythrocytes – anatomy and physiology - BC open textbooks, Available from: https://opentextbc.ca/anatomyandphysiology/chapter/18-3-erythrocytes.
[11] R.S. Franco, M.E. Puchulu-Campanella, L.A. Barber, M.B. Palascak, C.H. Joiner, P.S. Low, R.M. Cohen, Changes in the properties of normal human red blood cells during in vivo aging, Am. J. Hematol. 88 (1) (2013) 44–51.
[12] H. Mairbäurl, Red blood cells in sports: effects of exercise and training on oxygen supply by red blood cells, Front. Physiol. 4 (2013) 332.
[13] H. Mairbäurl, R.E. Weber, Oxygen transport by hemoglobin, Comp. Physiol. 2 (2012) 1463–1489.
[14] V.K. Hughes, The practical application of reflectance spectrophotometry for the demonstration of hemoglobin and its degradation in bruises, J. Clin. Pathol. 57 (4) (2004) 355–359.
[15] Best Health Outcomes for Pacific Peoples: Practice Implications. A Resource Booklet Prepared for the Medical Council of New Zealand by Mauri Ora Associates, Available from: https://www.mcnz.org.nz/assets/standards/349b83865b/Best-health-outcomes-for-Pacific-Peoples.pdf.
[16] Standard Treatment Guidelines and Essential Medicines List, fourth ed., The United Republic of Tanzania. Ministry of Health and Social Welfare, May 2013. Available from: https://www.who.int/selection_medicines/country_lists/Tanzania_STG_052013.pdf.
[17] International Statistical Classification of Diseases and Related Health Problems, 2010 Edition, World Health Organization, 2010-2016 (The) ICD-10. 10th Revision. V. 1 -3.
[18] H.S. Gear, Y. Biraud, S. Swaroop, International Work Health in Statistics. 1948-1958, World Health Organization. Palais des Nations, Geneva, 1961.
[19] Methodologies and Working Papers. 6 – 7 December 2007, Conference on Modern Statistics for Modern Society, 2008 Edition, Eurostat, Luxembourg, 2008.
[20] Effective home remedies for bruises, Available from: https://www.stylecraze.com/articles/effective-home-remedies-for-bruises/#gref.
[21] Ways to get rid of bruises, Available from: https://www.healthline.com/health/how-to-get-rid-of-bruises.pdf.
[22] C.J. Biermann, Essentials of Pulping and Papermaking, Academic Press, Inc., San Diego, 1993.
[23] K. Hunger (Ed.), Industrial Dyes: Chemistry, Properties, Applications, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, 2003. Third, Completely Revised Edition. 2003.
[24] A. Marzec, The effect of dyes, pigments, and ionic liquids on the properties of elastomer composites, Polymers (2014). Université Claude Bernard - Lyon I; English.
[25] A. Urakov, N. Urakova, A. Reshetnikov, M. Kopylov, L. Chernova, Solvents of pus-medicines with physical-chemical aggressive action, IOP Conf. Series: J. Phys. Conf. 790 (2017), 012033.
[26] A. Urakov, N. Urakova, L. Chernova, Possibility of dissolution and removal of thick pus due to the physical-chemical characteristics of the medicines, J. Mater. Sci. Eng. B 3 (11) (2013) 714–720.
[27] B.J. Shea, J.M. Grimshaw, G.A. Wells, M. Boers, N. Andersson, C. Hamel, A.C. Porter, P. Tugwell, D. Moher, L.M. Bouter, Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews, BMC Med. Res. Methodol. 7 (2007) 10.
[28] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009 Jul 21), e1000097.
[29] S.A. Miller, J.L. Forrest, Enhancing your practice through evidence-based decision making: PICO, learning how to ask good questions, J. Evid. Base Dent. Pract. 1 (2) (2001) 136–141.
[30] M.B. Eriksen, T.F. Frandsen, The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review, J. Med. Libr. Assoc. 106 (4) (2018) 420–431.
[31] B. Boehm, Spiral development: experience, principles, and refinements, in: Wilfred J. Hansen (Ed.), Spiral Development Workshop. February 9, 2000, July 2000. Available from: http://www.sei.cmu.edu/reports/00sr008.pdf.
[32] A. Alshamrani, A. Bahattab, A Comparison between three SDLC models waterfall model, spiral model, and incremental/iterative model, Int. J. Comput. Sci. 12 (1) (2015) 106–111.
[33] M.H. Baron, J. Isern, S.T. Fraser, The embryonic origins of erythropoiesis in mammals, Blood 119 (21) (2012) 4828–4837.
[34] N.E. Langlois, G.A. Gresham, The aging of bruises: a review and study of the color changes with time, Forensic Sci. Int. 50 (2) (1991) 227–238.
[35] Italy is bleaching old seafood to make it look fresh, Available from: https://www.vice.com/en_us/article/gvkmgq/italy-is-bleaching-old-seafood-to-make-it-look-fresh.
[36] Use of hydrogen peroxide in finfish aquaculture, Available from: https://thefishsite.com/articles/use-of-hydrogen-peroxide-in-finfish-aquaculture.pdf.
[37] A. Urakov, N. Urakova, Rheology and physical-chemical characteristics of the solutions of the medicines, J. Phys. Conf. 602 (2015), 012043.
[38] A.L. Urakov, Development of new materials and structures based on managed physical-chemical factors of local interaction, IOP Conf. Ser. Mater. Sci. Eng. 123 (2016), 012008.
[39] T.C. Bithell, Blood coagulation, in: R.G. Lee (Ed.), Wintrobe's Clinical Haematology, Lea & Febiger, Philadelphia, 1993, pp. 566–615.
[40] S.M. Dinehart, L. Henry, Dietary supplements: altered coagulation and effects on bruising, Dermatol. Surg. 31 (2005) 819–826.
[41] B.M. Seeley, A.B. Denton, M.S. Ahn, C.S. Maas, Effect of homeopathic Arnica Montana on bruising in face-lifts: results of a randomized, double-blind, placebo-controlled clinical trial, Arch. Facial Plast. Surg. 8 (1) (2006) 54–59.
[42] D. Alonso, M.C. Lazarus, L. Baumann, Effects of topical arnica gel on post-laser treatment bruises, Dermatol. Surg. 28 (8) (2002) 686–688.
[43] F. Xu, W. Zeng, X. Mao, The efficacy of melilotus extract in the management of postoperative ecchymosis and edema after simultaneous rhinoplasty and blepharoplasty, Aesthetic Plast. Surg. 32 (2008) 599–603.
[44] M.A. Molenda, N. Sroa, S.M. Campbell, M.A. Bechtel, E.M. Opremcak, Peroxide as a novel treatment for ecchymoses, J. Clin. Aesthet. Dermatol. 3 (11) (2010) 36–38.
[45] A.L. Urakov, N.A. Urakova, A.A. Gadelshina, New medicines: the bleachers of bruises, blue nails, hematomas, blood stains and bloody crusts, Australas. Med. J. 10 (11) (2017) 942–943.

[46] R.K. Albright, R.P. White, Red blood cell susceptibility to hydrogen peroxide ($H_2O_2$) lysis in chronic hemodialysis patients, Clin. Exp. Dial. Apher. 6 (4) (1982) 223–228.
[47] A.L. Urakov, K. Ammer, N.A. Urakova, L.V. Chernova, E.L. Fisher, Infrared thermography can discriminate the cause of skin discolourations, Thermol. Int. 25 (4) (2015) 209–215.
[48] A. Urakov, N. Urakova, A. Kasatkin, L. Chernova, Physical-chemical aggressiveness of solutions of medicines as a factor in the rheology of the blood inside veins and catheters, J. Chem. Chem. Eng. 8 (1) (2014) 61–65.
[49] A.L. Urakov, The change of physical-chemical factors of the local interaction with the human body as the basis for the creation of materials with new properties, Epitoanyag – J. Silicate Based Comp. Mater. 67 (1) (2015) 2–6.
[50] Hydrogen peroxide: practical, environmentally friendly and antibacterial (2007-2008) Did you know there were so many uses for hydrogen peroxide?, Available from, http://www.using-hydrogen-peroxide.com/.
[51] K. Amreen, A.S. Kumar, A human whole blood chemically modified electrode for the hydrogen peroxide reduction and sensing: real-time interaction studies of hemoglobin in the red blood cell with hydrogen peroxide, J. Electroanalyt. Chem. [Internet] 815 (2018 Apr) 189–197. Elsevier BV.
[52] A. Urakov, N. Urakova, A. Reshetnikov, Oxygen alkaline dental's cleaners from tooth plaque, food debris, stains of blood and pus: a narrative review of the history of inventions, J. Int. Soc. Prev. Community Dent. 9 (5) (2019) 427–433.
[53] E.l. Fisher, Bleach bruising: a new group of medicines, Health Educat. Millennium 17 (3) (2015) 48–54.