

## Updates on non-peroxide dental bleaching agents

DANIEL C.N. CHAN, DMD, MS, DDS & DENSEN CAO, PhD

**ABSTRACT:** This article critically examines the most recent developments in peroxide-based and non-peroxide bleaching agents, with a focus on phthalimido-peroxy-caproic acid (a peroxy derivative), cysteine proteases and sodium dithionites (non-peroxide agents). The rationale for seeking non-peroxide agents, elucidating their mechanisms of action, and potential safety concerns are addressed. While newer non-peroxide agents show promise in laboratory studies, clinical studies are essential to determine their safety and efficacy in a real-world setting. (*Am J Dent* 2025;38 Sp Is A:32A-37A).

**CLINICAL SIGNIFICANCE:** Both peroxide-based and non-peroxide-based agents have their merits and side effects. It is crucial that practitioners and patients choose whitening products based on sound scientific evidence.

✉: Dr. Daniel C.N. Chan, Department of Restorative Dentistry, University of Washington, 1959 NE Pacific Street, Seattle, Washington, 98195 USA. E-✉: dcnchan@uw.edu

### Introduction

Dental bleaching procedures employing hydrogen peroxide and one of its derivatives, carbamide peroxide, are widely used due to their demonstrated effectiveness.<sup>1</sup> These agents are stabilized in a thickener agent and traditionally used in both at-home and in-office whitening methods, which involve the application of varying concentrations of the active agents and may also incorporate energy sources such as LED or thermal energy. The concentrations of hydrogen and carbamide peroxide typically range from 10% to 38% in these procedures.<sup>2</sup> The delivery of these agents is through a gel plus a tray, or a gel, or a varnish, or a strip.

Hydrogen and carbamide peroxides exert their teeth-whitening effects through oxidation reactions that remove electrons from the chromophores of extrinsic and intrinsic stains, resulting in a perceived increase in lightness value. Hydrogen peroxide and its derivatives demonstrate stability in acidic pH environments but become increasingly unstable as the pH approaches neutrality (pH 7). Bulk hydrogen peroxide is typically stored at a pH below 2 to maintain its stability.<sup>3</sup> Upon decomposition, hydrogen peroxide yields water and oxygen, while carbamide peroxide breaks down into urea and ammonia. The latter has led to sensational, although inaccurate, bad press claims that bleaching agents are merely ammonia or sewage-water treatment agents.

The use of acidic hydrogen and carbamide peroxides in whitening systems can be detrimental to tooth enamel, as these agents etch and dissolve tooth structure. This has led to stringent regulations for oxidative teeth whitening in the European Union and other countries. It is crucial that whitening systems maintain a pH of at least neutral to prevent damage to tooth structure. The pH factor significantly impacts the shelf-life stability of peroxide-based whiteners and contributes to their short-term degradation.

While whitening systems have proven efficacy, tooth sensitivity is a common adverse outcome of the bleaching procedure. This is particularly true when high concentrations of hydrogen peroxide are used. A study<sup>4</sup> reported that 85% of patients undergoing in-office bleaching reported tooth sensitivity. It is hypothesized that the degradation of hydrogen peroxide into reactive oxygen species allows these species to

diffuse to the pulp chamber via dentin tubules, triggering the release of inflammatory mediators and resulting in tooth sensitivity.

Research<sup>5</sup> has demonstrated that bleaching agents can significantly diminish the surface gloss and increase roughness of resin composites, negatively impacting the esthetic quality of restorations. Additionally, laboratory studies<sup>6</sup> have shown that bleaching gels can adversely affect bulk properties such as microhardness and flexural strength of restorative composites.

Clinicians have employed several strategies to mitigate these adverse effects, including the preemptive use of desensitizers or anti-inflammatory drugs.<sup>7,8</sup> While oral medications can help manage pain and inflammation, they are not effective in preventing the structural damage caused by bleaching agents. A promising approach is the development of non-peroxide alternatives that maintain a neutral pH. Table 1 summarizes the optimal pH that the bleaching agents operate best in.

This review discussed the merits and side effects of both peroxide-based and non-peroxide-based agents. Practitioners and patients can choose whitening products based on sound scientific evidence.

### Peroxide formula

*Sodium perborate and sodium percarbonate* - Sodium perborate and percarbonate are peroxide derivatives that undergo hydrolysis in the presence of water. Sodium perborate decomposes into hydrogen peroxide and borate, while sodium percarbonate decomposes into hydrogen peroxide and carbonate. These compounds are widely used in various applications, including detergents and cleaning products, due to their ability to release hydrogen peroxide. However, the amount of freely available hydrogen peroxide differs between the two compounds. Sodium percarbonate is known for its ability to release three molecules of hydrogen peroxide, making it a more potent oxidant than sodium perborate, which only releases one molecule of hydrogen peroxide.

In the healthcare field, sodium perborate and percarbonate are used by dentists for internal bleaching of endodontically treated teeth. The literature supports the efficacy of both agents, with minimal side effects reported. However, caution is

Table 1. Optimal pH where different bleaching agents are most effective. Bleaching mechanisms and potential side effects are also depicted.

	pH	Bleaching mechanism	Side effects
Hydrogen peroxide (30-38%)	< 2	Oxidation	High concentration etches and dissolves tooth structure. Tooth sensitivity.
Carbamide peroxide (10%)	< 2	Oxidation	Less enamel damages. Mild tooth sensitivity.
Sodium percarbonate	10-11	Oxidation	High concentration and heat can cause cervical root and internal resorption.
Sodium perborate	10-11	Oxidation	High concentration and heat can cause cervical root and internal resorption.
Phthalimido-peroxy-caproic acid (5%)	~7	Oxidation	HA nano powder and potassium citrate added to reduce damage to composites.
Sodium bicarbonate	8-9	Mild abrasion	Mild or no side effects.
Sodium chloride	7	Mild abrasion	Mild or no side effects.
Cysteine protease (bromelain, papain, ficin)	Optimum range 5.5	Cleaving peptide bonds	Less enamel damages.
Sodium dithionite (6%)	< 9	Reduction	Mild or no side effects; Need more clinical studies

advised when using high concentrations and heat together, as this can occasionally lead to resorption.<sup>9,10</sup>

Sodium perborate and percarbonate powder can be mixed with distilled water or a 30%-35% hydrogen peroxide solution and heat has been used as an auxiliary driving force. With the internal bleaching technique, instead of applying the whitening agent on the external tooth surface as the at-home and the in-office techniques, the mixed paste goes right to the tooth's pulp chamber via endodontic access. While this technique can be effective, it is important to note that high concentrations of bleaching agents combined with heat can potentially cause cervical root resorption (internal resorption).<sup>9,10</sup>

Recently, sodium percarbonate has been reformulated to be used as a bleaching gel (Beaming White's sodium percarbonate gels<sup>a</sup>). The gel's efficacy has been tested by an independent testing agent and was found to give an average bleaching efficacy of 3.6 shades, with subjects yielding up to seven shades whiter after a single treatment. It must be cautioned that claiming unit shade changes do not tell the whole story since manufacturer's shade tabs are not fabricated based totally on science and are also not equally spaced between adjacent shade tabs. Rather, they are made as arbitrary standalone shades selected by manufacturers with no statistical relevance to coverage or being spaced at equal distances apart.

*Phthalimido-peroxy-caproic acid (PAP)* - In 2011, the European Union implemented restrictions on the use of hydrogen peroxide in teeth whitening products, limiting it to only 0.1% for products sold directly to customers. However, this concentration is too low to visibly whiten teeth. This challenge inspired scientists to develop a solution that is both effective and safe.<sup>11</sup> Thus, the PAP formula was created.<sup>12</sup>

PAP is also a peroxide derivative which was originally discovered in vanilla beans and was found to be an ingredient capable of whitening teeth (Fig. 1). The currently used PAP is a synthetic organic peroxy acid primarily used as a bleaching activator. Recently, it has also been utilized as a tooth whitening agent. As the name "peroxy" suggests, PAP causes oxidation like hydrogen peroxide, which dissolves or breaks down the stains.

An investigation<sup>13</sup> revealed that PAP-containing gel caused etching of enamel with reduced microhardness. To address these issues, a new formulation called PAP+ has been introduced to the market. The PAP+ formulation includes ingredi-

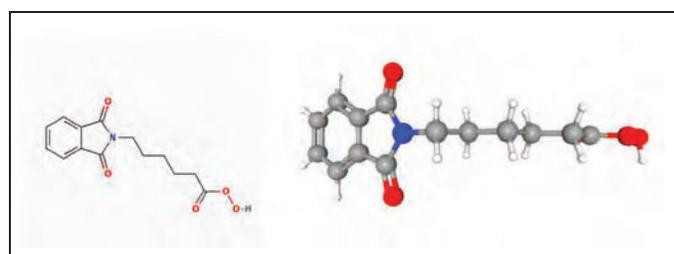


Fig. 1. 2D and 3D chemical formula of PAP. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 9860421, Phthalimidoperoxyacetic acid.

dents such as hydroxyapatite nano powder and potassium citrate, which maintain a neutral pH during the treatment through an effective citrate buffering mechanism. Recent laboratory studies<sup>13</sup> uncovered that the use of hydrogen peroxide-based bleaching gel affects the surface properties of a material, while PAP+-based home bleaching gel did not exert a negative influence on the surface and bulk properties of restorative composites. A patient with composite restorations can use PAP+ home bleaching gel without damaging them.

A Belgian product iWhite Instant<sup>b</sup> can be bought over the counter and is reported to be a whitening agent. In addition to caproic acid, the product also contains lactic acid. The manufacturer claimed that lactic acid is found in dairy milk products and helps prevent periodontitis by hampering the growth of bacteria. The added ingredients are all acidic in nature and may cause direct harm to enamel and yet the manufacturer claimed 100% safety. It is reported<sup>14</sup> that the manufacturer added buffering agents to their new formula to minimize the effects

*PAP safety* - Since PAP has only recently been used as a tooth whitening substance, there are not many studies available. However, some studies<sup>4</sup> showed that it is as effective as hydrogen peroxide. By comparing new whitening gels containing PAP with traditional gels containing hydrogen peroxide, it was found that polymer composite gels with 5% PAP had the same whitening effect as gels with 3% hydrogen peroxide, and composite gels with 12% PAP were equivalent to gels with 8% hydrogen peroxide. Importantly, it was also proven that PAP tooth whitening gel is safer and more reliable than hydrogen peroxide-based products. This suggests that PAP-

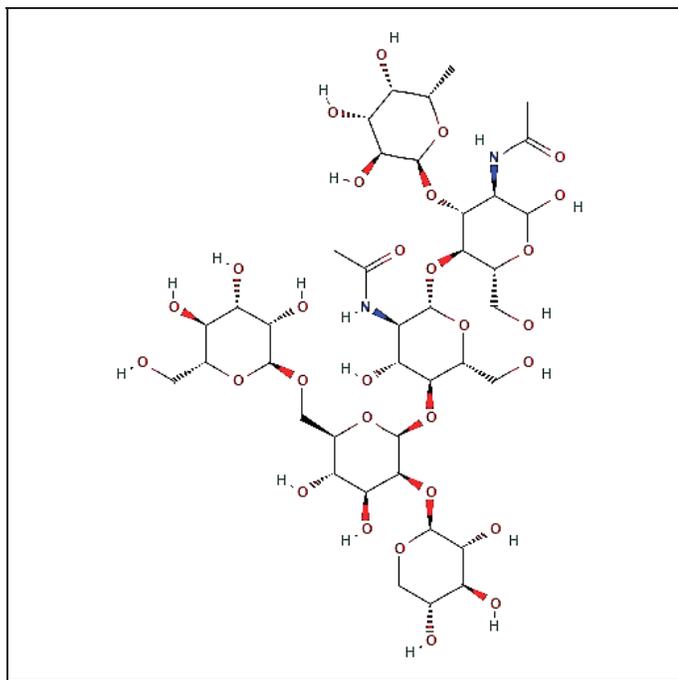


Fig. 2. 2D chemical formula of bromelain. 3D conformer generation is disallowed since too many atoms, and too flexible. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 44263865, Carbohydrate moiety of bromelain.

based tooth whitening products can replace low-concentration peroxide gels in the home-market.

### Non-peroxide formula

Due to the new legislation on peroxide content in cosmetic products, 'peroxide-free' teeth whitening has experienced a remarkable growth over the last few years. Products sold in the European Union do not release more than 0.1% hydrogen peroxide, in compliance with the European Union Cosmetics Directive.

Although European Union products with less than 0.1% hydrogen peroxide are considered safe and environmentally friendly, this amount is way too small to visibly whiten teeth albeit with mild or no side effects. The newer products like cysteine proteases and sodium dithionite as discussed in subsequent sections have varying degrees of laboratory success and are considered safer. Both agents need clinical studies to prove their efficacy.

*Sodium bicarbonate and sodium chloride* - As a mild abrasive, sodium bicarbonate helps remove superficial stains from teeth. Also, it has a cleansing action by loosening food debris, neutralizes the production of acid in the mouth, and prevents bacteria overgrowth. However, if not used in the correct proportion, especially with plain baking soda, it can eventually erode the enamel and lead to tooth decay.<sup>15</sup> In terms of efficacy, it is important to understand that these products cannot remove deep discoloration inside the tooth, like peroxide does.<sup>15</sup>

Unrefined sea salt, or sodium chloride (NaCl), has historically been used as a brushing agent for individuals with limited access to modern dental care. However, a recent study<sup>15</sup> noticed that adding sea salt to traditional toothpaste abrasives can cause excessive wear on dentin without providing any addi-

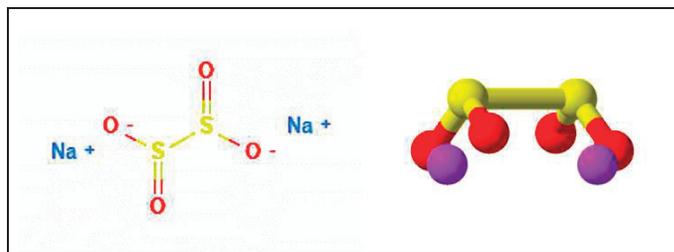


Fig. 3. 2D and 3D chemical formula of papain. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for papain.

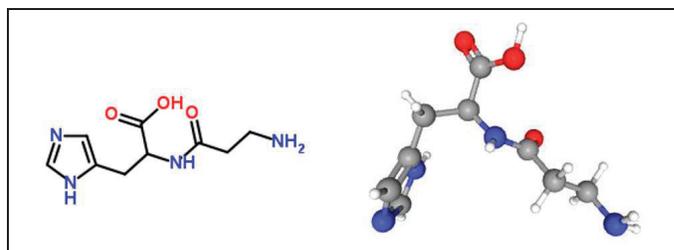


Fig. 4. 2D and 3D chemical formula of ficin. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 71586822, Carnosine hydrochloride.

tional dental benefits. Another study<sup>16</sup> examined a non-peroxide at-home bleaching product based on sodium chloride in laboratory tests and found that it had detrimental effects on dental enamel. While not directly related to natural bleaching, a study<sup>17</sup> using a sodium chloride saturated solution<sup>c</sup> to treat silver diamine staining found it to be ineffective in reducing stains. The cleansing mechanism may be like that of sodium bicarbonate, focusing on abrasive action. Both sodium bicarbonate and sodium chloride are not being marketed as bleaching agents.

*Cysteine proteases (CP)* - An alternative to reduce or solve the enamel etching and sensitivity problem is the use of natural compounds such as cysteine proteases (CP). CP are commonly encountered in fruits including pineapple (bromelain), papaya (papain) and fig (ficin). The main characteristic of this type of enzyme is the capability to improve the hydrogen peroxide-dependent oxidation-reduction and reduce the toxicity of electron donors' compounds, such as peroxides and some aromatic compounds.

Bromelain (Fig. 2), papain (Fig. 3), and ficin (Fig. 4) are widely used in everyday life because of their medicinal properties, such as anti-inflammatory, antithrombotic, fibrinolytic activity, anticancer activity, and immunomodulatory effects. Due to their enzymatic feature, these enzymes could be considered as an active agent with a whitening effect. All three have recently been tested as whitening gels in the laboratory and as dentifrices in clinical and laboratory studies. Discovered in 1873, the first CP to be isolated and characterized was papain, obtained from *Carica papaya*, and is commonly used as an ingredient in meat tenderizers. CP, also known as thiol proteases, are hydrolase enzymes that degrade proteins. These proteases share a common catalytic mechanism that involves a nucleophilic cysteine thiol in a catalytic triad or dyad. The proportion of protease tends to be higher when the fruit is unripe.

CP chemically breaks down proteins by cleaving peptide

bonds and thus, may represent a possible alternative for whitening teeth. The cleavage of peptide bonds changes the light reflection, which leads to a higher L value and lighter appearance. This is an interesting whitening approach since it differs from existing whitening ingredients and the primary mechanism of action is not oxidation.

A novel tooth whitening formulation containing papain, ficin, or bromelain was tested on its bleaching ability, the effect on enamel surface and cytotoxicity.<sup>12</sup> The whitening gels were prepared and applied on the bovine dental discs three times per day once a week for 4 weeks and color measurements taken. The study found that non-peroxide bromelain and ficin gels were effective in dental bleaching, being like the carbamide peroxide-based gel. Another paper<sup>4</sup> relating to the use of natural compounds as dental bleaching agents did not find CP to be more effective than the traditional techniques.

Enamel Knoop microhardness and roughness were evaluated. Carbamide peroxide gel was found<sup>12</sup> to increase enamel roughness and decrease enamel hardness. The use of bromelain and ficin-based tooth-whitening gels resulted in less enamel damage than carbamide peroxide. The authors concluded that tooth bleaching gels containing bromelain, papain, or ficin have substantial clinical potential as active ingredients of peroxide-free whitening products. Another paper<sup>18</sup> in this issue also confirmed that rubbing action with bromelain was effective though not as much as hydrogen peroxide.

*CP safety* - Given their natural origin, these types of products have a certain guarantee on their non-toxic biological behavior, resulting in little or no harmful effects. For example, ficin is naturally widely distributed among living organisms. Due to their availability, CP isolated from plants has a special place in pharmacy and medicine. From pharmaceutical and preclinical studies, bromelain is safe enough to be recommended as an orally given drug for complementary tumor therapy.<sup>19</sup> Papain is also widely used in medical and paramedical practice. No mentioning of ficin was found in the literature for its use as therapeutic agent. Although the toxicity of the above-mentioned enzymes is rather low, exposure to the dust or aerosols of their solutions is still harmful.<sup>20</sup>

The study<sup>12</sup> used the WST-1 assay to evaluate the cell viability of mouse fibroblast cells (L929) and conclude that the experimental CP whitening gels did not affect cell viability. Thus, the development of new whitening agents based on natural products could provide similar esthetic results and minor side effects.

*Novel reductive sodium dithionite (sodium hydrosulfite)* - Dithionites (hydrosulfite) belongs to a group of reducing bleaching agents which include sulfur dioxide, sulfurous acid, bisulfites, sulfites, sodium sulfoxylate formaldehyde, and sodium borohydride. These materials are used mainly in pulp and textile bleaching. The bleaching action is thought to occur by reduction of a chromophoric carbonyl group. For example, sodium dithionite (Fig. 5) is a powerful reducing agent commonly used in dyeing processes, water treatment, gas purification, photography, and other industries. It has not been previously used in dental whitening products. Sodium dithionite is highly reactive in the presence of water, quickly decomposing to thiosulfates and bisulfates when exposed. Dental bleaching studies using dithionites are non-existent.

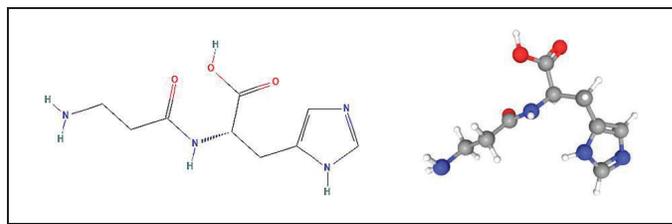


Fig. 5. 2D and 3D chemical formula of sodium dithionite. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 24489, Sodium Dithionite.

As discussed in the section of peroxides, low acidic pH can cause enamel damage and tooth sensitivity. Thus, a reductive composition, suitable for the dental industry, which utilizes a salt of dithionite may be provided to create an alkaline tooth whitening compound.<sup>3</sup> Either sodium or potassium dithionite may be used with marked effectiveness. A simple buffered solution of dithionite and water may whiten teeth in an alkaline environment that lessens damage to tooth enamel. When placed in a solution with buffered water, the resultant composition will maintain an alkaline pH and provide effective reduction of the stains found on tooth enamel.

Dithionite becomes most stable at a pH of or over 8.5, but the preferred pH range of the solution would be between 9.0-10.0. A buffering agent may be added to maintain the pH of the resultant solution. Buffers such as sulfite, pyrosulfite, phosphate, and borax salts may be combined with a pH modifier, such as sodium or potassium hydroxide, to build a pH buffer especially above pH 8. Other pH buffering anions not listed above could also be used.

The reducing group of this bleaching agent works exactly opposite to the common bleaching agent of hydrogen peroxide and carbamide peroxide. Hydrogen peroxide is a weak acid with strong oxidizing properties. The mechanism of bleaching is to steal the electrons that hold the atoms together, causing the staining molecules to fall apart. The result is that a substrate is whitened since color-producing substances are solubilized and the substrate's light-absorbing properties are altered.

Reduction reactions could also provide whitening effects. Reduction is the opposite reaction of oxidation in that electrons are added to a molecule and is often seen in conjunction with oxidation reactions (together being called redox reactions). Reduction of the chromophores of intrinsic and extrinsic enamel stains also renders them white. However, powerful reducing agents present an interesting challenge with respect to reactivity and compatibility when formulating various compositions. What usually occurs is an immediate reaction that results in a permanently reduced ingredient.

The salts of dithionite are stable in alkaline pH and become increasingly unstable as the pH drops below pH 7. Therefore, a true alkaline tooth whitening system that lacks the ability to etch tooth enamel can be manufactured utilizing the dithionite anion as an active, reductive, agent.

To evaluate these solutions, a collection of extracted teeth was examined and selected for dark color stains ranging from light yellow to brown.<sup>3</sup> These teeth were then categorized and scored for color by comparing them to a classical VITA shade guide. Half of the teeth were then placed in a fresh solution of 15% sodium dithionite in water with unadjusted pH. The second half was placed in the solution adjusted to pH > 10. All

Table 2. Summary of toxicology study for sodium dithionite.

	Animal and cell model	Results
Skin irritation tests	Japanese large-eared white rabbit (4 females, 2.24~2.31 kg)	No irritation.
Acute oral toxicity test	10 ICR mice, half male, and half female. (20~22 g)	No mortality & non-toxic
Skin sensitization test	Dunkin Hartley guinea pigs (30 males, 264~295 g)	No skin sensitization seen
In vitro chromosome aberration test	Chinese hamster lung (CHL) cells	Negative.

teeth became whiter after remaining in solution overnight, especially light yellow to yellow stained teeth. The brown teeth showed less of an effect but nevertheless had whitened significantly. Therefore, the results demonstrated that dithionite whitens teeth. These results have been confirmed by other laboratory results<sup>21</sup> that will be discussed in another paper in this issue.

### Human health

The manufacturer (CAO Group<sup>d</sup>) of a commercial product containing 6% sodium dithionite has undertaken detailed toxicological test results and the results are encouraging.<sup>22,23</sup> The results are summarized in Table 2 and indicated the following:

1. Results of multiple skin irritation tests: non-irritating.
2. Acute oral toxicity test results: practically no toxicity.
3. Skin sensitization test results: no skin sensitization seen.
4. Results of in vitro chromosome aberration test: negative.

These results agree with safety data fact sheets that no occupational exposure limits have been established and the wide use of sodium dithionite is in part attributed to its low toxicity.<sup>22</sup> However, sodium dithionite does possess properties indicating a hazard to human health in large scale industries such as dyeing processes, water treatment, gas purification and photography industries. Potential hazards include sulfite asthma and irritant effects on the eye. There is only limited information on the exposure of workers in manufacturing and down-stream industries, and consumers may be exposed through household products (detergents, stain removers).

Sodium dithionite, upon contact with moisture, is oxidized to hydrogen sulfite, sulfite and hydrogen sulfate, and under strongly acidic conditions it may liberate sulfur dioxide. Under anaerobic conditions (such as in the lower gastrointestinal tract), hydrogen sulfite and thiosulfate may be formed. Hydrogen sulfite can be absorbed after ingestion. It is efficiently metabolized, and the major part rapidly excreted as sulfate into the urine.

There were no acute dermal and no valid acute inhalation studies available. Sodium dithionite was slightly irritating to the skin and strongly irritating to the eyes of rabbits.<sup>23</sup> Under acidic conditions, sodium dithionite may liberate sulfur dioxide, which is known to induce respiratory irritation in humans. There was no animal data available regarding sensitization. In humans, allergic dermatitis from exposure to sulfites is rare and, consequently, sodium dithionite is not considered to possess a significant skin sensitization potential.

Sodium dithionite was not mutagenic in standard bacterial tests with and without metabolic activation (OECD TG 471, 472).<sup>23</sup> No experimental data was available on the potential of sodium dithionite to induce chromosomal aberrations in vitro. These results were confirmed by the manufacturer's own tests.

No experimental data was available on the carcinogenic potential of sodium dithionite. In 1992, IARC concluded that degradation products of dithionite, i.e. sulfur dioxide, sulfites, hydrogen sulfites and metabisulfites "are not classifiable as to their carcinogenicity to humans (Group 3)".<sup>24</sup> Sodium dithionite has not been tested for its effects on reproduction and development. Based on its physicochemical behavior and its rapid conversion in the body, it is not expected that the intact molecule reaches the reproductive organs or has any direct effect on reproduction and development. Data relating to the degradation products of sodium dithionite also does not indicate any adverse effects.

A formal study is being carried out at the University of Washington and at a foreign university and the results can confirm or disprove the hypothesis that neutral pH agent has the same bleaching efficacy but more importantly, no sensitivity when compared to peroxide-based agent.

### Conclusion

The efficiency of peroxide whitening systems is confirmed in the literature, but the bleaching procedure comes with a common adverse clinical event which is tooth sensitivity. As far as safety is concerned, non-peroxide-based agents will typically not cause any tooth sensitivity or gum irritation, so they are ideal for people with sensitive teeth or for those who are afraid of using products containing peroxide. Although the newer products seem to possess varying degrees of in vitro success, they will need clinical studies to prove their safety efficacy.

- a. Beaming White, LLC, Vancouver, WA, USA.
- b. Sylphar, Deurle, Belgium.
- c. Morton Salt, Chicago, IL, USA.
- d. CAO Group, West Jordan, UT, USA.

*Disclosure statement:* The authors declared no conflict of interest. Dr. Cao is President and founder, CAO Group, Inc., West Jordan, Utah, USA.

Dr. Chan is Professor and former Chair, Department of Restorative Dentistry, Washington Dental Service Endowed Chair in Dentistry, Department of Restorative Dentistry, University of Washington, Seattle, Washington, USA. Dr. Cao is President and founder, CAO Group, Inc., West Jordan, Utah, USA.

### References

1. Matis BA, Cochran MA, Eckert G. Review of the effectiveness of various tooth whitening systems. *Oper Dent* 2009;34:230-235.
2. Rezende M, Ferri L, Kossatz S, Loguercio AD, Reis A. Combined bleaching technique using low and high hydrogen peroxide in-office bleaching gel. *Oper Dent* 2016;41:388-396.
3. SD J. US Patent Pub Number 20230210732. 2023.
4. Muller-Heupt LK W-IN, Kaya S, Schumann S, Steiger, M, Bjelopavlovic M, Deschner, J, Al-Newas B, Lehmann KM. Effectiveness and safety of over-the-counter tooth-whitening agents compared to hydrogen peroxide in vitro. *Int J Mol Sci* 2023;24:1956-1968.
5. Patil PA, Ankola AA, Hebbal MI, Patil AC. Comparison of effectiveness of abrasive and enzymatic action of whitening toothpastes in removal of extrinsic stains - A clinical trial. *Int J Dent Hyg* 2015;13:25-29.
6. Majeed A GS, Moola MH, Oberholzer TG. Effect of four over-the-counter tooth-whitening products on enamel microhardness. *SADJ* 2011;66:412-415.

7. Paula EA LA, Fernandes D, Kossatz S, Reis A. Perioperative use of an anti-inflammatory drug on tooth sensitivity caused by in-office bleaching: A randomized, triple-blind clinical trial. *Clin Oral Investig* 2013;17:2091-2097.
8. Rezende M, Bonafe E, Vochikovski L, Farago PV, Loguercio AD, Reis A, Kossatz S. Pre- and postoperative dexamethasone does not reduce bleaching-induced tooth sensitivity: A randomized, triple-masked clinical trial. *J Am Dent Assoc* 2016;147:41-49.
9. Heller D, Skriber J, Lin LM. Effect of intracoronal bleaching on external cervical root resorption. *J Endod* 1992;4:145-8.
10. Barakah R, Alwakeel R. Non-vital endo treated tooth bleaching with sodium perborate. *Curr Health Sci J* 2019; 3:329-332.
11. Qin JY, Zeng L, Min W, Tan LC, Lv RZ, Chen YW. A bio-safety tooth-whitening composite gels with novel phthalimide peroxy caproic acid. *Compos Commun* 2019;13:107-11.
12. Ribeiro JS, Barbosa AS, Cuevas-Suárez, CE, da Silva AF, Piva E, Lund RG. Novel in-office peroxide-free tooth-whitening gels: Bleaching effectiveness, enamel surface alterations, and cell viability. *Sci Rep* 2020;10:10016.
13. Alsarani MM, Khan AA, Bautista LSJ, Alsunbul H, Matinlinna JP. Effect of peroxide-free and peroxide-based in-office bleaching on the surface and mechanical properties of CAD/CAM esthetic restorative materials. *Eur J Oral Sci* 2024;132:e13016.
14. Bizhang M, Domin J, Danesh G, Zimmer S. Effectiveness of a new non-hydrogen peroxide bleaching agent after single use - A double-blind placebo-controlled short-term study. *J Appl Oral Sci* 2017;25:575-584.
15. Ciancio, SG. Baking soda dentifrices and oral health *J Am Dent Assoc* 2017;148:S1 - S3.
16. Blend H, Moritz T, M Attin T, Wegehaupt, FJ. Dentin abrasivity and cleaning efficacy of novel/alternative toothpastes. *Oral Health & Preventive Dentistry* 2020;18:713-718
17. Trongtham RC, Lee, DK, DC Chan. Effectiveness of potassium iodide in preventing silver diamine fluoride staining. *J Dent Res* 2017;96(Spec Iss A):#1861.
18. Lee S, Mercado D, Feceu C, Davalos C, Rahgozar N, Oyoyo U, Kwon SR. Efficacy of natural teeth whitening remedies: Pineapple and banana. *Am J Dent* 2025;38 Sp Is A:16A-19A.
19. Pezzani R, Jiménez-García M, Capó X, Sönmez Gürer E, Sharopov F, Rachel TYL, Ntieche Woutouoba D, Rescigno A, Peddio S, Zucca P, Tsouh Fokou PV, Martorell M, Gulsunoglu-Konuskan Z, Ydyrys A, Bekzat T, Gulmira T, Hano C, Sharifi-Rad J, Calina D. Anticancer properties of bromelain: State-of-the-art and recent trends. *Front Oncol* 2023;12:1068778.
20. Babalola BA, Akinwande AI, Otunba AA, Adebami GE, Babalola O, Nwufe C. Therapeutic benefits of Carica papaya: A review on its pharmacological activities and characterization of papain, *Arabian Journal of Chemistry* 2024 17: -11.
21. Newman J, Youn T, Suk M, Dong C, Lu J, Sample M, Yang I, Chan DCN. Assessments of a novel bleaching agent containing sodium dithionite: A laboratory study *Am J Dent* 2025;38 Sp Is A:38A-43A
22. Cao Group I. Dithionite White Safety Data Sheet. 2022.
23. Chinese Academy of surveillance and testing Co.Ltd. Dithionite White. 2022(TJJT001720220002).
24. IARC, 1992: *Occupational Exposures to Mists and Vapours from Strong Inorganic Acids and Other Industrial Chemicals. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Vol. 54, 131-188, International Agency for Research on Cancer.