EGAS MONIZ SCHOOL of HEALTH & SCIENCE | INSTITUTO UNIVERSITÁRIO EGAS MONIZ

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MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

THE EFFECTIVENESS OF NON-INVASIVE WHITENING AGENTS IN ADULTS: A SYSTEMATIC REVIEW

Trabalho submetido por
Louis Marie Vianney Le Cheviller
para a obtenção do grau de Mestre em Medicina Dentária

julho de 2024

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Trabalho orientado por
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julho de 2024

AGRADECIMENTOS

Je tiens à remercier toutes les personnes qui m’ont accompagné lors de cette aventure.

RESUMO

Introdução: o branqueamento dentário é um tratamento estético cada vez mais popular, motivado pela crescente importância de um sorriso esteticamente agradável nas relações sociais. Os agentes branqueadores mais comummente utilizados são o peróxido de hidrogénio e o peróxido de carbamida. Esta revisão teve como **objetivo** sintetizar analiticamente a bibliografia científica relativa aos branqueamentos supervisionados pelo dentista, em termos de eficácia, durabilidade e impacto na segurança. Além disso, visou também identificar potenciais efeitos secundários e discutir as implicações clínicas para os profissionais de saúde oral. **Metodologia**: os dados foram recolhidos a partir de múltiplas bases de dados, seguindo as diretrizes PRISMA, garantindo uma pesquisa e análise abrangente e sistemática. A revisão incluiu a seleção de estudos relevantes, a extração de dados e a análise de risco de viés, para qual utilizamos três ferramentas: ROBIN-I, RoB 2, e Quin tool. **Resultados:** Dos 49 estudos selecionados, 42 focam na melhoria da cor, 40 no peróxido de hidrogénio, 19 no peróxido de carbamida, 20 na sensibilidade dentária, 12 nas fontes de luz, 5 em géis experimentais, 3 em tratamentos combinados, 3 em géis dessensibilizantes, 6 nos valores minerais e 4 na oximetria e composição bacteriana. Constatou-se que os agentes branqueadores utilizados nos artigos seleccionados tinham efeitos muito variáveis em função da concentração e da duração da aplicação. Devido à grande variabilidade de combinações de tempo/concentração nas aplicações, não foi possivel realizar uma análise quantitativa da eficácia/segurança das diferentes abordagens. **Discussão/Conclusão:** As recomendações para futuros estudos primários incluem a otimização e uniformização dos protocolos de branqueamento e a exploração de combinações inovadoras de concentrações e tempos de aplicação. A utilização de tecnologias como a inteligência artificial para analisar preferências e respostas dos pacientes também pode contribuir para tratamentos mais personalizados. São necessárias investigações adicionais para compreender os mecanismos biológicos que sustentam a reação do esmalte aos agentes branqueadores, potencialmente levando ao desenvolvimento de produtos mais seguros e eficazes.

Palavras-chave: Branqueamento dentário não invasivo, Branqueamento dentário à base de peróxido, Guia de cores dentárias

ABSTRACT

Introduction: Tooth whitening is an increasingly popular aesthetic treatment, driven by the growing importance of an aesthetically pleasing smile in social interactions. The most commonly used bleaching agents are hydrogen peroxide and carbamide peroxide. **The Objectives** are to analytically synthesize the scientific literature on dentist-supervised bleaching treatments in terms of efficacy, durability, and safety impact. Additionally, it sought to identify potential side effects and discuss the clinical implications for oral health professionals. **Methodology**: Data were collected from multiple databases following PRISMA guidelines, ensuring a comprehensive and systematic search and analysis. The review included the selection of relevant studies, data extraction, and risk of bias analysis, for which we used three tools: ROBIN-I, RoB 2, and QUIN tool. **Results**: Out of 49 selected studies, 42 focused on colour change, 40 on hydrogen peroxide, 19 on carbamide peroxide, 20 on tooth sensitivity, 12 on light sources, 5 on experimental gels, 3 on combined treatments, 3 on desensitizing gels, 6 on mineral values, and 4 on oximetry and bacterial composition. It was found that the bleaching agents used in the selected articles had highly variable effects depending on concentration and duration of application. Due to the high variability in time/concentration combinations in the applications, it was not possible to perform a quantitative analysis of the efficacy/safety of the different approaches.

Discussion/Conclusion: Recommendations for future primary studies include the optimization and standardization of bleaching protocols and the exploration of innovative combinations of concentrations and application times. The use of technologies such as artificial intelligence to analyze patient preferences and responses could also contribute to more personalized treatments. Further investigations are needed to understand the biological mechanisms underlying enamel reactions to bleaching agents, potentially leading to the development of safer and more effective products.

Keywords: Non-invasive Tooth whitening, Peroxide-based Tooth whitening, Dental shade guide

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LIST OF ABBREVIATIONS

B.C.E - Before common era

C - Combined

CP - Carbamide peroxide

G - Group

HB - Home bleaching

HP - Hydrogen peroxide

IO - In-office

PBM - Photobiomodulation

PUBMED - Public Medline

PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SaO2 - Oxygen saturation

SD - Standard deviation

TiO2 - Titanium dioxide

VL - Violet led

I. INTRODUCTION

Individual smiles represent one of the most important keys and skills of interpersonal interactive communication, considering the weight of a beautiful and aesthetically acceptable smile in interpersonal and social relationships. Tooth bleaching is one of the most sought-after treatments for improving facial attractiveness. Recent studies have demonstrated the effectiveness of tooth bleaching in correcting tooth colour and promoting greater social acceptance by fostering a positive psychosocial effect on patients (Maran *et al*., 2020).

Consequently, there has been a growing interest in aesthetic treatment through tooth bleaching in dentistry. It is regarded as a relatively straightforward, conservative and non-invasive technique that allows the colour of teeth to be altered, thereby improving the aesthetic colour of teeth. Some factors can affect permanent teeth' colour and aesthetic appearance, including pigment components and dyes in our everyday diet (such as coffee, tea, tomatoes, chocolate, and others). Adverse effects of certain medicinal substances, such as tetracycline, can also infiltrate the surface of the teeth, resulting in the persistence of pigmentations within the porous structure of the enamel. Furthermore, the toxins present in tobacco smoke also contribute to tooth discolouration. As a result of the accumulation of stains and the gradual erosion of enamel, teeth tend to become discoloured with age, exposing dentin to a colour closer to yellow (Benahmed *et al*., 2022).

In light of this concern regarding tooth colour change, several non-invasive tooth bleaching techniques have been developed for use in the dental office or at home under the supervision of a dentist. However, the effectiveness and long-term impact on oral health of these techniques remain crucial questions to explore (Kihn et *al*., 2019). The most used whitening agents are hydrogen peroxide and carbamide peroxide, which can be used in different concentrations (Faus-Matoses *et al*., 2019).

Thus, the effectiveness of tooth bleaching on vital teeth depends on many factors, such as the concentration or pH of the agent, chemical additives and different application protocols, and exposure times, frequency of use (Alkahtani *et al*., 2020).

The objective of this review was to collate evidence to assist oral health professionals in determining the most appropriate treatment strategy for tooth bleaching. In addition, the review aimed to provide sound scientific data to inform clinical decisions. Furthermore, the review sought to promote a more informed and personalised approach

to tooth bleaching, considering individual patient needs while minimising potential risks to oral health.

1.1 History of tooth bleaching

In recent years, there has been a notable increase in the prevalence of aesthetic dentistry, reflecting a growing interest among patients in enhancing their smiles. In aesthetic dentistry, the pursuit of whiter teeth and a more attractive smile is pervasive. Some studies on tooth colour and bleaching have demonstrated that whitened teeth are perceived as more favourable regarding personality traits, resulting in a more positive psychosocial effect on patients. The relevance of appearance and self-esteem has resulted in a growing demand for aesthetic procedures such as teeth bleaching, which is the most sought-after by patients in search of an attractive smile (Maran *et al*., 2020).

The practice of tooth bleaching can be traced back to antiquity. Rudimentary practices often characterised tooth bleaching. It is estimated that around 4000 years B.C.E., the Egyptians applied a paste containing a mixture of pumice powder and wine vinegar to whiten their teeth. Similarly, the Romans applied urine due to the bleaching effect of the ammonia. Nevertheless, these methods were primarily concerned with maintaining oral health rather than achieving aesthetic effects.

In the nineteenth century, the use of dental crowns to disguise teeth with discolouration was a common practice. However, this procedure was considered too invasive and would compromise the tooth structure (Alkahtani et *al*., 2020).

The beginnings of bleaching non-vital teeth date back to 1848 with calcium chloride. In 1864, Truman first described tooth bleaching. He introduced a more effective technique for bleaching, applying chlorine from a solution of calcium hydrochloride and acetic acid. At the end of the 19th century, several other bleaching agents were successfully used on non-vital teeth, including potassium cyanide, oxalic acid, sulphurous acid, aluminium chloride, sodium hypophosphate, mixtures containing 25% hydrogen peroxide in 75% ether (*pyrozone*), or even hydrogen dioxide and sodium peroxide by Kirk in 1893. All these substances are considered direct or indirect oxidisers, acting on the organic portion of the tooth, except for sulphuric acid. Oxidation involves the transfer of electrons from a substance (the reductant) to an oxidant. The oxidiser gains electrons during this process, while the reducer loses them. This transfer of electrons can result in

the degradation, transformation or decomposition of organic compounds (Alqahtani, 2014).

Some authors proposed the use of lights with different characteristics, such as Rosenthal in 1911 or Prinz in 1924. Other authors explored the use of heat, such as Brininstool in 1913, Merrell in 1954, Brown and Stewart in 1965, Caldwell in 1967, Hodosh in 1970, Lemieux & Todd in 1981 and Leendert in 1984. Some studied the use of electric currents, such as Kirk in 1890 and Westlake in 1895, to speed up the bleaching process by activating the bleaching agent (Attin *et al*., 2003).

The innovative at-home bleaching dates to the 1960s, when orthodontist Bill Klusmier recommended using an oral antiseptic called Gly-oxide during the orthodontic retention phase. It contained 10% carbamide peroxide and was applied to the whitening tray overnight to facilitate tissue healing. A significant tissue improvement and an additional benefit from bleaching the teeth were observed. Subsequently, Proxigel ® (a mixture of 10% carbamide peroxide, water, glycerin and carbopol) was marketed and replaced with Gly-Oxide ® for orthodontic patients. Later, the University of North Carolina clinically approved the clinical efficacy of Proxigel.

In-depth research utilising 10% carbamide peroxide in customised drips led to the inaugural publication in 1989 entitled "Nightguard Vital Bleaching" by Haywood V.B. and Heymann H.O. (Haywood, 1992). This technique represented a significant departure from previous approaches, paving the way for the introduction of at-home bleaching, which made the procedure accessible to a broader and more diverse population at a reduced cost.

Since the introduction of Nightguard Vital Home Whitening, the formula of the products has undergone continuous improvement. In response to concerns raised by some professionals about the potential erosion of enamel caused by the whitening gel, various forms of fluoride have been added to the original composition. One of the principal complaints from patients was tooth sensitivity, which led to the inclusion of desensitising agents such as potassium nitrate, sodium fluoride and amorphous calcium phosphate. Over-the-counter whitening agents were first introduced in the United States in the 1990s, containing lower concentrations of hydrogen peroxide or carbamide peroxide and sold directly to consumers for at-home use (Alqahtani, 2014).

Currently, two types of professional tooth bleaching are used for vital teeth. In-office tooth bleaching uses a concentration of hydrogen peroxide of up to 6% in Europe, while concentrations can reach up to 40% in other countries. At-home tooth bleaching

typically uses a 10-16% concentration of carbamide peroxide in Europe, whereas higher concentrations are used in other parts of the world (Alqahtani, 2020).

1.2 Physiological basis of colour

Colour results from various interactions of light, such as absorption, dispersion, refraction and transmission, on the surface of objects. The interpretation of these phenomena by the human visual system can be variable. The human eye only perceives these visual manifestations within the visible light spectrum, where three main colour ranges are observed: blue, green and red (Corcodel *et al*., 2010). In dentistry, colour capture systems often refer to Munsell's three-dimensional character of colour, as shown in Figure 1 (Carey, 2014). Colours are defined by their coordinates in space, as we can see in the table I :

Table I - Summary of the characteric colours and their coordinates in space (Carey, 2014).

Characteristic	**Description**
Value	Crucial for identifying the amount of light reflected by the tooth, influenced by factors such as the thickness of the enamel, its degree of mineralisation, the state of the surface, and the incidence of the light beam
Saturation	Represents the amount of pigment in a colour
Hue	Also called chromaticity, corresponds to the wavelength reflected by the object. Although less decisive, tonality is still an influential factor in the aesthetic quality of the restoration.

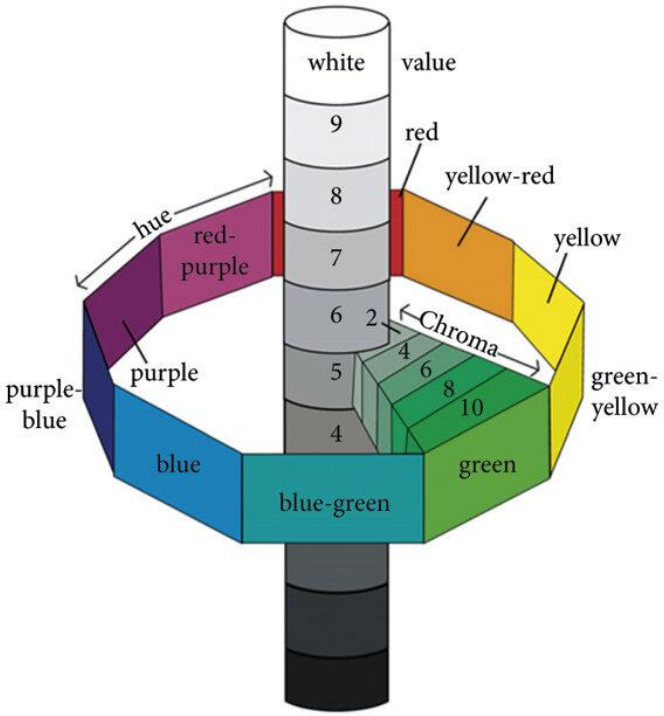


Figure. 1- Munsell colour system (adapted from redrawn, 1994 Encyclopédie Britannica. Inc.)

However, this three-component system does not consider other parameters that influence the perception of colour (Carey, 2014). We can integrate three more parameters into the colourimetric model as we can see in the table II:

Table II - Summary of supplementary colourimetric parameters (Carey, 2014)

Characteristic	**Description**
Fluorescence	induces a re-emission of visible light by the tooth exposed to non-visible ultraviolet radiation, with bluish fluorescence associated with dentin.
Translucency	Also called transparency, it measures the ability of light to pass through the material or tooth.
Opalescence	reflects the enamel's ability to differentiate wavelengths, generating bluish-white reflections, especially on the free edge of the tooth.

The assessment of tooth colour is generally subjective, depending on the operator and external factors such as the light source and the angle of observation. This phenomenon is called metamerism (Corcodel *et al*., 2010). A natural tooth considered perfect does not show whiteness or homogeneity but rather a mixture of colours around a yellowish-white base. The stratified and inhomogeneous tooth structure influences optical phenomena related to the arrangement of mineral crystals. Dentin plays a predominant role in the natural colour of teeth, especially as it ages due to hypermineralisation. The state of the surface, particularly its micro-geography, also impacts visual perception, with younger, rougher teeth reflecting more light, generally due to a higher value. Finally, any mechanical, chemical, or biological alteration of the tissue changes colour over time (Chouraqui, 2022).

1.3 Origin of tooth-colouring

A tooth is dyschromic when its colour deviates from its original colour. Dyschromia result from the formation of deposits of chromogenic chemical compounds. These dyschromias have various causes (Table III), often resulting from personal or behavioural factors. The nature of dyschromia varies according to its origin, location (partial, affecting one or several teeth, or total), appearance, composition, intensity and adherence to the tooth surface (Dahl & Pallesen, 2003).

1.3.1 Two categories of dyschromia

- Extrinsic dyschromia, also known as acquired dyschromia, is a change in tooth colouration that occurs on the tooth's exterior or on the restorative material following tooth eruption. This occurs when both the enamel and dentin are fully formed and exposed to the oral cavity. In some cases, extrinsic staining can be removed mechanically through dental prophylaxis procedures, which involve using a scaler and abrasive agents. Extrinsic dyschromia is more readily treatable than intrinsic dyschromia, as it is more superficial (Clifton, 2011).

- Intrinsic dyschromia, also known as congenital or systemic, is a condition characterised by the presence of discoloured teeth. Intrinsic staining results from the incorporation of chromogenic compounds into the enamel and dentin tissues during formation or shortly after eruption. This staining, which reflects the internal colour of the tooth, can originate from early exposure to tetracyclines, high fluoride levels, genetics, developmental or

aging disorders, pulp necrosis and iatrogenesis (Clifton, 2011). It is of the utmost importance to ascertain the source of the dyschromia to select the most efficacious bleaching treatment and assess the prognosis. In the case of intrinsic dyschromia, more complex bleaching procedures are required in order to achieve successful removal. It is also the case that recent pigmentations are more easily removed than those that have been present for several years (Carey, 2014).

Table III - Summary of tooth discolourations, their classification, and causes (Duc, 2012)

Classification	***Etiological factors***	***Causes***	***Colours***
DIRECT	Dental deposits	Materia alba	White
		Plaque/biofilm	Yellow
		Tartarus	White, yellow, brown
	Chromogenic microorganisms	Chromogenic fungi	Green
		Chromogenic batteries	Brown, black, orange, blue, green
	Eating habits	Chromogenic foods, acids, coffee, red wine and green tea, colour due to tannin	Brown, black
		Chlorophyll-rich diet	Green
	Various substances	Smoking/chewing tobacco	Brown, black
		Areca nut	Brown/red
		Chewing khat leaves	Yellow/brown
		Chewing kola nuts	Black
INDIRECT	Local use of medicines	Cationic antiseptic (chlorhexidine)	Yellow, brown
		Phenol/essential oils	Yellow
		Copper salt mouthwash	Green
		Potassium permanganate	Purple to black
		Silver nitrate	Grey, black

		Stannous fluoride	Yellow, brown
	Administration of oral medication	Oral iron solution	Black
		Amoxicillin and clavulanic acid	Yellow/brown
		Doxycycline	Yellow/brown
		Linezolid	Brown
	Professional activity and environmental factors	Iron, silver powder and manganese	Black
		Mercury powder and lead	Green/blue
		Copper and nickel	Green
		Chromic acid	Orange

1.4 Types of non-invasive tooth bleaching

Tooth bleaching is a procedure frequently performed by dental professionals and frequently requested by patients. The treatment is non-invasive, reliable, and the cost-benefit-safety ratio is highly favourable. The active agent employed is hydrogen peroxide and carbamide peroxide (which is converted into hydrogen peroxide and urea), which diffuses through the tooth, passing between the interprismatic spaces, and then interacts with the organic chromophores. This process results in a visible colour change (Carey, 2014). The lack of improvement after six weeks of treatment indicates that the therapy has reached its limits, regardless of the whitening agent or its concentration. It is unlikely that substantially better results will be achieved. Nevertheless, it is important to acknowledge that tooth bleaching is a highly controversial topic, with numerous contradictions. For instance, Sulieman (2008) posits that:

- In underage patients, due to the immaturity of the tissues
- Pregnant or breastfeeding women
- In patients allergic to the product
- In patients with fractures or fissures
- On decayed or severely damaged teeth
- On teeth with untreated dentin hypersensitivity
- In patients with certain general conditions such as erythroblastosis fetalis, congenital porphyria, haemolytic jaundice
- In dyschromia caused by metallic salts that have diffused into the dental structures

There are two types of bleaching: internal bleaching for non-vital teeth and external bleaching for vital teeth.

For external tooth bleaching, there are three different techniques (Figure 2):

In-office bleaching has the advantage of not depending on the patient and providing faster aesthetic results.

At-home bleaching, which allows the patient to self-administer the product. This results in fewer unwanted effects and lower costs, as less time is spent in the dentist's chair.

The combined technique includes in-office sessions followed by regular at-home applications.

1.5 At-home bleaching

This technique involves applying a whitening gel with a low concentration of peroxides in a customised tray adapted to the patient's teeth. This procedure is carried out under the supervision of a dentist, following a specific protocol. Generally, 10% to 16% carbamide peroxide is used. In the at-home system, it is also possible to use hydrogen peroxide in concentrations of 3% to 14% (concentrations higher than 6% are only used outside the European Union), with a shorter application time (Fioresta *et al.*, 2023).

The at-home bleaching gives patients flexibility, allowing them to continue treatment until they get the desired results, with no additional costs for consultations, just the necessary materials. This bleaching can also be applied during the day, at night or both (Haywood, 1998).

The colour of the teeth tends to return to its previous state, allowing the patient to monitor and adjust the results, if necessary, thus avoiding frequent visits to the dentist and, as such, any additional costs. Devices made from a flexible material are essential to prevent unwanted forces from being applied to the teeth. Special compartments can be added, as well as extensions that extend beyond the gum line (Haywood, 1998).

These compartments on the front of the teeth facilitate the administration of more whitening agents inside the whitening tray. However, these compartments are sometimes used to reduce sensitivity by creating a space between the tray and the tooth and to hold the whitening agent more effectively, thus reducing the patient's ingestion of the product (Perdigao, 2016).

1.6 In-office bleaching

The in-office tooth bleaching generally uses a whitening gel of hydrogen peroxide in higher concentrations. In this method, the product is applied directly to the patient's teeth after protecting all the surrounding soft tissues, for example, using a rubber dam (Carey, 2014). This avoids the possibility of tissue irritation and a burning sensation or ulcer, which can occur if the product is in direct contact with these tissues. In this scenario, the dentist has complete control over the process and can stop it when the desired objectives have been achieved. This procedure is sometimes combined with a light or heat source to obtain a more effective result. (Fioresta *et al.*, 2023).

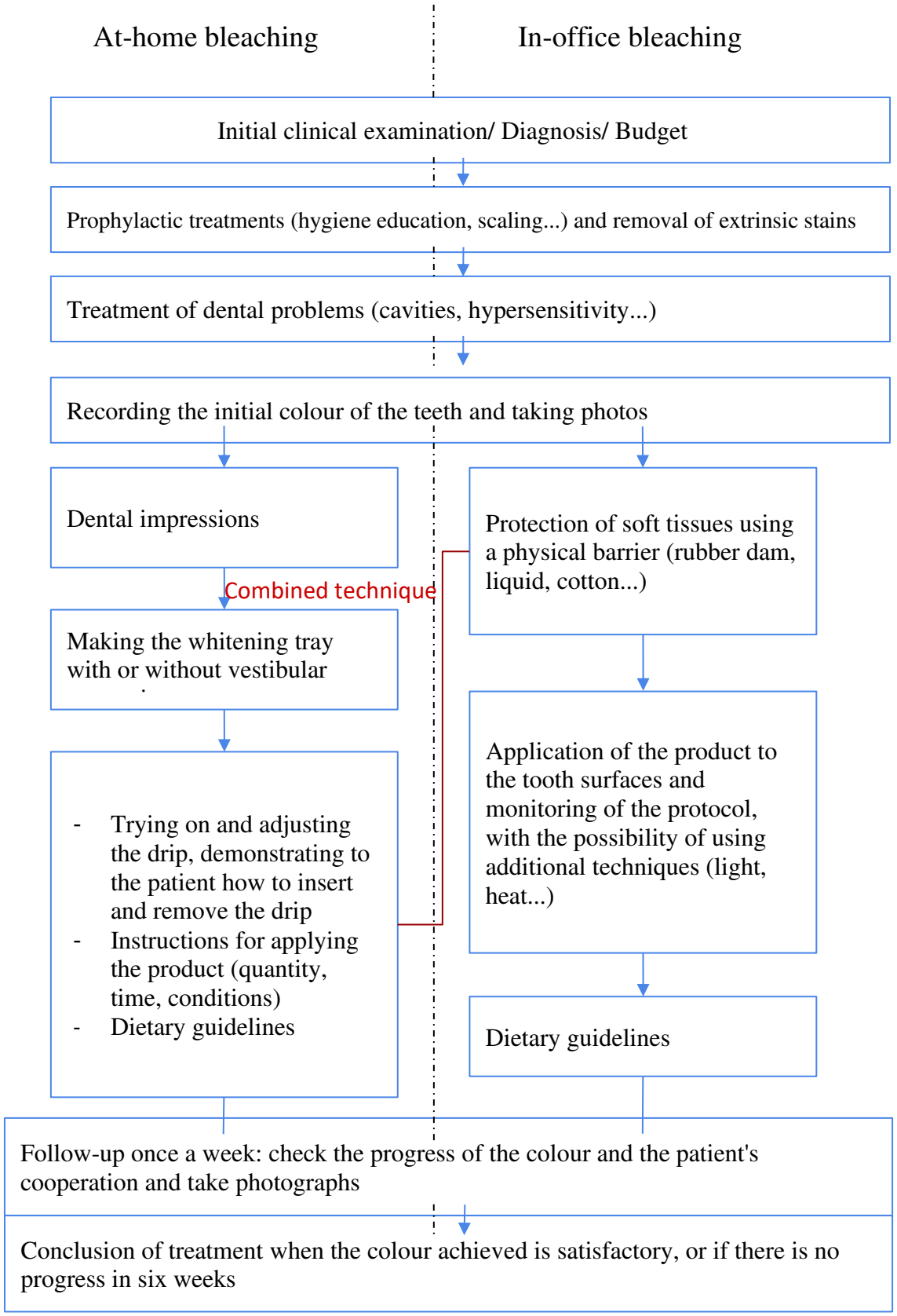


Figure 2 - Summary of the tooth bleaching process (Duc, 2012)

1.7 Objectives

In this systematic review, we examined the different non-invasive professional tooth bleaching methods for vital teeth supervised by a dentist in an office or at-home. The main **objectives** are to evaluate these methods' effectiveness, durability and safety.

II. MATERIAL AND METHODOLOGY

Systematic review is a fundamental step in research to consolidate existing knowledge on a given subject. Its methodological rigour distinguishes it, making it possible to collect, evaluate and synthesise data from different studies. This process aims to provide an in-depth and objective understanding, which is essential for guiding clinical practice and future research. Therefore, precisely defining the methodology of a systematic review is crucial to guaranteeing the accuracy and reliability of the conclusions obtained.

The question of interest was formulated using the PICO strategy, which stands for **Patient**, **Intervention**, **Comparison**, and **Outcome**, indicating the research outcome. Below are the PICO parameters used in this study:

- **Population (study unit)**: Teeth of adult patients extracted or in mouth
- **Intervention**: Professional tooth bleaching for vital teeth with a combination of different concentrations of whitening agents and application techniques
- **Comparison**: Not applicable
- **Outcome (1)**: Effectiveness
- **Outcome (2)**: Durability
- **Outcome (3)**: Safety

Following PICO, a research question was addressed: In the teeth of adult patients, how does non-invasive professional tooth bleaching with various concentrations of whitening agents and application techniques affect effectiveness, durability, and safety during the follow-up period?

The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The inclusion criteria consisted of:

Studies in which adult patients' teeth are whitened *in vitro* or *in vivo*.

The exclusion criteria specified are as follows:

- Teeth that have previously undergone bleaching procedures
- Teeth of patients with cavities or restorations before treatment
- Teeth of pregnant or breastfeeding participants
- Teeth of patients with oral health problems or systemic diseases that may affect the mouth and its function
- Teeth of patients with severe internal tooth discolouration (e.g. tetracycline stains), taking medication that affects tooth colouration, bruxism or any other condition that can cause tooth sensitivity (such as gum recession or dentin exposure)
- Teeth of participants who smoke
- Articles with redundant data
- Articles without quantitative results
- Internal or non-vital bleaching

2.1 Research strategy

The search strategy for this systematic review has been meticulously crafted to identify pertinent studies on non-invasive professional tooth bleaching. The research was conducted using the following databases: the Cochrane Library, PubMed, B-on, Scielo, Science Direct, Scopus, and Embase. In order to ensure the comprehensiveness and relevance of the research, the following keywords were employed: The search terms employed were "tooth whitening", "non-invasive tooth whitening", "Peroxide-based tooth whitening", and "adult patients". The aforementioned keywords were combined with Boolean operators (AND, OR) to form the following search algorithm.

2.1.1 Detailed Research Algorithm

("Teeth Whitening"[MeSH] OR "Tooth Bleaching"[MeSH] OR "Tooth Whitening" OR "Dental Bleaching" OR "Peroxide-Based Tooth Whitening" OR "Chairside Whitening" OR "In-Office Whitening" OR "At-Home Whitening" OR "Bleaching Gels"[MeSH] OR "Hydrogen Peroxide"[MeSH] OR "Carbamide Peroxide"[MeSH]" OR "Dental Aesthetics"[MeSH]) AND ("Adult"[MeSH] OR "Adult Patients" OR "Patients" OR "Adults") AND ("Treatment Outcome"[MeSH] OR "Treatment Efficacy" OR "Treatment Durability" OR "Safety"[MeSH] OR "Adverse Effects"[MeSH] OR "Oral Health"[MeSH] OR "Dental Safety" OR "Follow-Up Studies"[MeSH] OR "Clinical Trials"[MeSH] OR "Randomised Controlled Trials as Topic"[MeSH] OR "Outcome Assessment (Health Care)"[MeSH]).

Filters were employed to restrict the results to studies published in the last five to six years, thereby ensuring the inclusion of current data. Furthermore, only studies published in English, French and Portuguese were considered. For each database, the search equation was adapted to align with the specific syntactic characteristics and filtering options available. For instance, supplementary filters were applied in PubMed to exclude opinions, comments and letters.

2.2 Selection of studies and data collection process

The investigation team consisted of Doctor Cecilia Rozan (C.R), Master Paulo Mascarenhas (P.M), and Louis Le Cheviller (L.L.C). Each step was carried out by L.L.C under the supervision of Doctor Rozan and Paulo Mascarenhas. The articles retrieved by the literature search were reviewed in three stages. Initially, all studies were examined for their relevance based on the title. This preliminary stage aimed to quickly filter out studies that were clearly irrelevant to the research question. Studies passing this first stage then had their abstracts evaluated in the next stage. During this phase, the abstracts were scrutinized to determine if the study's objectives, methods, and results aligned with the inclusion/exclusion criteria.

In the final stage, the full texts of the remaining studies were obtained and reviewed comprehensively. This detailed review involved a thorough assessment of the study's methodology, data analysis, results, and relevance to the research question. If any doubts arose regarding the study's alignment with the inclusion/exclusion criteria at any of these stages, the study was not retained for the subsequent stage. For instance, studies with ambiguous abstracts were often excluded unless the full text could clarify the relevance.

Moreover, to maintain the integrity of the review, all duplicates identified during the search process were removed. Duplicates were often the result of articles appearing in multiple databases or being indexed multiple times under different categories. Their removal was crucial to avoid any potential bias or overrepresentation of certain studies.

2.2.1 Data extraction

All the essential data from each selected article were inserted into four tables. Three tables provide a comprehensive overview of all studies investigating the efficacy of bleaching treatments over three distinct periods. First one encompasses a range of assessment periods, from 24 hours up to three months. Second one encompasses assessment periods extending from three months to one year. Third one encompasses studies with assessment periods of one year or more.

These three tables include:

- The author, date, region
- The number of participants/ Study experimental design
- Bleaching techniques
- The type of measurement and the Colour measurement
- Colour measurement:ΔE
- Observation

The fourth table is about the safety and the tooth sensitivity, with assessment periods ranging from every follow-up period. This table includes:

- The author, date, region
- The number of participants/ Study experimental design
- Bleaching techniques
- Tooth sensitivity
- Security and others
- Observation

2.3 Risk of bias and tools used

Case-control studies:

To analyze the case-control studies, the Newcastle-Ottawa Scale (NOS) was used by two calibrated reviewer (CR and PM). For calibration, a random sample of 10 studies was evaluated and re-evaluated two days later (to calculate Cohen's kappa).

The term "risk of bias" describes a systematic error or deviation from the truth in the results or inferences of a study. A systematic error is defined as a deviation from the truth in the results or inferences (Higgins *et al*., 2011, Cochrane Handbook for Systematic Reviews of Interventions). It is important to consider the risk of bias in systematic reviews. By evaluating the risk of bias in a systematic review, readers can gain a more comprehensive understanding of the reliability of its conclusions and make a more informed decision about its relevance to their area of research or practice. Various tools are available to assess the risk of bias in systematic reviews, such as the risk of bias assessment tool we have used:

RoB 2:

The Cochrane Risk of Bias Tool (RoB 2) is a validated and widely used tool for assessing the risk of bias in randomised clinical trials. It was developed by the Cochrane Collaboration and is considered the "gold standard" for assessing the risk of bias in systematic reviews of randomised trials.

ROBIN-I:

The Robin I tool (Risk Of Bias in Non-randomised Intervention Studies) is a validated and widely used tool for assessing the risk of bias in non-randomised observational studies. It was developed by a team of international researchers and is recommended by the Cochrane Collaboration for assessing the risk of bias in systematic reviews.

QUIN Tool:

The QUIN tool is less well-known than the Cochrane risk of bias assessment tool (RoB 2). This tool was developed with the specific purpose of evaluating the risk of bias in vitro dental studies.

III. RESULTS

The search strategy yielded a total of 214 potentially relevant studies. Following the removal of the articles that were not accessible in full (n=40), a total of 174 records were screened for title and abstract against the eligibility criteria. Consequently, 49 articles were identified as meeting all the eligibility criteria and were selected for qualitative synthesis (Figure 3).

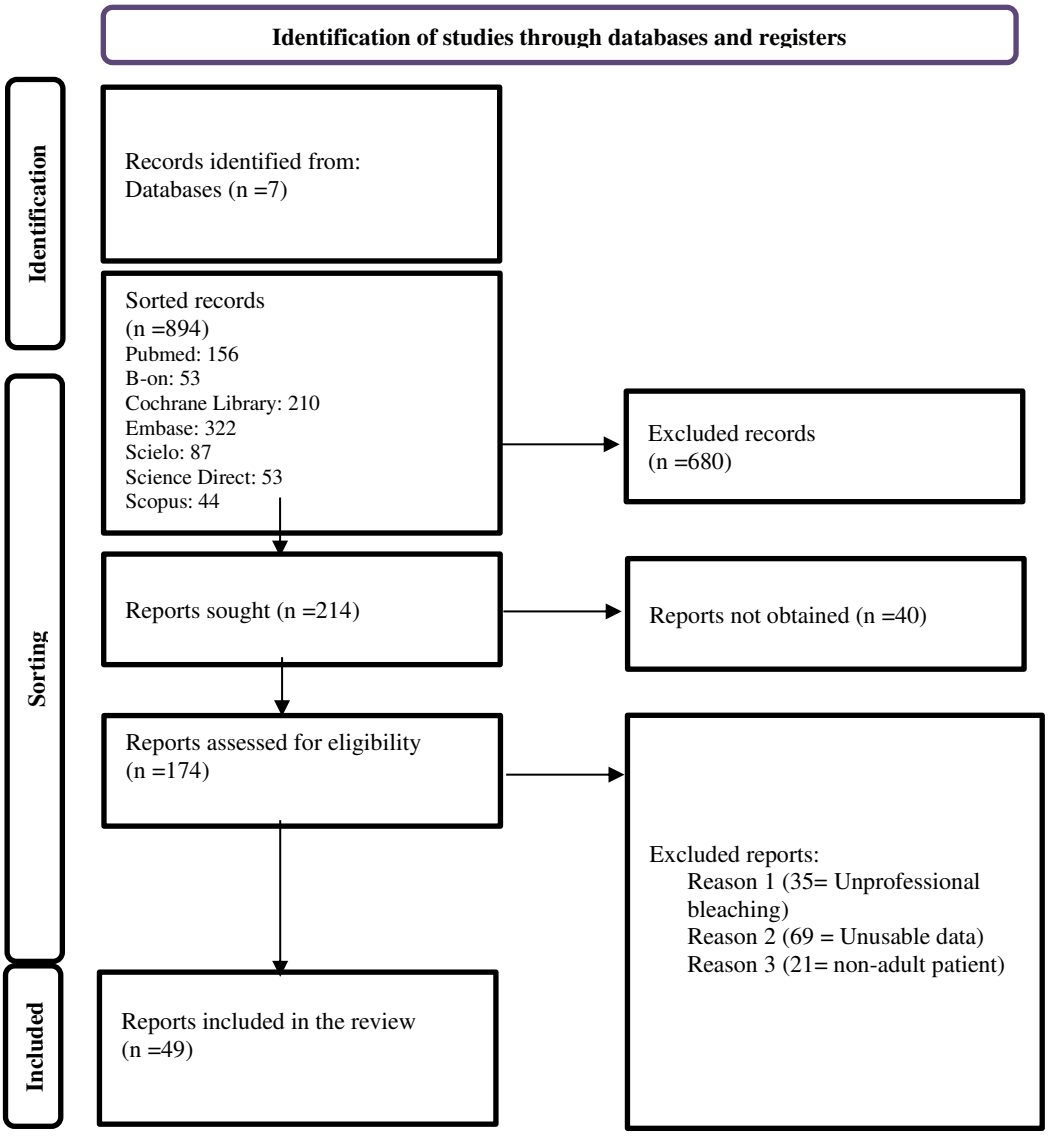


Figure 3 - Prisma flow chart showing the exclusion and inclusion process of the literature review

3.1 Synthesis table

A total of 49 studies were subjected to a comprehensive review across four synthesis tables. The initial three tables, Table IV, Table V, and Table VI, provide a comprehensive overview of all studies investigating the efficacy of bleaching treatments over three distinct periods. Table IV encompasses a range of assessment periods, from 24 hours up to three months. Table V encompasses assessment periods extending from three months to one year. Table VI encompasses studies with assessment periods of one year to more than three years. The last table, Table VII, provides a comprehensive overview of all studies that have investigated the outcomes of bleaching treatments in terms of sensitivity and security, encompassing all follow-up periods.

3.1.1 Synthesis of the short-term colour results

Table IV offers a comprehensive summary of all studies investigating the outcomes of bleaching treatment efficacity ranging from 24 hours up to 3 months.

Table IV – Summary of the short-term effectiveness of various dental bleaching techniques on tooth colour, with assessment periods ranging from 24 hours to 3 months

Autor/Date/ Region	**Subjects/ Type of Study**	**Bleaching techniques**	**Type of Measurement and Colour measurement**	**Colour measurement:ΔE**	**Observation**
Martini *et al.*/2019/ America	90/ In vivo	Group 1: desensitizing gel applied 10 min before bleaching with 35% HP 45 minutes application, and then application of placebo gel after. Group 2: desensitizing gel applied before and after the bleaching	VITA Classical (SGU means and SD between baseline vs 1 month): Group 1: 7.2 ± 2.2; Group 2: 7.2 ± 2.3,	ΔE values means with SD: Group 1: 13.9 ± 8.3; Group 2: 14.5 ± 10.5	No difference observed in the colour

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Kurt/2020/ America	100/ In vivo	Group 1 -LED, Group 2- LED/CP, Group 3- CP, Group 4- LED/HP and Group-5 HP Bleaching protocol following manufacturer instructions.	Vita classical SGU means values: • LED: Initial is 3.5, to 2.5 at 14 days. • LED/CP: initial of 7.0, decreasing to 6.0 at 14 days. • CP: initial of 5.5 initially, to 3.0 at 14 days. • LED/HP: initial of 10.0, to 9.0 after 14 days. • HP: Initial of 7.0, to 7.0 at the 14-day.	ΔE values means with SD: Group 1 : mean change of 3.4 (SD 1.3) immediately after bleaching and 3.7 (SD 1.4) at 14 days. Group 2: 7.8 (SD 2.0) initially and 8.6 (SD 2.1) after 14 days. Group 3: 5.7 (SD 2.5) at the start and 6.6 (SD 3.0) at 14 days. Group 3: 12.9 (SD 2.6) and 14.4 (SD 2.2) after 14 days. Group 3: 8.8 (SD 3.0) to10.0 (SD 4.1) at 14-day	Violet Led and HP reached the best result. Violet LED alone produced the lowest bleaching effect, but enhanced HP and CP bleaching results. Patients treated with LED/CP reached the same efficacy of HP
Subtil/2021/ America	80/ In vivo	Group 1- 10% CP; Group 2- 37% CP. In both groups, patients performed bleaching for 3 weeks, 4 h/day for 10% group and 30 min/day for 37% group.	Vita classical SGU means values: Group 1: baseline 10.8 ± 2.7; ΔSGU 6.2 ± 2.1 (1 month after bleaching). Group 2: baseline 10.5 ± 2.1; ΔSGU: 7.2 ± 2.3 (1 month after bleaching)	ΔE values means with SD: Group 1: • at 1 month : 10.5 ± 4.8 Group 2: • at 1 month: 11.4 ± 4.5	The use of 37% CP 30 min/day showed equivalent results to 10% 4 h/day
Chemin/2018/ America	78/ In vivo	Group 1- 4% HP; Group 2- HP 10%. In both groups, at-home bleaching performed 30 minutes twice a day for two weeks.	Vita classical shade guide SGU values: Group 1: at 1 month, the mean SGU was 4.1 ± 1.3. Group 2: at 1 month, the mean SGU was 4.1 ± 0.9.	ΔE values means with SD: Group 1 started with a mean ΔE of 9.0 ± 4.5, later reaching 11.4 ± 4.5 at 1 month. Group 2: initial mean ΔE of 8.0 ± 4.2, changing to 10.5 ± 4.8 at 1 month.	Colour variation after one month of bleaching for both groups showed significant bleaching, with no difference between groups

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Bersezio/2019/ America	33/ In vivo	One side of each mouth randomly treated with 37.5% HP,Group 1, other bleached with 6% HP, Group 2. Each group received 3 to 12 minutes . Two sessions each week.	Vita classical SGU means values: Group 1: from 3.90 at baseline to 6.71 one month post-bleaching. Group 2 : from 3.52 to 5.87.	ΔE values means with SD: Group 1: 3.79± 4.43 at baseline to 9.06± 2.96 at the one-month mark. Group 2: and the mean ΔE altered from 3.53± 1.90 to 5.69± 1.08 over the same period.	There was a significant difference between both groups
Chemin/2021/ America	72/ In vivo	Group 1- 10% HP applied once daily for 15 minutes Group 2- 10% HP applied once daily for 30 minutes. Bleaching performed 14 days.	Vita classical SGU values: Group 1: • Baseline: 1 ± 1.6 • ΔSGU: 4.2 ± 1.9 after 1 month Group 2: • Baseline: 5.4 ± 1.0 • ΔSGU: 4.7 ± 1.1 after 1 month	ΔE values means : Group 1: • 9.0 after 1 month Group 2: • 8.0 after 1 month	Bleaching were similar for both groups
Lima/2018/ America	25/ In vivo	Group 1- 15% HP Group 2- HP35% treatment. The bleaching agent was applied in three 15-min applications per session. Two bleaching sessions were separated by a 1-week interval.	Vita Classical scale, the SGU values: Group 1: 5.2 ± 2.3 at 1 week to 5.5 ± 2.5 at 1 month after bleaching. Group 2: 5.1 ± 2.3 to 6.0 ± 2.5 across the same period.	ΔE values means with SD: Group 1 colour change went from 6.7 ± 2.7 to 6.9 ± 2.6, while Group 2 experienced a change from 7.9 ± 3.3 to 8.7 ± 3.0 from the 1-week mark to 1 month post-bleaching.	The HP15% gel is less effective in bleaching, compared to the HP35% gel

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Bersezio/2021/ America	40/ In vivo	In-office bleaching performed using 6% HP with nitrogen TiO2. Groups were randomized by hemiarch: Group 1 one application of 72 minutes and Group 2 two applications of 36 minutes.	Simple spectrophotometer	ΔE values means with SD: Immediately post-bleaching, 2.74 ± 1.65 for Group 1; Group 2: 2.53 ± 1.15. One week after bleaching, Group 1: 2.65 ± 2.11; Group 2: to 3.16 ± 1.31 . After one month, Group 1:3.19 ± 2.15; Group 2: 3.44 ± 1.43 respectively.	There were no significant differences in the effectiveness between Group 1 and 2
Peixoto/2018/ America	40/ In vivo	2 groups : two sessions of in-office tooth bleaching using either 35% HP or 37% CP during 45 minutes. A second session was performed after one week.	VITA Bleachedguide 3D-MASTER.	ΔE values means with SD: Group HP: 7.0± 1.6 first session to 9.0± 1.7(15 days after) to 9± 1.6 (after 30 days). Group CP: starting 5.5± 1.5, 15 days 6.5± 1.6 to 7.0± 1.5 at 30 days.	An increased bleaching effect was observed for HP and reduced sensitivity for CP
Donassollo/ 2021/America	130/ In vivo	Group 1: in-office 35% HP and underwent placebo at-home. Group 2 underwent the at-home treatment with 10% CP and a placebo in-office.	Vita Easyshade and VITA classical	ΔE values means with SD: 35% HP: • Final ΔE: 4.01 (1.77), • ΔE at 2 weeks-post bleaching: 4.03 (1.02), 15% CP: • Final ΔE: 4.33 (2.35), • ΔE at 2 weeks-post bleaching: 4.27 (1.59),	10% CP produced a higher bleaching effect

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Surmelioglu/ 2020/ Europe	36/ In vitro	3 groups : Group 1: 6% HP + TiO2, Group 2: 6% HP + TiO2 + chitosan, Group 3: 35% HP. Procedure was repeated 3 times for 15 min each for a total of 45 min. Two bleaching sessions with an interval of 1 week.	VITA Easyshade Advance 4.0 spectrophotometer	ΔE values means with SD: • Group 1 :Initial—3 mo: 6.4 ± 1.1 • Group 2 : Initial—3 mo: 6.2 ± 1.9 • Group 3 : Initial—3 mo: 7.9 ± 2.3	Group 2 presented prolonged bleaching efficiency and reached a bleaching level similar to the 35% HP treatment after 14 and 30 days
Colares/2019/ America	22/ In vivo	2 groups HP, 15 and 35% applied for 15 min, three times in each session. Two bleaching sessions were performed with a 1-week interval between them.	Vita Classic and Vita Easyshade (ΔSGU): baseline tooth shades were similar amongst individuals (7.30 ± 2.6 shade guide units (SGU); 15% HP group 3.59± 2.2 after 21 days. 35% HP group 4.00± 2.3 after 21 days.	ΔE values means with SD: • With 15% HP, the ΔE (colour change) was 5.9 after 7 days and 6.6 after 21 days. • With 35% HP, the ΔE was 5.87 after 7 days and 6.88 after 21 days.	The efficacy of HP-containing products does not depend on the used concentration
Paula/2022/ America	86/ In vivo	2 groups: two daily applications of 30 minutes each or a 1-h single application with 4% HP.	Vita classical shade guide: Group 1-h twice-daily: • SGU Baseline: 10.4 ± 2.2 • ΔSGU Vita Classical: • 1-month follow-up: 7.7 ± 2.2 Group 2-h once-daily: • SGU Baseline: 9.3 ± 3.0 • ΔSGU Vita Classical: • 1-month follow-up: 6.7 ± 2.8	ΔE values means with SD: Group 1-h twice-daily: • 1-month follow-up: 8.3 ± 3.1 Group 2-h once-daily: • 1-month follow-up: 7.3 ± 4.0	30 minutes twice daily did not increase the bleaching degree

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Surmelioglu/ 2021/ Europe	108/ In vitro	Opalescence Boost PF 40% HP; applied for 20 minutes in Group 1, 40 minutes in Group 2, and 60 minutes in Group 3.	VITA Easyshade Advance 4.0 spectrophotometer	ΔE values menans with SD: • Group 1: Initial-14d: 3.8 ± 1.87 • Group 2: Initial-14d: 4.8± 1.91 • Group 3: Initial-14d: 5.4± 1.96	Based on the results evaluated for whiteness, colour alteration, the optimal bleaching duration of application was in 40 minutes
Surmelioglu/ 2021/ Europe	60/ In vitro	Opalescence Boost PF 40% (Ultradent Products, USA) was applied for 20 min (min) in Group 1, 40 min in Group 2 and 60 min in Group 3	VITA Easyshade Advance 4.0 spectrophotometer	ΔE values means with SD: • Group 1: Initial-after 14 days : 4.84 ± 1.91 • Group 2 : Initial-after 14 days: 6.60 ± 1.82 • Group 3 Initial-after 14 days: 8.37 ± 2.15	For the bleaching, the optimal bleaching duration of application was in 40 minutes
Surmelioglu/ 2020/ Europe	72/ In vitro	TiO2/chitosan added to gel 6% HP Group 1, activated D-Light Duo LED device for 45 minutes. Group 2, Opalescence Boost PF 40% HP for 45 minutes. Group 3, Philips Zoom 25% HP activated with Zoom Advanced Power for 45 minutes. A second bleaching session one week later.	VITA Easyshade Advance 4.0 spectrophotometer	ΔE values means with SD: • Group 1: mo: 6.8 ± 1.0/Initial—3 mo: 6.4 ± 1.1 • Group 2: 1 mo: 7.1 ± 3.1/Initial—3 mo: 6.2 ± 1.9 • Group 3: 1 mo: 8.2 ± 2.1/Initial—3 mo: 7.9 ± 2.3	Philips Zoom showed a higher value of colour change than the other groups at all times

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Monteiro/2020/ America	40/ In vitro	4 groups : CP - 10% (1 hour daily/21 days). CPN - CP incorporated into TiO2; HP - 40% (three 40-minute sessions/7 days apart); HPN - HP incorporated into TiO2.	Vita classical shade guide means and SD: CP: Baseline: 10.40 ± 2.06/ 7 days after end of bleaching treatment: 4.40 ± 2.63 CPN: Baseline: 10.50 ± 2.12/7 days after end of bleaching treatment: 8.20± 4.10 HP: Baseline: 10.20 ± 2.10/7 days after end of bleaching treatment: 4.30 (3.27). HPN: Baseline: 9.90± 2.02/7 days after end of bleaching treatment: 2.70± 0.95	ΔE values means: • CP: 7 days after– baseline: 8.09 • CPN: 7 days after treatment – baseline: 5.36 • HP: 7 days after treatment – baseline: 8.88 • HPN: 7 days after treatment – baseline: 9.12	TiO2 did not influence physicochemical properties of the bleaching agents. HPN presented more effective tooth bleaching than CPN
Bersezio/2018/ America	58/ In vivo	Bleaching with 10% CP for 1 h daily for 3 weeks.	Vita Classical shade guide. Baseline SGU: 7.26 ± 1.17 • 1-month post-bleaching: ΔSGU is 2.4 ± 1.7.	For the ΔE results: • 1-month post-bleaching: ΔE is 5.9 ± 1.8.	The bleaching procedure was effective
Alsheikh/2018/ Europe	60/ In vivo	Group 1: 25% HP and light activation/ Group 2: 40% HP without light activation. Three applications of 45 minutes	Crystal Eye spectrophotometer. Group 1: • Baseline: 4.03± 2.29. • 4 weeks: 5.25 ± 2.31. • 8 weeks: 5.15 ± 2.96. Group 2: • Baseline: 4.77 ± 2.20. • 4 weeks: 4.85 ± 4.97. • 8 weeks: 4.89 ± 6.22.	/	25% HP and light activation in teeth bleaching was slightly more effective

C – Combined, **CP -** Carbamide peroxide, **G –** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Brugnera/2019/ America	50/ In vivo	Group 1: two bleaching sessions of 30min each, with 7-day interval; Group 2: same protocol associated with violet LED light, 30 min each session	VITA Easyshade; means values for Group 1 of the central incisor after first application from 3.0 (SD 1.5) to 2.3 (SD 1.3) after 14 days; Group 2, from 3.7 (SD 2.4) to 1.4 (SD 1.0).	/	The violet LED light could improve dental bleaching effectiveness
Monteiro/2018/ America	40/ In vivo	Group 1 : 35% HP/ Group 2: 37% CP. Gel was applied 45 minutes one per week/for 3 weeks	Vita classical stade guide	ΔE values Group 1: 10 ± 3.99 immediately after bleaching, 15 days later at 11 ± 2.83. For Group 2: 2.9 ± 3.75 immediately after bleaching, concluding at 9 ± 2.54 after 15 days.	Every bleaching were effective
Mahmoud/2018/ America	45/ In vivo	Group 1: ozone for 60 seconds, then 38% HP (20 minutes). Group 2: 38% HP (20 min) was followed by ozone (60 s). Group 3: air produced by the healOzone machine (60 s) followed by 38% HP (20 min)	Vitapan classical shades;Group 1:before bleaching from 10.52 (SD 1.40) to 14.80 (SD 2.35) after 1 month. Group 2:from 10.41 (SD 1.25) to 15.04 (SD 1.47). Group 3: from 10.45 (SD 1.30) to 13.18 (SD 1.54).	/	Group 2 showed more effective bleaching

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Goettems/2021/ America	130/ In vivo	Group 1 :At-home treatment performed using 10 % CP(2 h/day; 3 weeks)and an in-office placebo; Group 2: 35 % HP used for in-office (1/week; 3 weeks) and an at-home placebo	Vita Classical Shade; The mean ΔSGU: Group 1:(-3.68)± 2.12 Group 2: (-3.37)± 2.31	ΔE values means: Group 1: 3.93 after 21 days ; Group 2: 4.73 after 21 days	Results demonstrate more effective bleaching for Group 1
Leite/2023/ America	100/ In vitro	Randomly distributed into 5 groups: 10% HP (HP10), 10% CP (CP10), 10% HP with violet LED (VHP10), 10% CP with violet LED (VCP10) and 35% HP (HP35)	EasyShade spectrophotometer	ΔE values means: • HP35: 6.37 ± 3.83. • HP10: 6.96 ± 9.93. • CP10: 2.50 ± 1.77. • VHP10: 8.92 ± 8.16. • VPC10: 4.21 ± 2.66.	All bleaching protocols showed effective bleaching results
Gallimard/2020/ America	30/ In vivo	Bleaching 10 % CP, for 8 h daily, for 21 days. All patients underwent in-office irradiation of only one hemiarch with VL for 30 min, twice per week	Digital spectrophotometry was done using the Visual Analog Scale	ΔE values means: Without LED: T1: initial 4.82 (SD 2.96); After bleaching: 7.06 (SD 2.49);7 days: 7.86 (SD 2.64264); 14 days T4: 8.09 (SD 3.39);21 days:88 (SD 2.74) Violet LED: T1: 6.18 (SD 2.82); T2: 9.79 (SD 3.53); T3: 10.60 (SD 3.67); T4: 9.88 (SD 3.29); T5: 9.93 (SD 3.42)	It can be concluded that the Violet Light provided a positive effect on colour alteration when used in conjunction with 10 % CP

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Meireles/2021/ America	40/ In vivo	Group 1- Two application (37.5% HP) Group 2- Three application (37.5% HP) 8 min applications/clinical session. Three clinical sessions performed with a 1 week interval.	Colour evaluations were done with a spectrophotometer	ΔE values means with SD: Group 1: after one week post-bleaching: 10.2 ± 2.7; Group 2: 9.7 ± 2.7	Group 2 produced the same bleaching degree, risk and intensity of Tooth sensivity

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

3.1.2 Synthesis of the medium-term colour results

Table V offers a comprehensive summary of all studies investigating the outcomes of bleaching treatment efficacity ranging from 3 months up to 1 year.

Table V – Summary of the mid-term effectiveness of various dental bleaching techniques on tooth colour, with assessment periods ranging from 3 months to 1 year

Autor/Date/ Region	**Subjects/ Type of Study**	**Bleaching techniques**	**Type of Measurement and Colour measurement**	**Colour measurement:ΔE**	**Observation**
Jum'ah *et al.*/2023/ Oceania	105/ In vivo	Group 1: Home bleaching: 10% CP gel during 14 days 30 min/day Group 2: In-office bleaching: 37.5% HP was applied for 8 min . process repeated 3 times Group 3: Combination: Participants underwent IO followed by HB, with the same protocole	Digital spectrophotometry device (ES-ΔeVS).	ΔE values means with SD: Group 1 : •Baseline: 9.9 (2.32) ΔE 15 days : 5.4 (1.92)/ ΔE 6 Months : 5.1 (1.87) Group 2: •Baseline: 10.6 (2.12)/ΔE 15 days: 4.0(2.08)/ΔE 6 Months: 3.3 (2.21) Group 3 : •Baseline: 10.7(1.85)/ΔE 15 days: 3.3(2.12)/ΔE 6 Months: 2.9(2.25)	Combined in-office and home bleaching resulted in a more pronounced colour improvement

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Rodrigues *et al.*/2018/ America	40/ In vivo	One session in-office bleaching 38% HP with 45minutes application. Second session, Group 1: in-office bleaching, Group 2: tray containing 10% CP during 7 days/4h.	Vita classical stade guide. Median: Group 1: 7 days :4.2; 6 months: 5.6 Group 2 : 7 days 5.0 ;6 months 5.7. standard deviation with no statistical difference	ΔE values means with standard deviation: Group 1: 7 days 6.9 (1.6); 6 months 9.5 (2.0) Group 2: 7 days 7.8 (2.7), 6 months 8.4 (3.1).	After one in-office bleaching session, there was no difference between performing a second in-office session and associating it with 1-week at-home bleaching
Mayer-Santos/2022/ America	100/ In vivo	Group 1 - 35% HP (4 sessions, 1x/week); Group 2 - violet LED (4 sessions, 1x/week); Group 3 - violet LED (4 sessions, 2x/week); Group 4 - hybrid technique (violet LED +35% HP; 4 sessions, 1x/week). Gel was always applied 45 minutes.	VITA colour scale values SGU means and SD: • G1: Initial 3.53±1.03, 3 months 2.06±0.27 • G2: Initial 3.66±2.72, 3 months 2.93±2.25 • G3: Initial 4.68±2.72, 3 months 3.81±2.28 • G4: Initial 4.40±2.27, 3 months 2.00±0.67	/	Bleaching with violet LED light combined with HP promoted dental colour change similar to HP
Piknjac Amar/2020/ Europe	20/ In vivo	Patients treated with 40% HP, three applications each 20 minutes, one appointment	Spectrophotometer based on the CIE Lab	ΔE values means: from baseline to the the first assessment of 3.3 (SD) of 1.9. At 3 months, the mean ΔE is reduced to 1.8 (SD 1.3), and at 6 months, 1.2 (SD 1.1).	40% HP was effective, and the results showed a statistically significant decrease in colour change during the period of 6-month observation

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Darrian/2019/ Europe	50/ In vivo	Group 1: 14-day treatment, Group 2: 21-day treatment. For both 10% CP was applied for 2 h a day in custom trays	Easyshade dental spectrophotometer recording ΔSGU values: Group 1: Initial mean change of -3.30 ± 3.12 units, to -3.45 ± 4.04 units after 6 months. Group 2: Initial change was -4.93 ± 3.91 units, which changed to -5.15 ± 4.20 units at the 6-month mark.	ΔE values means: Group 1: after treatment 4.74. One month post-treatment, 5.62 combined. At six months, 4.81. Group 2: after bleaching 5.77. One month post-treatment, 5.62. At six months, 5.56.	Daytime application of at-home bleaching for 3 weeks achieves greater bleaching results than for 2 weeks, immediately after treatment and 1 and 6 months afterwards
Ferraz/2019/ America	54/ In vivo	Group 1: 6%HP, Group 2: 15% HP in-office bleaching activated via hybrid LED/laser light	Spectrophotometer Classical vita shade guide.	ΔE values median and SD: • HP 6% Group: 1st week of bleaching 3.6 (1.82), after 6 months 4.9 (2.01) • HP 15% Group: 1st week of bleaching 2.1 (2.12), after 6 months 8.2(1.98)	Both agents showed bleaching effectiveness, but HP15% presented greater colour stability than HP6%, at 6-month follow-up
Zhao/2023/Asia	40/ In vitro	Group 1: at home 6% HP for 30 min/d for a total of 7 h in 14 days (HP6), Group 2: 10% CP for 10 h/d for 140 h in 14 days (CP10), Group 3: in office 35% HP for 10 min × 3 (HP35) , Group 4: 40% HP for 20 min × 3 (HP40)	Olympus CrystalEye dental spectrophotometer	ΔE values means ± SD: Group 1: After bleaching: 10.60 ± 1.62. After 6 months: 9.04 ± 1.86 Group 2: After bleaching: 11.38 ± 1.69. After 6 months: 9.19 ± 2.52 Group 3: After bleaching: 5.92 ± 1.19. After 6 months: 7.20 ± 1.61 Group 4: After bleaching: 5.28 ± 1.74. After 6 months: 7.68 ± 1.30	The two at-home bleaching systems achieved significantly better bleaching than the two in-office products immediately after. However, at six months after treatments, the differences between at-home and in-office treatments were not significant

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Sobral/2021/ America	60/ In vivo	Group 1: 35% HP with 40 minutes application; Group 2: violet light (405–410 nm) without HP, total illumination time of 20 min and a total procedure time of 30 min. A second bleaching session was performed after 7 days for both groups.	Vita Classical Shade guide, reorganized by Value Scale: Group 1: • Baseline: 12 • 1 month: 13 • 6 months: 13 Group 2: • Baseline 12: • 1 month: 13 • 6 months: 13. standard deviation with no statistical difference	/	The two bleaching protocols results were similar regarding the immediate effectiveness and 6-month stability of tooth bleaching

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

3.1.3 Synthesis of the long-term colour results

Table VI provides a comprehensive overview of all studies investigating the efficacy of bleaching treatments, with data spanning over one year.

Table VI - This study presents a comprehensive overview of the long-term effectiveness of dental bleaching techniques on tooth colour, with assessment periods ranging from one year to more than three years

Autor/Date/ Region	**Subjects/ Type of Study**	**Bleaching techniques**	**Type of Measurement and Colour measurement**	**Colour measurement:ΔE**	**Observation**
Llena *et al.*/2020/ Europe	95/ In vivo	CP 16% was applied for 90 minutes a day for 4 weeks using individualized trays	Vita easyshade	ΔE values means : 1 month: 8.5±2.0/6 months: 8.3±1.9/12 months: 9.5±2.1/18 months: 9.6±1.2/24 months: 9.2±1.4/30 months: 8.9±0.8/36 months: 8.1±1.6/42 months: 8.0±1.8	The bleaching remained stable over the 42 months of follow-up
Stay/2020/ America	25/ In vivo	Group 1 : in-office 6% HP Group 2: in-office 37.5% HP with 45 minutes application	Vita Classical shade guide. ΔSGU (median and range): Group 1: 1 month, 6 (1-9); at 6 months, 6 (1-8); 12 months, 5 (0-7). Group 2: 1 month: 7 (2-9); 6 months: 7 (3-8); 12 months: 6 (1-8).	ΔE values means: Group 1: 5.08 ± 2.11 at 1 month; 5.07 ± 2.98 at 6 months; 5.27 ± 2.53 at 12 months. Group 2: 1 month: 9.05 ± 2.74; 6 months: 8.01 ± 2.84; 12 months: 8.37 ± 2.73.	Group 2 was significantly better than that of Group 1

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Mondelli/2018/ America	34/ In vivo	Group I and II : enamel acid etching with 37% phosphoric acid. Group I HP 35% 3 x 15min and activated by VL; Group II same protocol without VL	Spectrophotometer with the CIELab colour system	ΔE values means: Group 1 : •ΔE 1 month: 8.23 ± 2.64;ΔE 6 months: 7.72 ± 1.95; ΔE 1 year: 7.25 ± 2.06 Group II : •ΔE 1 month: 7.46 ± 1.72; ΔE 6 months: 7.77 ± 2.28; ΔE 1 year: 7.36 ± 1.42	No statistical differences were observed between the groups regarding colour change (ΔE) and sensitivity in all evaluations
Urgulu/2022/ Europe	30/ In vivo	The 25% hydrogen peroxide gel (Philips Zoom) was applied with a supplementary LED light for 15 min in four cycles.	Spectrophotometer with the CIELab colour system	ΔE values means: 1. After bleaching(ΔE1): 14.22 ± 1.31 2. 1 years after (ΔE2): 14.74 ± 1.27 3. 2 years after (ΔE3): 10.51 ± 1.06 4. 3 years after(ΔE4): 7.51 ± 0.98	The data show that 25% bleaching is effective. The colour stability remained during 1 year. The colour significantly decreases after 2 years

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

3.1.4 Synthesis of the tooth sensitivity, security and others

Table VII provides a comprehensive overview of all studies that have investigated the outcomes of bleaching treatments in terms of sensitivity and security, encompassing all follow-up periods.

Table VII - Summary all studies dealing with the results of sensitivity and security after treatments ranging from over every follow-up period

Autor/Date/Region	**Subjects/ Type of Study**	**Bleaching techniques**	**Tooth sensivity**	**Security/Others**	**Observation**
Peixoto/2018/ America	40/ In vivo	2 groups : two sessions of in-office tooth bleaching using either 35% HP or 37% CP during 45 minutes. A second session of bleaching was performed after one week.	Tooth sensivity : Group HP :1st session: 12 out of 20 participants reported sensibility. Group CP: 4 out of 20. 2st session, group HP: 9 out of 20 participants. Group CP: 1 out of 20.	/	An increased bleaching effect was observed for HP and reduced sensitivity for CP

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Donassollo/ 2021/America	130/ In vivo	Group 1: in-office 35% HP and underwent placebo at-home. Group 2 underwent the at-home treatment with 10% CP and a placebo in-office.	15% CP: • First day: 55 (84.6%) no sensitivity, 7 (10.8%) mild, 3 (4.6%) moderate • One week: 62 (95.4%) no sensitivity, 3 (4.6%) mild, 0 moderate • Two weeks post-bleaching: 63 (96.9%) no sensitivity, 2 (3.1%) mild 35%: • First day: 41 (63.1%) no sensitivity, 13 (20%) mild, 10 (15.4%) moderate, 1 (1.5%) considerable, and 1 (1.5%) severe. • One week: 60 (92.3%) no sensitivity, 3 (4.6%) mild, 2 (3.1%) moderate • Two weeks post-bleaching: 65 (100%) no sensitivity	/	10% CP produced a higher bleaching effect. Tooth sensitivity rates were similar for the two techniques tested
Surmelioglu/ 2020/ Europe	36/ In vitro	3 groups : Group 1: 6% HP + TiO2, Group 2: 6% HP + TiO2 + chitosan, Group 3: 35% HP. Procedure was repeated 3 times for 15 min each for a total of 45 min. Two bleaching sessions with an interval of 1 week.	/	Mineral values: Calcium : • Group 1: Initial - 63.5 ± 1.0; After 14 days - 64.6 ± 1.6 • Group 2: Initial - 63.8 ± 2.7; After 14 days - 69.3 ± 0.9 • Group 3: Initial - 65.3 ± 2.30; After 14 days - 68.2 ± 3.28 • Phosphorus (P): • Group 1: Initial - 36.1 ± 2.7; After 14 days - 32.2 ± 2.2 • Group 2: Initial - 35.8 ± 2.5; After 14 days - 34.3 ± 3.1 • Group 3: Initial - 36.1 ± 1.6; After 14 days - 29.2 ± 3.4	Group 2 presented prolonged bleaching efficiency and reached a bleaching level similar to the 35% HP treatment after 14 and 30 days. The increases in Ca were similar in Groups 2 and 3 and were significantly higher than that in Group 1 . P was similarly decreased among all groups

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Colares/2019/ America	22/ In vivo	2 groups HP, 15 and 35% applied for 15 min, three times in each session. Two bleaching sessions were performed with a 1-week interval between them.	Tooth Sensitivity: • With 15% HP, tooth sensitivity measured 1 hour after the first session averaged 1.22, and 0.25 after 24 hours. • With 35% HP, sensitivity averaged 4.33 after the first session and 1.54 after 24 hours, indicating increased sensitivity compared to the 15% HP group.	/	The efficacy of HP-containing products does not depend on the used concentration. 35% HP promotes greater tooth sensitivity than 15% HP
Paula/2022/ America	86/ In vivo	2 groups: two daily applications of 30 minutes each or 1h single application with 4% HP	Tooth sensivity values : 1-h twice-daily group : • Patients with sensitivity : 32 • Patients without sensitivity : 11 2-h once-daily group : • Patients with sensitivity : 35 Patients without sensitivity : 8	/	30 minutes twice a daily did not increase the bleaching degree not affect the risk and intensity of tooth sensivity
Surmelioglu/ 2021/ Europe	108/ In vitro	Opalescence Boost PF 40% HP; applied for 20 minutes in Group 1, 40 minutes in Group 2, and 60 minutes in Group 3.	/	• Microhardness (HV): • Group 1: Started at 308.0, 304.0 after 14 days. • Group 2: Started at 297.1, 293.8 after 14 days. • Group 3: Began at 319.7.307.4 after 14 days. • Roughness (μm): • Group 1: Initial 0.61, 0.65 after 14 days. • Group 2: Initial 0.57, 0.63 after 14 days. • Group 3: Initial 0.71, 0.79 after 14 days.	Based on the results evaluated for whiteness, colour alteration, microhardness, and roughness, the optimal bleaching duration of application was in 40 minutes

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Surmelioglu/ 2021/ Europe	60/ In vitro	Opalescence Boost PF 40% (Ultradent Products, USA) was applied for 20 min (min) in Group 1, 40 min in Group 2 and 60 min in Group 3	/	Mineral Values Alteration after bleaching (± SD): • Group 1: (Ca): 68.85 ± 4.54. (P): 28.01 ± 4.05. (Mg): 1.03 ± 1.04. (Na): 1.89 ± 1.57 • Group 2: (Ca): 66.08 ± 1.50/ (P): 29.86 ± 2.26/ (Mg) 1.05 ± 0.82/ (Na) 3.13 ± 1.04 • Group 3: (Ca) 69.91 ± 5.34/ (P) 26.54 ± 5.92/ (Mg) 0.79 ± 0.39/(Na) 1.91 ± 0.59	For the bleaching, microhardness, and roughness, the optimal bleaching duration of application was in 40 minutes
Chemin/2021/ America	72/ In vivo	Group 1- 10% HP applied once daily for 15 minutes Group 2- 10% HP applied once daily for 30 minutes. Bleaching performed 14 days.	Tooth sensivity • Group 1: Out of 36 participants, 17 experienced tooth sensitivity • Group 2: Similarly, 17 out of 36 participants experienced tooth sensitivity	/	Teeh sensivity and colour were similar for both groups
Martini *et al.*/2019/ America	90/ In vivo	Group 1: Desensitising gel applied 10 min before bleaching with 35% HP 45 minutes application, and then application of placebo gel after. Group 2: desensitizing gel applied before and after the bleaching	Tooth sensitivity (mean score) ; during bleaching Group 1: 2.7 ± 2.9, and the mean difference with group 2: 2.9 ± 3.0. Up to 1 hour, Group 1: 4.4 ± 2.9, and the mean difference with Group 2: 4.5 ± 3.0. Up to 24 hours, Group 1: 2.1 ± 2.9, and the mean difference with group 2: 2.0 ± 3.0. Up to 48 hours, Group 1: 0.3 ± 0.9, and the mean difference with group 2: 0.3 ± 0.8.		No difference observed in the colour. Efficient in reducing the sensitivity, when applied before the procedure, or before and after

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Kurt/2020/America	100	Group 1 - VL, Group 2- VL/CP, Group 3 - CP, Group 4- VL/HP and Group-5 HP Bleaching protocol following manufacturer instructions.	The tooth sensitivity median values: • Group 1: 1st session: 0.0, 2nd session: 0.0, 3rd session: 0.0 • Group 2: 1st session: 0.0, 2nd session: 0.0, 3rd session: 0.0 • Group 3: 1st session: 0.0, 2nd session: 0.0, 3rd session: 0.0 • Group 4: 1st session: 2.0, 2nd session: 1.0, 3rd session: 2.0 • Group 5: 1st session: 2.5, 2nd session: 0.0, 3rd session: 0.0	The mean Ca/P values at baseline (TO), after bleaching (TB, and 14 days after bleaching : Group 1: TO 2.33 (SD 0.88), TB 1.98 (SD 0.68) T14 1.96 (SD 0.80). Group 2: TO 1.76 (SD 0.98), TB 1.59 (SD 1.12) T14 2.30 (SD 1.52). Group 3: TO 2.65 (SD 1.38), TB 2.37 (SD 1.59) T14 2.49 (SD 1.02) . Group 4: TO 1.79 (SD 0.94), TB 1.40 (SD 0.88) T14 1.68 (SD 1.07) . Group 5: TO 2.14 (SD 0.71), TB 1.85 (SD 0.87), T14 2.19 (SD)	Violet Led and HP reached the best result. Violet LED alone produced the lowest bleaching effect, but enhanced HP and CP bleaching results. Patients treated with LED/CP reached the same efficacy of HP. Led didn't interfere with risk and intensity of tooth sensitivity and none of the bleaching protocols adversely affected enamel mineral content
Subtil/2021/ America	80/ In vivo	Group 1- 10% CP; Group 2- 37% CP. In both groups, patients performed bleaching for 3 weeks, 4 h/day for 10% group and 30 min/day for 37% group.	Tooth sensivity values: Group 1, 23 patients experienced tooth sensitivity, while 17 did not Group 2, 27 patients reported sensitivity compared to 13 who did not	/	The use of 37% CP 30 min/day showed equivalent results to 10% 4 h/day

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation, **VL -** Violet Led

Darrian/2019/ Europe	50/ In vivo	Group 1: 14-day treatment, Group 2: 21-day treatment. For both 10% CP was applied for 2 h a day in custom trays	During the bleaching treatment, group 1 had 80% of participants report no sensitivity, 12% mild sensitivity, and 8% moderate. Gingival irritation was reported by 28%. Group 3, 70% reported no sensitivity, 22% mild , and 8% moderate, Gingival irritation was slightly higher at 32%.	/	Daytime application of at-home bleaching for 3 weeks achieves greater bleaching results than for 2 weeks
Ferraz/2019/ America	54/ In vivo	Group 1: 6%HP, Group 2: 15% HP activated via hybrid LED/laser light	Tooth sensivity (median): Group 1: baseline and at 1 month remained at 0.00 , showing no change over time. Group 2 had a baseline median of 2.00 for tooth sensitivity, which decreased to 0.00 after 1 month, indicating an improvement.	/	Both agents showed bleaching effectiveness, but HP15% presented greater colour stability than HP6%, at 6-month follow-up. The agents showed low levels of tooth sensitivity
Zhao/2023/Asia	40/ In vitro	Group 1: at home 6% HP for 30 min/d for a total of 7 h in 14 days (HP6), Group 2: 10% CP for 10 h/d for 140 h in 14 days (CP10), Group 3: in office 35% HP for 10 min × 3 (HP35) , Group 4: 40% HP for 20 min × 3 (HP40)	/	Surface roughness in micrometers (Mean Sa ± SD)treated/untreated surfaces after six months Group 1: Treated: 7.76 ± 1.13; Untreated: 6.01 ± 1.67 Group 2: Treated: 6.44 ± 2.88; Untreated: 7.55 ± 2.29 Group 3: Treated: 6.93 ± 1.27; Untreated: 7.62 ± 1.49 Group 4: Treated: 8.72 ± 0.99; Untreated: 7.12+/- 2.31	There were no statistically significant differences with respect to the Sa values between the treated and untreated surfaces

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Rodrigues *et al*./2018/ America	40/ In vivo	One session in-office bleaching 38% HP with 45minutes application. Second session, Group 1: in-office bleaching, Group 2: tray containing 10% CP during 7 days/4h	Tooth sensitivity absolute and relative risk assessment: 1st bleaching: Absolute risk 0.85 (CI 0.64 - 0.95), Relative Risk 1.00 (CI 0.77 - 1.30), . 2nd bleaching: Group 1: Absolute risk 0.80 (CI 0.58 - 0.92), Group 2: Absolute risk 0.50 (CI 0.30 - 0.70), Relative Risk 0.63 (CI 0.38 - 1.02)	/	The bleaching protocol did not affect the risk for and the maximum level of sensivity
Mayer-Santos/2022/ America	100/ In vivo	Group 1 - 35% HP (4 sessions, 1x/week); Group 2 - violet LED (4 sessions, 1x/week); Group 3 - violet LED (4 sessions, 2x/week); Group 4 - hybrid technique (violet LED +35% HP; 4 sessions, 1x/week). Gel was always applied 45 minutes	Tooth Sensibility values and SD: -G1: 2.48 ± 0.54 -G2: 0.21 ± 0.48 -G3: 0.18 ± 0.68 -G4: 1.38 ± 1.12	/	Bleaching with violet LED light combined with HP promoted dental colour change similar to HP with less sensivity
Mondelli/2018/America	34/ In vivo	Group I and II : enamel acid etching with 37% phosphoric acid. Group I HP 35% 3 x 15min and activated by VL; Group II same protocol without VL	Tooth sensitivity values : Group I : • Baseline : 0.94 ± 1.47 • Immediately after : 3.58±3.41 • 24h : 1.58±2.03 • 1 week : 0.41±0.70 Group II : • Baseline : 1.41±2.03 • Immediately after : 3.58±3.32 • 24 h : 1.41 ±1.90 • 1 week : 0.52±1.23	/	No statistical difference were observed between the groups regarding colour change and sensitivity in all evaluations

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation, **VL -** Violet Led

Miranda/2022/ America	64/ In vivo	Two groups; placebo (PG) and LED (LG). The LG received PBM irradiation and tooth bleaching (35% hydrogen peroxide gel, while the PG received tooth bleaching and simulation of the irradiation.	During first session, LED group tooth sensitivity 53.3% of cases, significantly less than the PG group's 93.8%, (p-value of 0.0001). After treatment, LED group reporting 30% sensitivity compared to 90.6% in the PG group, (p-value of 0.0001). Second session, tooth sensitivity was reported by 36.7% in the LED group immediately after treatment, significantly lower than the 93.8% in the PG group, (p-value of 0.0001). After 24 hours, sensitivity was observed in 80% of the LED group, while in the PG group, sensitivity was 100%, (p-value of 0.010). At 72 hours post-second session, no significant difference in sensitivity (p=1.0), PG group: 3.1%/Led Group 0%.	/	PBM with LED decreases sensitivity risk and sensibility intensity during and after office bleaching

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **PBM -** Photobiomodulation, **PG** – Placebo Group, **SD -** Standard deviation

Ferreira/2023/ America	75/ In vivo	G1 (35% hydrogen peroxide), G2 (35% hydrogen peroxide + Green LED), G3 (35% hydrogen peroxide at 35% + Blue LED), G4 (35% hydrogen peroxide + Violet LED) and G5 (Violet LED)	Sensitivity analysis by groups at VAS-T0 and VAS-T1: • Group 1: T0 - No sensitivity 80%/Mild sensitivity 10%/ Considerable sensitivity 10% T2- No sensitivity 70%/Mild sensitivity 10%/Moderate sensitivity 10%/ Considerable sensitivity 10% • Group 2: Initial mild sensitivity higher compared to Group 1, with an increase in moderate sensitivity at T1. • Group 3: Starts with no moderate sensitivity, which then escalates to a quarter of the group by T1. • Group 4: Similar pattern to Group 3, with a significant rise in moderate sensitivity at T1. • Group 5: Exhibits the lowest initial sensitivity, with no considerable sensitivity at either T0 or T1.	/	With regard to sensitivity, no statistically significant differences were found between groups
Lima/2019/ America	80/ In vivo	Group 1- In-office bleaching two applications of 35% HP (20 minutes), then home bleaching 10% CP (2 hours/day for 16 days); Group 2 - Same protocol as G1, plus desensitising toothpaste; Group 3 - In-office bleaching 35% HP and application of placebo gel, then at-home bleaching 10% CP (2 hours/day for 16 days); and Group 4 - Same protocol as G3, plus desensitising toothpaste	/	SaO2 level, T0(baseline), T1(After one week), T4 (After 4 weeks), T7 (After 7 weeks) : Group 1: • T0: 84.29%. T1: 81.96%. T4: 83.34%. T7: 86.55%. (p = 0.093,) Group 2: • T0: 84.38%. T1: 82.06%. T4: 84.54%. T7: 86.60%. (p = 0.004) Group 3: • T0: 84.79%. T1: 82.19%. T4: 84.33%. T7: 87.15%. (p = 0.875) Group 4: • T0: 85.83%. T1: 81.15%. T4: 85.33%. T7: 87.15%. (p = 0.006, significant)	The pulp SaO2 level in maxillary central incisors was similar at baseline, reducing immediately after in- office bleaching, regardless of the use of desensitising toothpaste and increasing at 30 days after dental bleaching

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SaO2 –** Oxygen saturation

Briso/2018/America	30/ in vivo	Group CP, bleaching using 10% CP 4 h daily for 21 days; Group HP, using 6% HP 1.5 h daily for 21 days	/	P-values for comparison between evaluation times after 30 days: • G CP: Saliva: 0.169 (statistically significant)/ Subgingival: 0.169/ Supragingival: 0.056/ Oral mucosa: 0.290 • G HP: Saliva: 0.484/ Subgingival: 0.534/ Supragingival: 0.064/ Oral mucosa: 0.058	Although HP reduced Sreptococus mutans during treatment, the levels returned to baseline when assessed 30 days after the treatment

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Solda/2018/ America	136/ In vivo	10% CP gel placed in individual trays and used for four hours daily for 14 days	Oxygen saturation levels (SaO2) measured/standard error (SE): • T0 (Baseline): SaO2 85.1% with a(SE of 0.21). • T1 (Immediately after the first bleaching): SaO2 84.9% (SE of 0.19) with a statistically significant difference ($p < 0.001$) • T2 (7 days of treatment): SaO2 84.7% (SE of 0.18), also with $p < 0.001$ • T3 (15 days of treatment): SaO2 84.3% (SE of 0.18), $p < 0.001$ • T4 (30 days post-home treatment): SaO2 85.0% (SE of 0.19), with $p < 0.001$	/	Gradual reductions in SaO2 levels were observed, significant differences ($p<0.001$). However, 30 days after the end of the bleaching protocol, SaO2 levels returned to baseline levels
Mahmoud/2018/ America	45/ In vivo	Group 1: ozone for 60 seconds, then 38% HP (20 minutes). Group 2: 38% HP (20 min) was followed by ozone (60 s). Group 3: air produced by the healOzone machine (60 s) followed by 38% HP (20 min)	Tooth sensensivity; Group 1: 0.00 (SD 0.00) at baseline, 3.20 (SD 2.21) after bleaching. Group 2: 0.00 (SD 0.00) both at baseline and after bleaching. Group 3: (SD 0.00) at baseline, 1.60 (SD 1.78) after bleaching.	/	Group 2 showed more effective bleaching and caused less sensitivity

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HP -** Hydrogen peroxide, **IO -** In-office, **SaO2 –** Oxygen saturation, **SD -** Standard deviation, **SE -** Standard error

Goettems/2021/ America	130/ In vivo	Group 1: At-home treatment performed using 10 % CP (2 h/day; 3 weeks)and an in-office placebo; Group 2: 35 % HP used for in-office (1/week; 3 weeks) and an at-home placebo.	Tooth sensivity : Group 2: 49% reported sensivity; Group 1: 35% reported sensivity		Results demonstrate more effective bleaching for Group 1 associated with less sensitivity
Leite/2023/ America	100/ In vitro	Randomly distributed into 5 groups: 10% HP (HP10), 10% CP (CP10), 10% HP with violet LED (VHP10), 10% CP with violet LED (VCP10) and 35% HP (HP35).	/	• HP35: Starting microhardness was 277.36, to 198.76 after bleaching, then after 7 days 255.88. • CP10: 271.16, to 232.2, to 292.12. • HP10: 250.52, 215.76 at T1, 251.68. • VCP10: 261.84, to 274.66 at T1, to 265.42 at T2. • VHP10: 255.12, to 277.98, to 279.36.	All bleaching protocols showed effective bleaching results, and no reduction on microhardness was observed seven days after the end of the bleaching protocol for any group
Meireles/2021/ America	40/ In vivo	Group 1- Two application (37.5% HP) Group 2- Three application (37.5% HP); 8 min applications/clinical session. Three clinical sessions performed with a 1 week interval.	Tooth sensivity: Group : 16 participants experienced sensitivity, and 4 did not. Group 2: 15 participants reported sensitivity while 5 did not	/	Group 2 produced the same bleaching degree, risk and intensity of tooth sensivity

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation, **VL -** Violet Led

Bersezio/2021/ America	40/ In vivo	In-office bleaching performed using 6% HP with nitrogen TiO2. Groups were randomized by hemiarch: Group 1 one application of 72 minutes and Group 2 two applications of 36 minutes	Sensitivity values: Both Group 1 and Group 2 reported no sensitivity at baseline and one month after treatment. Immediately after treatment, Group 1 had a maximum score of 2, while Group 2 had a score of 2. One week post-treatment, score of 1 for Group 2, with no change reported in Group 1. No significant differences.	/	There were no significant difference in the effectiveness between Group 1 and 2

C – Combined, **CP -** Carbamide peroxide, **G -** Group, **HB -** Home bleaching, **HP -** Hydrogen peroxide, **IO -** In-office, **SD -** Standard deviation

Our systematic review examined 49 studies evaluating various tooth-bleaching protocols. The analysis revealed notable trends in improving tooth colour, sensitivity or other factors (oximetry, mineral values, and others).

49 <u>Studies:</u>

Out of the 49 selected studies, 42 consider the improvement of colour in whitened teeth, 40 consider the use of hydrogen peroxide, 19 consider the use of carbamide peroxide, 20 address tooth sensitivity, 12 consider the use of a light source during a tooth bleaching protocol, 5 investigate the use of experimental gels, 3 consider a combination of in-office and home treatment, 3 consider the use and influence of a desensitising gel within a tooth bleaching protocol, 6 address mineral values, and 4 address oximetry and bacterial composition.

3.2 Colour change after tooth bleaching

3.2.1 Long-term effectiveness

Different bleaching methods have shown varying degrees of effectiveness and longevity. Carbamide peroxide gel at a concentration of 16%, when applied at home for 90 minutes a day over a period of 4 weeks, proved effective with stable bleaching results lasting for 42 months (Llena *et al*., 2020). In contrast, an in-office bleaching treatment using 6% hydrogen peroxide showed significant results at 1, 6, and 12 months follow-up, while a 37.5% hydrogen peroxide application proved even more effective over the same periods (Stay, 2020). Additionally, a 25% hydrogen peroxide gel used with supplementary LED light for 15 minutes initially showed significant bleaching, but the colour stability declined after 2 years (Urgulu, 2022).

3.2.2 Concentration of whitening agent

Studies have shown that higher concentrations of agents like hydrogen peroxide or carbamide peroxide generally improve tooth colour (Monteiro 2018, Bersezio 2019, Lima 2018, Stay 2020, Peixoto 2018, Angel 2018, Ferraz 2019). For example, hydrogen peroxide at 37% has been demonstrated to be more effective than carbamide peroxide at the same concentration (Monteiro 2018). Additionally, the effectiveness of hydrogen peroxide increases with its concentration, as seen with 40% hydrogen peroxide proving to be more effective than 10% carbamide peroxide (Monteiro 2020). Similar findings are observed with 37.5% hydrogen peroxide, which shows superior results compared to 6% hydrogen peroxide (Angel 2018, Bersezio 2019, Stay 2020). In the case of carbamide peroxide, a concentration of 37% is more effective than 6% (Subtil 2021).

3.2.3 Lower concentrations can still achieve effective and even more effective bleaching

Hydrogen peroxide at a concentration of 6% has been shown to enable effective and stable bleaching for a duration of 3 months (Angel 2018). Additionally, both 4% and 10% concentrations of hydrogen peroxide produce significant bleaching effects, with no noticeable difference between the two groups (Chemin 2018). Carbamide peroxide at a concentration of 10% has also demonstrated its efficacy in tooth bleaching (Bersezio 2018). Interestingly, hydrogen peroxide at a concentration of 15% yields slightly better results than a higher concentration of 35% (Colares 2019). Furthermore, comparing the application protocols, 10% carbamide peroxide, applied for 2 hours daily over 2 weeks, shows slightly better efficacy than a single in-office application of 35% hydrogen peroxide (Donassollo 2021).

3.3 Tooth sensitivity after tooth bleaching

3.3.1 Prevalence of tooth sensitivity

Most studies reported tooth sensitivity in participants after tooth bleaching, with

prevalences ranging from 23% to 80% (Subtil *et al*. 2021, Darrian *et al*. 2019).

3.3.2 Influence of whitening agents

3.3.2.1 Peroxyde concentration

Higher concentrations of hydrogen peroxide or carbamide peroxide are generally associated with greater tooth sensitivity (Subtil 2021, Peixoto *et al*. 2021, Colares *et al*. 2019, Lima 2018, Ferraz 2019). However, carbamide peroxide tends to cause less sensitivity than hydrogen peroxide at similar concentrations (Peixoto *et al*. 2021).

For instance, carbamide peroxide at a concentration of 10%, when applied for 2 hours daily over two weeks, resulted in similar tooth sensitivity to a single in-office application of 35% hydrogen peroxide (Donassollo 2021).

3.3.2.2 Other agents

The addition of nano-bioactive to the whitening gel did not show a significant improvement in tooth sensitivity (Burey *et al*. 2021).

3.3.3 Impact of bleaching protocols

3.3.3.1 Application of desensitising gel

The application of a desensitising gel before, or before and after bleaching shows no significant difference in the level of tooth sensitivity (Martini *et al*. 2019).

3.3.3.2 Combined bleaching (in-office and at-home)

Combining in-office and at-home bleaching does not seem to increase sensitivity compared to a single technique (Rodrigues *et al*. 2018).

3.3.3.3 Duration and application time

The relationship between tooth bleaching treatments and tooth sensitivity varies with the concentration and duration of application. For instance, using a low concentration whitening gel, such as 4% hydrogen peroxide, for 30 minutes instead of one hour does not seem to affect tooth sensitivity (Paula *et al*. 2022). Similarly, hydrogen peroxide at a concentration of 37.5% shows no difference in sensitivity, whether applied twice or thrice, with applications spaced one week apart (Meireless 2021).

Furthermore, carbamide peroxide at a concentration of 10% does not increase sensitivity when applied for 30 minutes daily compared to 15 minutes over two weeks (Chemin 2021). In another study, a single application of 72 minutes or two applications of 36 minutes of 6% hydrogen peroxide with nanoparticles in nitrogen showed no significant difference in sensitivity levels (Bersezio 2021).

Interestingly, carbamide peroxide at 10%, with a 2-hour daily application, results in better sensitivity outcomes compared to 35% hydrogen peroxide applied for 40 minutes weekly (Goettems 2021). Moreover, a three-week protocol using 10% carbamide peroxide shows better sensitivity results compared to a two-week protocol (Darrian 2019).

3.4 Use of light sources in tooth bleaching

3.4.1 Positive effect of violet LED light (405-410 nm) on bleaching

The impact of violet LED light on tooth bleaching treatments has been the subject of various studies. When associated with bleaching agents like hydrogen peroxide or carbamide peroxide, violet LED light can enhance the effectiveness of bleaching compared to using the bleaching agent alone (Alsheik *et al*., 2018; Mayer-Santos *et al*., 2021; Brugnera et al., 2019; Kurt *et al*., 2020; Leite *et al*., 2023; Gallimard, 2020). However, there are differing opinions on its influence. According to Miranda (2022), LED light does not influence the performance of whitening agents.

Interestingly, while violet LED light alone produces a lesser bleaching effect (Kurt *et al*., 2020), it has been found to enhance bleaching results achieved with 35% hydrogen peroxide using the same application protocol (Sobral, 2021). Importantly, violet LED light does not appear to increase tooth sensitivity (Mayer-Santos *et al*., 2021; Kurt *et al*., 2020; Gallimard, 2020). Moreover, some studies concluded that it can reduce tooth sensitivity compared to whitening agents alone (Gallimard, 2020; Miranda, 2022).

3.4.2 Variable effect of other light sources

A combination of LED and laser has been shown to be effective for tooth bleaching (Ferraz *et al*., 2019). However, not all types of light yield the same results. For instance, when associated with hydrogen peroxide, green or blue LED light did not demonstrate improved bleaching efficacy or better tooth sensitivity compared to using hydrogen peroxide alone (Ferreira *et al*., 2023).

3.4.3 Long-term effectiveness

Tooth bleaching with a light source can offer a stable colour for 6 months to 1 year (Ferraz *et al*., 2019; Urgulu *et al*., 2022).

3.5 Use of experimental Titanium dioxide (TiO2) gels

3.5.1 Experimental gels with TiO2

Using various compounds and nanomaterials with hydrogen peroxide for tooth bleaching has shown mixed results. An experimental 6% hydrogen peroxide gel with TiO2 and chitosan demonstrated bleaching efficacy similar to a 35% hydrogen peroxide gel after 14 and 30 days (Surmelioglu, 2020). Additionally, a 6% hydrogen peroxide gel reinforced with TiO2 was effective in tooth bleaching, though it was less effective than a gel similar to TiO2 and chitosan. In the same study, 35% hydrogen peroxide provided slightly better bleaching than the other two experimental gels (Surmelioglu, 2020).

Furthermore, the incorporation of 40% hydrogen peroxide into TiO2 resulted in a more effective bleaching process than other methods, including 10% carbamide peroxide, 10% carbamide peroxide with TiO2, and 40% hydrogen peroxide alone. Notably, the combination of 10% carbamide peroxide with TiO2 exhibited a diminished efficacy compared to 10% carbamide peroxide alone (Monteiro, 2020). Nevertheless, incorporating synthetic nanomaterials into 40% hydrogen peroxide did not result in an enhanced bleaching efficacy compared to using hydrogen peroxide alone (Burey *et al*., 2021).

3.5.2 Comparison of commercial products

According to Surmelioglu (2020): Philips Zoom (hydrogen peroxide 25%) activated by Zoom Advanced Power showed more significant bleaching than the experimental gel (hydrogen peroxide 6% reinforced activated by D-Light Duo Led), and Opalescence Boost PF (hydrogen peroxide 40%), but the bleaching effect of the experimental gel was similar to Opalescence Boost PF.

3.5.3 Number of applications in the office

According to Bersezio (2021), a single 72-minute or two 36-minute application of 6% hydrogen peroxide with TiO2 nanoparticles in nitrogen showed no significant difference in bleaching efficacy.

3.6 Combining treatments in the office and at home

3.6.1 Main conclusions of the studies

The effectiveness of combining in-office and at-home tooth bleaching has been examined with varying results. According to a study by Jum'ah (2023), combining in-office and at-home bleaching produced more significant bleaching results than individually using each technique. However, this finding is not universally supported. A study by Rodrigues *et al*. (2018) indicates that the combined technique is no more effective than simply performing a second in-office bleaching session.

3.7 Influence of a desensitising gel on a tooth bleaching protocol

3.7.1 Desensitising gel and pulp SaO2 levels

According to Lima *et al*. (2019), the application of a desensitising gel does not significantly influence pulp SaO2 levels.

3.7.2 Desensitising gel and bleaching efficacy

According to Martini *et al*. (2019) there is no evidence that the application of desensitising gel affects the effectiveness of the bleaching process, whether the gel is applied before or before and after the bleaching protocol (Donassollo *et al*. 2021) also supports this argument.

3.8 The impact of bleaching on dental minerals

3.8.1 No adverse effect on dental minerals

Several studies have found no adverse effects of bleaching treatments on enamel hardness (micro-hardness) or surface roughness (Kurt *et al*., 2020; Leite *et al*., 2023; Zhao *et al*., 2023; Surmelioglu *et al*., 2021).

3.8.2 Optimum application time for some products

One study showed that an application duration of 40 minutes was more effective than 20 or 60 minutes of application for tooth bleaching, preserving the hardness of the enamel (Surmelioglu *et al*., 2021).

3.8.3 Mineral maintenance with specific protocols

A further study demonstrated an increase in enamel calcium following the use of a bleaching agent containing hydrogen peroxide and chitosan, with an even more pronounced increase observed when TiO2 was added (Surmelioglu *et al*., 2020).

3.9 Impact of tooth bleaching on oximetry and bacterial composition

3.9.1 Temporary decrease in pulp oximetry

All the studies observed a decrease in the oxygen saturation (SaO2) of the dental pulp immediately after bleaching, regardless of the protocol or bleaching agent used (Lima *et al*., 2019; Névés Henriques *et al*., 2022; Solda *et al*., 2018; Briso *et al*., 2018). This decrease appears to be temporary and usually returns to baseline levels within 30 days of the end of treatment (Lima *et al*., 2019; Solda *et al*., 2018).

3.9.2 Variable effect on bacterial flora

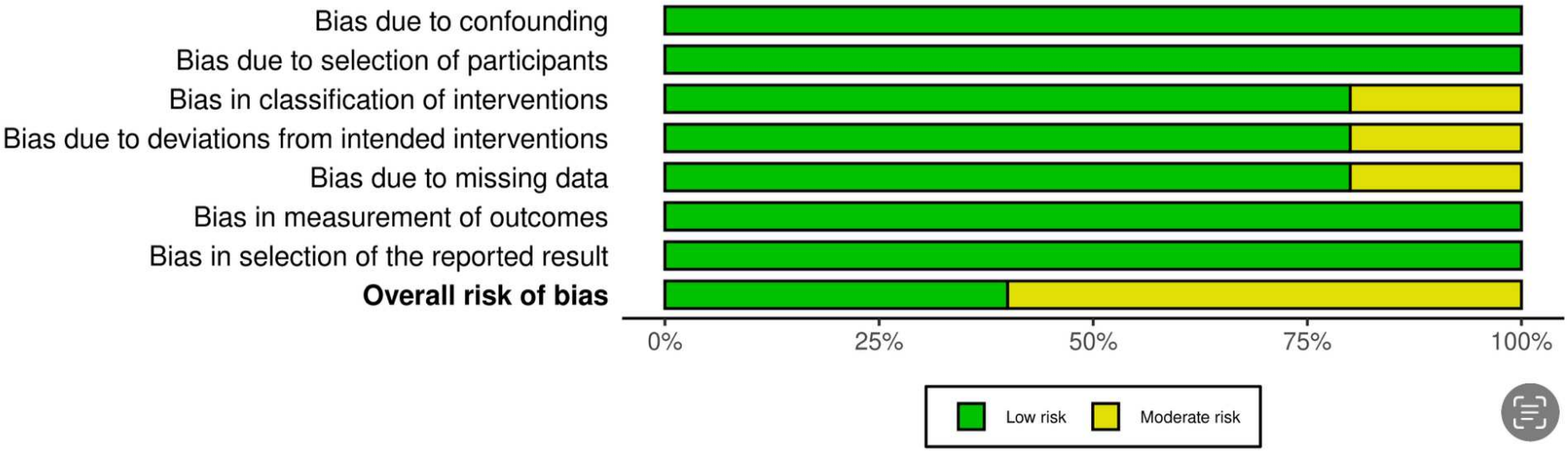
One study suggested a reduction in *Streptococcus mutans,* a cariogenic bacterium, during hydrogen peroxide bleaching, but this level returned to normal after 30 days (Briso *et al*., 2018).

3.10 Risk of bias analysis

Our thesis contains 5 studies using the ROBIN-I tool, 37 using the RoB 2 tool and 7 using the QUIN tool.

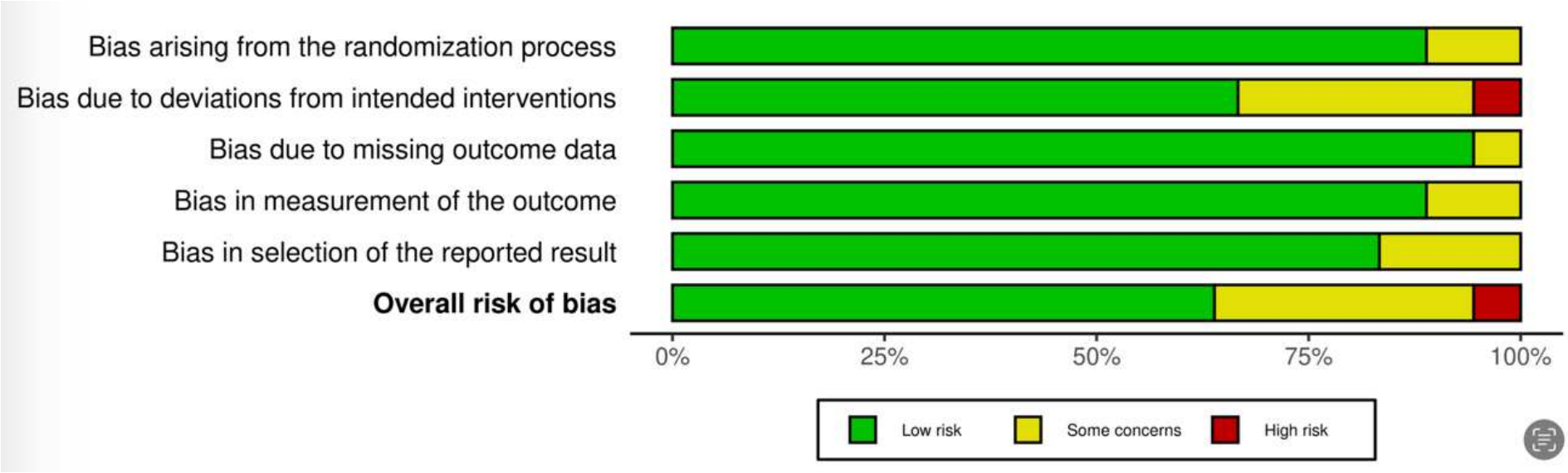
ROBIN-I results:

Table VIII - Summary plot ROBIN-I



RoB 2 results:

Table IX - Summary plot RoB 2



Quin Tool results:

Table X - First Summary Quin Tool results risk of biais for in vitro studies

Autor, Date	Clearly stated aims/ objectives	Detailed explanationn of sample size calculation	Details explanation of sampling technique	Details of comparison group	Detailed explanation of methodology
Leite, 2023	Low risk	High risk	Low risk	Low risk	Low risk
Surmelioglu, 2020	Low risk	High risk	Low risk	Medium risk	Low risk
Zhao, 2023	Low risk	High risk	Low risk	Low risk	Low risk
Surmelioglu, 2021	Low risk	Low risk	High risk	Medium risk	Low risk

Surmelioglu, 2021	Low risk	Low risk	Low risk	Low risk	Low risk
Surmelioglu, 2020	Low risk	High risk	Low risk	Low risk	Low risk
Piknjac Amar, 2020	Low risk	High risk	Low risk	Low risk	Low risk

Table XI - Second Summary Quin Tool results risk of biais for in vitro studies

Autor, Date	Operator details	Randomization	Method of measurement of outcome	Outcome assessor details	Blinding	Statistical analysis	Presentation of results	Score	Biais evaluation
Leite, 2023	Low risk	Low risk	Low risk	Low risk	Medium risk	Low risk	Low risk	21	Low risk
Surmelioglu, 2020	Low risk	Low risk	Low risk	Low risk	Medium risk	Low risk	Low risk	20	Low risk
Zhao, 2023	High risk	High risk	Low risk	Medium risk	High risk	Low risk	Low risk	15	Medium risk
Surmelioglu, 2021	High risk	High risk	Low risk	Medium risk	High risk	Low risk	Low risk	13	Medium risk
Surmelioglu, 2021	Low risk	High risk	Low risk	Medium risk	High risk	Low risk	Low risk	20	Low risk
Surmelioglu, 2020	Low risk	Medium risk	Low risk	Medium risk	High risk	Low risk	Low risk	18	Low risk
Piknjac Amar, 2020	Low risk	Medium risk	Low risk	Low risk	Medium risk	Low risk	Low risk	20	Low risk

Of all the studies selected, only two have a "high risk of bias". All the other studies, according to their tool, are classified as "low or moderate risk of bias". Thus, all of our studies tend to have relatively low risks of bias, which reinforces the credibility and reliability of their conclusions. It is essential to note that even studies classified with a moderate risk of bias require critical analysis when interpreting the results, as even a moderate bias can significantly influence the results.

IV. DISCUSSION

This discussion aims to analyse the results obtained within the framework of this dental thesis, identify the study's strengths and limitations and suggest future research prospects in this area.

A systematic analysis of the 49 studies included in this thesis reveals several noteworthy trends regarding the efficacy and safety of tooth bleaching. Nevertheless, despite the clear efficacy of most of the systems employed, there are numerous contradictions in the conclusions and results of the different studies. Therefore, It is essential to interpret this thesis's results with caution and to take these methodological and clinical limitations into account. Acknowledging the heterogeneity of the results observed across the different studies is crucial.

4.1 Effectiveness of tooth bleaching

For most studies, tooth bleaching shows significant results. However, not all studies reach the same conclusions. Several factors can explain this variability:

- Methodology used: Bleaching protocols, colour measurement instruments, and efficacy assessment criteria may differ from one study to another.

- Patient characteristics: Age, initial tooth colour, tooth sensitivity, and oral hygiene habits can influence teeth bleaching results.

- Quality of bleaching products: The exact composition and stability of bleaching agents can vary from one test to another.

Despite rigorous data processing, it is challenging to guarantee that each protocol has been applied with the same rigour in all studies. This variation considerably influences the results, especially when the studies use similar protocols. Our studies generally acknowledge that a more concentrated product produces better bleaching results. Nevertheless, other studies included in our systematic review also indicate that less concentrated products can be just as effective. These two observations are consistent with another study by Maran, who, during a systematic review and meta-analysis, found that more concentrated dental bleaching achieved better results with certain measurement tools, while others found no significant difference (Maran, 2020). Although there is a common belief that the higher the bleaching agent's

concentration, the higher is the bleaching efficacy, this may be valid only to a certain extent. As observed by Mera-Serrano *et al*. (Mera-Serrano *et al*., 2016), the rate of chemical reactions may be accelerated by increasing the concentration of reactants, as this increases the number of collisions between reactants per unit time. Nevertheless, numerous reactions are intricate due to the existence of molecules in disparate phases, such as the solid dental structure and the liquid whitening agent, as elucidated by Maran (2020).

It is evident that the dosage exerts a significant influence on the results. However, the protocol, which encompasses the frequency and duration of application, is equally crucial. Studies have demonstrated that a less concentrated product, when applied over a prolonged period of time, can produce comparable or superior results to a more concentrated product. Similarly, the results indicate that bleaching is more effective when applied over a prolonged period of time, up to a certain limit where the tooth reaches its maximum bleaching potential.

Finally, it seems that fragmenting the bleaching protocol (for example, dividing the treatment into two or three 15-minute sessions instead of a single 45-minute session) does not significantly improve the effectiveness of bleaching.

4.2 Tooth sensitivity: a side effect not to be overlooked

Although the effectiveness of tooth bleaching is generally proven, it is important not to overlook the potential side effects, especially tooth sensitivity. The prevalence of this side effect varies according to the studies, but it can affect a large percentage of patients.

Most studies indicate that a higher concentration of the substance in question is associated with an increased risk of inducing increased tooth sensitivity. Furthermore, numerous studies have identified the duration of treatment as a key factor contributing to increased tooth sensitivity. The majority of studies, regardless of the application method (whether in-office, at home, or even combined), demonstrate a time/concentration relationship influencing sensitivity. This is consistent with the observations and conclusions of Maran's (2020) research.

Some additives to the whitening agent, such as violet LED light or even the addition of nano-bioactive particles, do not seem to affect the results very much. Research still needs to be carried out in several studies to understand the mechanisms in question better.

4.3 Impact on dental minerals: reassuring results but nuances to be clarified

Most of the studies included in this thesis did not observe deleterious effects of bleaching treatments on dental minerals, such as enamel hardness or surface roughness.

However, it is important to note that some studies have suggested that prolonged application durations or high concentrations of whitening agents could have a negative impact on enamel mineralisation.

Further research would be necessary to clarify the long-term impact of bleaching treatments on the health of dental hard tissues. These studies were not sufficiently in-depth regarding patient follow-up, generally not exceeding 30 days of follow-up.

4.4 Oximetry and bacterial composition: still open questions

The studies included in this thesis provide evidence of the impact of tooth bleaching on pulp oximetry and oral bacterial composition.

In some studies, a temporary decrease in the oxygen saturation of the dental pulp (SaO2) was observed after bleaching. However, this effect seems to be reversible within 30 days of the end of treatment.

The effect of bleaching on oral bacterial flora remains a matter of debate, with some studies suggesting a reduction in cariogenic bacteria while others find no significant change.

Further research is needed to understand better the mechanisms involved and confirm or refute these preliminary observations.

4.5 Limitations of the Thesis and Future Prospects

It is important to consider the limitations of this study in order to contextualise the results obtained. It is recommended that further research be conducted in order to enhance the practice of tooth bleaching. Firstly, it is paramount to conduct long-term studies with standardised protocols to assess the durability of bleaching effects and the potential for stain recurrence. The sample sizes employed in the studies examined vary considerably, which may affect the generalisability of the conclusions. The presence of two studies with a high risk of bias highlights the importance of rigorous evaluation of the methodologies employed in the

research. It is recommended that these studies be examined with caution. To enhance the quality of future research and minimise the risk of bias, it is recommended that robust research practices, such as double-blinding, randomisation and prior registration of studies, be adopted. This will help ensure that the results accurately reflect the effects studied, and not the consequence of methodological bias.

Next, exploring the effects of innovative combinations of concentrations and application times of whitening agents to optimise results while minimising side effects such as tooth sensitivity would be pertinent. Using technology, such as artificial intelligence to analyse patient preferences and reactions could also help personalise treatments precisely. In addition, a better understanding of the biological mechanisms that underpin the enamel's reaction to whitening agents would help to develop safer and more effective products. This could include studying the molecular interactions between whitening agents and dental structures to revolutionise these treatments' formulations and potential applications.

The limitations identified and the avenues for future research demonstrate a clear need to continue research in this area to improve standards of practice and increase patient satisfaction. Future research should establish an optimal balance between efficacy, safety, and patient comfort to provide tooth bleaching care that is aesthetically beneficial and safe in the long term.

Furthermore, additional research is needed to explore other aspects of tooth bleaching, such as its long-term effectiveness, its impact on periodontal health, and the development of new, more effective, safer whitening agents.

V. CONCLUSION

This thesis analyses the efficacy and safety of tooth bleaching through a systematic review of 49 studies and tries to answer **the following question**: In the teeth of adult patients, how does non-invasive professional tooth bleaching with various concentrations of whitening agents and application techniques affect the effectiveness, durability, and safety during the follow-up period?

Most studies have demonstrated the efficacy of tooth bleaching, although the outcomes of these studies have been found to vary. The outcomes of the articles are influenced by some factors, including the methodology employed, the characteristics of the patients, and the quality of the products used. It can be observed that products with a higher concentration often yield better results, although less concentrated products can also be equally effective. Furthermore, the frequency and duration of application appear to be crucial factors influencing the effectiveness of the treatment.

Tooth sensitivity is a common side effect, with higher concentrations and longer durations increasing the likelihood of this occurring. The impact of additives such as violet LED light remains inconclusive and requires further research.

The effects on dental minerals appear minimal; however, concerns about prolonged application suggest the need for long-term studies. Furthermore, the impact of these products on pulp oximetry and oral bacteria also requires further investigation.

Despite the limitations of the current evidence base, future research should prioritise the conduct of standardised long-term studies, the development of innovative product combinations, and the implementation of personalised treatments utilising advanced technology. Further research will enable the refinement of protocols, the improvement of safety, and the enhancement of patient satisfaction. This will result in a more balanced approach to efficacy and long-term dental health.

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ANNEX

Additional information on the risk of bias assessment of the articles

Table XII – Traffic light plot RoB 2

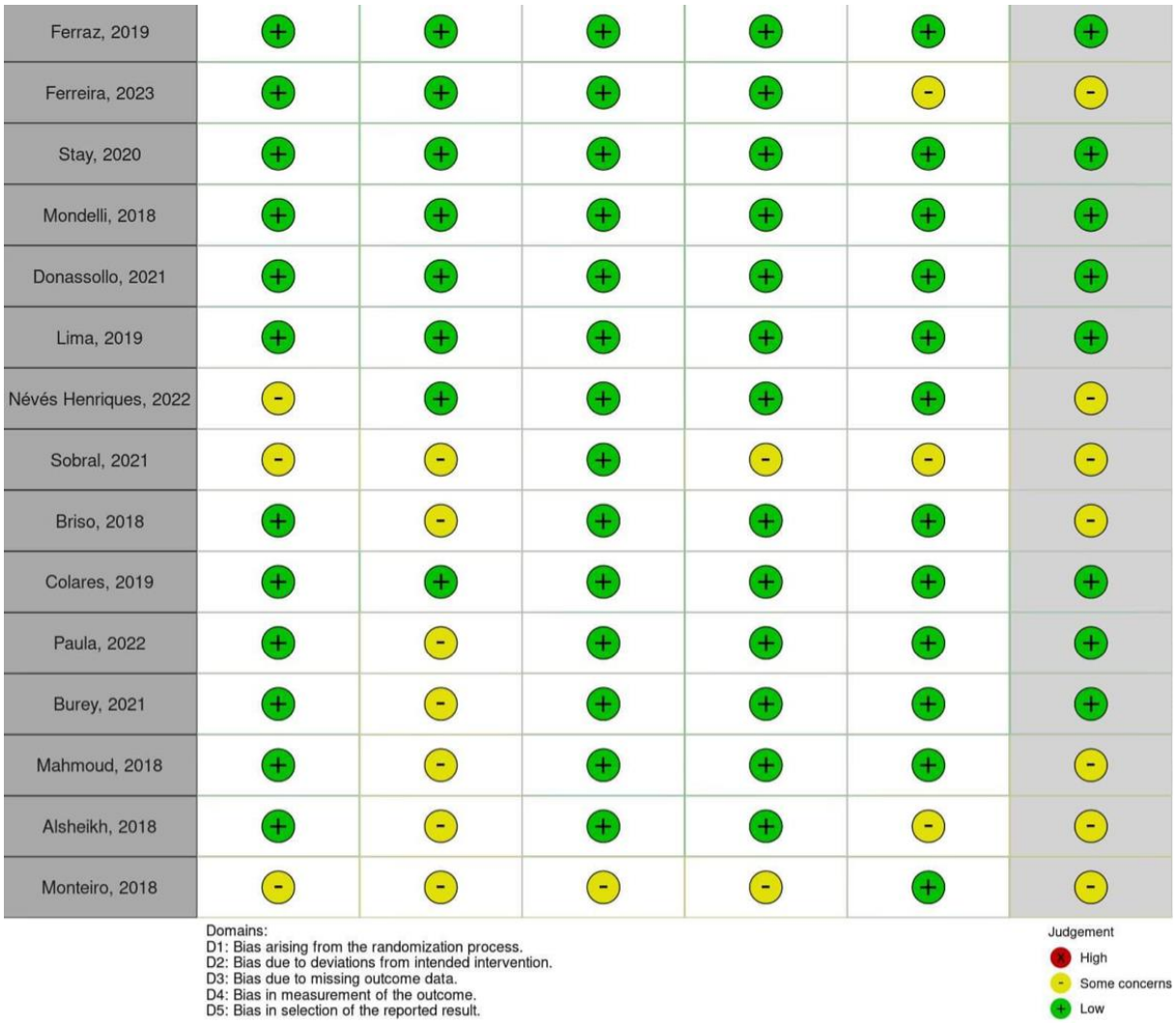
Ferraz, 2019
Ferreira, 2023
Stay, 2020
Mondelli, 2018
Donassollo, 2021
Lima, 2019
Névés Henriques, 2022
Sobral, 2021
Briso, 2018
Colares, 2019
Paula, 2022
Burey, 2021
Mahmoud, 2018
Alsheikh, 2018
Monteiro, 2018
Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.
Judgement
High
Some concerns
Low

Table XIII - Traffic light plot ROBIN-I