Efficacy of 585-595 nm Pulsed Dye Laser, 1064 nm Nd: YAG Laser and 10600 nm Fractional CO_2 Laser for Keloid Treatment: A Systematic Review

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Abstract

Keloids are pathological scars resulting from excessive abnormal wound healing and are associated with pain and itchiness. There are no recognized treatment guidelines since the etiology of keloids is yet unknown. As laser technology advances, a variety of lasers can now effectively treat keloids alongside conventional corticosteroid injection therapy. This systematic review investigates the efficacy of three laser devices in treating keloids: a 585-595 nm pulsed dye laser (PDL), a 1064 nm Nd: YAG laser, and a 10600 nm fractional CO_2 laser. We searched SCOPUS, PubMed, and the Cochrane Controlled Trials Register for pertinent publications published between January 1, 2010, and September 6, 2023.

This review comprised 21 papers (10 RCTs and 11 NRCTs), and the studies varied widely in terms of laser parameters, treatment duration, etiology, age and size of scars, skin type, scar evaluation scales, and follow-up care. The use of laser in conjunction with intralesional corticosteroids or verapamil was found to have a greater improvement in scar characteristics and higher levels of patient satisfaction compared to laser alone and other traditional methods. PDL improved scar vascularity at a higher rate than other laser types, and flexibility was the most evident scar characteristic with a fractional CO_2 laser. Fractional CO_2 laser and Nd: YAG laser treatment somehow showed recurrence, but these results had only been reported in a few studies. More research in the form of randomized trials using comparable standardized scar measures with longer follow-ups is needed to validate these findings.

Keywords**:** *Keloid Scar, Pulsed Dye Laser, Carbon Dioxide Laser, Nd: YAG Laser*

1. Introduction

When the skin's integrity is broken by an injury or intrusive operation, a wound develops, and the body tends to heal it. The four phases of the typical wound healing process include hemostasis, inflammation, proliferation, and remodeling. One type of scar that develops because of fibroproliferative disorientation during the healing process of wounds is keloids. They can expand over time to extend beyond the original site of damage and frequently recur following excision. Furthermore, large keloidal scars can cause pain, itching, and discomfort, in addition to being cosmetically deformative. The psychological and physical effects of the scars might occasionally lower a patient's quality of life (Slemp, & Kirschner, 2006).

Even after several hypotheses have been postulated, the pathophysiology of keloids is still not fully understood. As a result, there are many best ways to treat keloids, which is challenging for clinicians. Although corticosteroid injection is the most widely used and recommended course of treatment for keloid patients, its long-term application is limited by adverse effects. A variety of treatment options include adhesive tape supports, silicone-based products, pressure therapy, cryotherapy, surgical excision, radiotherapy, and laser therapy. Furthermore, newer treatments comprise intralesional bleomycin, 5-fluorouracil (5-FU), interferon, mitomycin C, botulinum toxin type A, tamoxifen, growth factors, ACE inhibitors, calcium channel blockers, light therapy, stem cell therapies, genetic, and epigenetic therapies (Ogawa et al., 2020; Ojeh et al., 2020). However, evidence-based medicine does not properly support the safety and efficacy of most treatments because there aren't enough controlled prospective studies.

In the 1980s, laser therapy was developed for the treatment of keloid lesions, and several types of lasers with different wavelengths were studied and documented (Apfelberg et al., 1984). Medical professionals have recently focused on laser treatment for keloids due to its improved results, and they are conducting research to evaluate its effectiveness compared to other available treatments. Vascular, ablative, and non-ablative lasers are now being extensively utilized (Limmer, & Glass, 2020; Manuskiatti et al., 2007; Ogawa et al., 2020). In addition, Mamalis et al. (2014) compared the results of the various laser machines

and concluded that laser therapy methods produce better patient outcomes than alternative approaches. Most of the earlier research contrasts a monotherapy regimen with combination therapy (laser plus additional therapeutic methods) but not many studies compare the efficacy and safety of different laser machines. This systematic review will evaluate the available evidence regarding the outcomes of the different laser systems to support the choice of laser treatment options for dermatologists.

2. Objectives

1) To provide dermatologists with an overview of the available information on current laser treatment options for keloid scars

2) To compare the efficacy of 585-595 nm pulsed dye laser (PDL), 1064 nm Nd: YAG laser, and 10600 nm fractional CO2 laser in treating keloids

3. Materials and Methods

3.1 Search Strategy

In September 2023, a thorough systematic evaluation of relevant literature was conducted utilizing databases such as PubMed, SCOPUS, and the Cochrane Central Register of Controlled Trials. The MeSH terms utilized were: "Lasers, Dye", "Lasers, Solid-State", "Lasers, Gas" linked with the keywords: keloid scar, carbon dioxide laser, pulsed dye laser, and Nd: YAG laser using Boolean searching (AND and OR). Field tags [tw] and [tiab] were put behind each keyword to involve the search terms in titles, abstracts, and text words. Truncation (*) was used to avoid the risk of bias due to spelling variations. Moreover, reference lists of selected papers, related studies, and review articles were reviewed to find more relevant research. Two independent reviewers conducted the search and screened the published works, then discussed any disagreements on the inclusion and exclusion of research.

The following requirements had to be fulfilled for a study to be included: (1) randomized controlled trials (RCTs), retrospective and prospective studies of laser therapy treating keloid scars using PDL, Nd: YAG laser, and fractional CO2 laser (FCL); (2) patients with keloid scars from any causes without considering age, gender, and ethnic origin; (3) these lasers being compared with a control group or other intervention or no intervention or comparing two different laser machines; (4) articles that were written in English and published after December 31, 2009. The Oxford Centre for Evidence-Based Medicine Levels of Evidence 2011 was used to evaluate each article's study quality critically. In addition, the Cochrane Collaboration's tool (RoB2) was used to assess the risk of bias in controlled clinical trials and the Newcastle-Ottawa Scale for non-randomized controlled trials.

Both reviewers performed data extraction using Microsoft Excel and cross-checked the extracted data, which covered the following aspects: each article's main author, year of publication, study design, patient demographic, scar type, size, and duration, number of participants, laser settings, treatment duration, participants lost to follow-up, duration of follow-up, and response rate according to validated scar scales, for instance; the Vancouver Scar Scale (VSS), Patient and Observer Scar Assessment Scale (POSAS), modified VSS, modified Manchester Quartile Score (MQS), Japan Scar Workshop Scar Scale, and modified Vancouver General Hospital (VGH) Burn Scar Assessment.

Significant heterogeneity in the data from the included studies precluded meta-analysis. Therefore, each study's characteristics were integrated into a comprehensive table (see Table 1), and a discussion and overview of the findings were featured in the text.

Table 1 Characteristics of included studies

Author	Study Location	Scar type	No. of Participants (n)	Age (years)	M, F	Intervention	Follow-up period	Quality of evidence
SB Cho (2010)	Korea	HTS & Keloid	12	23.8	10, 2	1064 nm Q - switch Nd: YAG laser alone	3 months	Level 3
Madan V (2011)	UK	Keloid	99	NR	41, 58	1: 595 nm PDL alone 2: 595 nm PDL in conjunction with IL TAC (10 mg or 40 mg/ml)	6 months	Level 4
Satoshi Akaishi (2012)	Japan	HTS & Keloid	22	34.95	4 , 18	LP - Nd: YAG laser followed by topical steroid (betamethasone butyrate propionate or clobetasol propionate ointment)	NR	Level 3
Qiaorong Yang (2012)	China	Keloid	26	26.35 ± 6.50	12, 14	595 nm PDL alone	3 weeks	Level 2
Anthony Rossi (2013)	US	Keloid	44	31.00 (8.34) for laser, 31.93 (12.74) for Laser + IL TAC, 38.06 (11.96) for IL TAC	NR	1:1064 nm Nd: YAG laser only 2:1064 nm Nd: YAG laser + IL TAC 3:IL TAC 10 mg/cc, total volume of 3 cc per session	NR	Level 3
Sachiko Koike (2014)	Japan	HTS & Keloid	102	34.8	23, 79	LP - Nd: YAG laser alone	6 months	Level 3
Al-Mohamady A.E (2016)	Egypt	HTS & Keloid	28	22.6 ± 8.1	9, 11	1: 595 nm PDL alone 2:1064 nm LP - Nd: YAG laser	1 month	Level 2
O. A. Azzam (2016)	Egypt	HTS & Keloid	30	31.4 ± 11.1 (keloid group) 24.5 ± 9.4 (HTS group)	15, 15	10600 nm fractional CO_2 laser	6 months	Level 2
Xiao-E Chen (2017)	China	Keloid	69	26.7± 7.5	NR	1: IL Diprospan 2: IL Diprospan 1 ml + 5-FU 0.5 ml	NR	Level 2

Author	Study Location	Scar type	No. of Participants (n)	Age (years)	M, F	Intervention	Follow-up period	Quality of evidence
						3: IL Diprospan 1 ml + 5-FU 0.5 ml + 1064 nm Nd: YAG alone		
Sunil Srivastava (2018)	India	Keloid	60	12-50	29, 31	1: Fractional CO_2 laser alone 2: IL 2 ml of TAC (40 mg/ml) 3: IL 2 ml of Verapamil (2.5 mg/ml)	NR	Level 2
Sajin Alexander (2019)	India	HTS & Keloid	50	>18	38 , 12	1: Fractional CO_2 laser therapy followed by IL TAC 10 mg/ml 2: IL TAC alone	1 month	Level 3
Shereen O. Tawfic (2020)	Egypt	HTS & Keloid	30	25.97 ± 9.32	8, 22	1: Fractional CO_2 laser alone 2: LP - Nd: YAG laser alone 3: Fractional CO_2 laser followed by Nd: YAG laser after half an hour	1 month	Level 2
Chi Xu (2020)	China	Keloid	21	17-51	9, 12	585 nm PDL followed by 1064 nm Nd: YAG laser (dual wavelength laser)	1 month	Level 3
Nadia H. Sahib (2020)	Iraq	HTS & Keloid	22	14-37	13, 9	1: Fractional CO_2 laser followed by IL TAC 2: IL TAC alone	4 months	Level 2
Jue Wang (2020)	China	Refractory keloids	41	27.4	20, 21	Ultrapulse fractional CO_2 laser followed by application of topical TAC (40 mg/ml) occluded under a transparent film dressing for 4 hours	24 months	Level 3
Fathia M. Khattab (2020)	Egypt	Keloid	40	18-70	20, 20	1: 595 nm PDL followed by IL Verapamil 2: IL Verapamil 2.5 mg/ml	6 months	Level 3
Heba Ramadan (2021)	Egypt	HTS & Keloid	40	27.35 ± 8.46 in Nd: YAG laser followed by IL Bleomycin and 28.40 ± 9.79 in Nd: YAG laser alone group	NR	1: Nd: YAG laser + IL Bleomycin 0.1 ml (blenoxane vial) (1.5 IU/ml) 2: Nd: YAG laser alone	6 months	Level 2

Author	Study Location	Scar type	No. of Participants (n)	Age (years)	M, F	Intervention	Follow-up period	Quality of evidence
Nabeel K. Alhamzawi (2021)	Iraq	Keloid	22	24.25 ± 9.49	14, 10	Fractional CO_2 laser followed by 5-FU injection	NR	Level 3
Mona Soliman (2021)	Egypt	Keloid	45	30.5 ± 6.8	20, 25	1: Fractional CO_2 laser only 2: LP - Nd: YAG laser only 3: FCL followed by LP - Nd: YAG with a 15-minute interval	2 months	Level 2
Niti Tawaranurak (2022)	Thailand	Keloid	22	44.8 ± 19.9 (Laser + topical TAC), 42.6 ± 18.3 (IL TAC alone)	8, 14	1: FCL followed by TAC applied over the scar immediately & occluded under a transparent film dressing for 30 minutes 2: IL TAC alone (40 mg/cm³) diluted (1:1) with 1% xylocaine + adrenaline (1:200000)	1 year	Level 2
El-Hamid El-Azhary EA (2022)	Egypt	Keloid	45	33.69 ± 11.02	21, 24	1: FCL alone 2: FCL followed immediately by TAC at a dose of 0.25 ml/cm³ for keloid < 3 cm and 0.5 ml/cm³ for keloid > 3 cm then occluded using transparent film dressings for 3 hours 3: FCL followed immediately by TCA 20% application then occluded for 3 hours	2 months	Level 3

HTS hypertrophic scar, IL TAC intralesional triamcinolone acetonide, PDL pulsed dye laser, 5-FU 5-fluorouracil, LP Nd: YAG long pulsed neodymium-doped yttrium aluminum garnet, FCL fractional carbon dioxide laser, TCA trichloroacetic acid, NR not reported, M male, F female

4. Results and Discussion

4.1 Results

Searches done in the databases yielded a total of 1375 articles (PubMed = 1058, Scopus = 263, and Cochrane = 54), and 794 citations remained after removing duplicates and studies before January 2010. There were 244 studies left after the title screening. Following the abstract screening, 100 publications were selected for full text retrieval, and underwent an in-depth review. However, four reports could not be retrieved and two reports were ongoing trials (ChiCTR2300071347, 2023; TCTR20230304002, 2023); and then 73 studies were excluded for various reasons. Figure 1 summarizes the detailed record of the selection of included and excluded studies.

A total of 21 studies are included in this systematic review, 10 RCTs and 11 prospective and retrospective studies. A total of 872 participants were included, with an age range of 5-70 years, and most of the study participants were female. All skin phototypes were included. Almost all studies reported adverse reactions such as pain, hypo/hyperpigmentation, erythema, edema, discharge, telangiectasia, ulceration, skin dystrophy, lipodystrophy, purpura, and blisters. There had only been four studies that provided data on loss to follow-up (Al-Mohamady et al., 2016; Azzam et al., 2016; Chen et al., 2017; Wang et al., 2020).

Of the 11 RCTs, six trials reported simple randomization methods such as sealed envelopes, flipping coins, or research randomization programs available on the internet (www.randomizer.org). Four trials did not describe the method of random allocation. No allocation concealment was adopted in any trials. All trials were assessor-blinded only. Seventeen studies included a follow-up period that lasted from 4 weeks to 2 years. Recurrent rates were reported only in four studies, two from Nd: YAG laser and two from fractional CO_2 laser studies.

585-595 nm Pulsed Dye Laser (PDL)

Five studies regarding PDL are included in this systematic review, comparing PDL with Nd: YAG laser (Al-Mohamady et al., 2016), PDL with PDL + IL triamcinolone acetonide (TAC) (Madan et al., 2011), PDL + IL Verapamil with IL Verapamil (Khattab et al., 2020), PDL with no treatment (Yang et al., 2012), and PDL + Nd: YAG laser (Xu et al., 2021). Three trials (Al-Mohamady et al., 2016; Xu et al., 2021; Yang et al., 2012) reported a statistically significant decline in VSS scores, and there were improvements in scar texture, redness, vascularity, pliability, and height, as well as relief of itchiness. In a retrospective case series comparing PDL with PDL + IL triamcinolone acetonide, the outcomes were measured by a satisfaction questionnaire, and 76% rated moderate to excellent results, with the most improvement was seen in thickness followed by relief in pruritus and redness. Khattab et al. (2020) reported that a combination of PDL and IL Verapamil significantly improved the vascularity of the scar and reduced the height and pliability; >50% improvement in overall appearance, dyschromia, and the degree of hypertrophy was seen with the modified Manchester Quartile Score (MQS). Moreover, patient satisfaction was the highest in combination treatment. According to these results, PDL mainly improves the scar's redness, height, and pliability. The relief of the itchiness is unclear whether due to the PDL or the combination of therapies.

1064 nm Nd: YAG Laser

All six studies included in this review used various outcome measures. In the mVSS tests done by Ramadan et al. (2021), the Nd: YAG + IL Bleomycin group had significantly different vascularity, pigmentation, pliability, height, and itchiness compared to the Nd: YAG alone group. In Chen et al. (2017) research, improvement was rated highest by patients in the laser + IL Diprospan + 5-FU group by 78% and lowest in IL Diprospan alone by 20%. According to observer evaluation, the laser + IL Diprospan + 5-FU group scored 69%, and IL Diprospan alone scored 12%. Erythema, toughness, and pruritus scores were statistically significant among all study groups ($P < 0.05$). Rossi et al. (2013) assessed clinical improvement in scars with a grading system and found that the greatest outcome was seen in the Nd: YAG + IL triamcinolone combined group, with all patients showing >75% reduction in erythema and thickness, where moderate change was seen in Nd: YAG laser alone group. Patients' quality of life was said to be improved in these two groups. One trial studied Nd: YAG + topical corticosteroid and stated that significant improvement was seen in all parameters (erythema, hypertrophy, hardness, itching, and pain), and the average total scar

assessment score fell from 9.86 to 6.34 after irradiation. There was a remarkable improvement in the itchiness score (Akaishi et al., 2012).

Koike et al. (2014) and Cho et al. (2010) performed retrospective studies on Nd: YAG laser alone treatment in hypertrophic scars and keloids using the Japan Scar Workshop Scar Scale and modified VGH burn scar assessment, respectively. Koike reported that the overall score was considerably reduced in both keloids and hypertrophic scars, but the latter became a more mature scar. According to Cho et al., the VGH scale decreased from 8 to 6 ($P < 0.0001$), and the greatest change was experienced in flexibility where height was the least improved. Most of the patients were satisfied with the result, which was said to be influenced by pigmentation and vascularity. The improvement of vascularity, pliability, and itchiness was mainly seen in laser combined with other treatment therapies, and patient satisfaction was seen to be higher in the combination treatment group. However, Nd: YAG laser was said to be better in hypertrophic scars than keloids, which contrasted with Akaishi, who said improving keloids was better than hypertrophic scars (Akaishi et al., 2012).

10600 nm Fractional CO_2 Laser

Azzam et al. (2016) indicated that the significant reduction in VSS score by fractional CO_2 laser treatment alone was mainly due to pliability, and pain and pruritus were said to be relieved after the treatment. However, most patients were poorly satisfied with the result. In another trial (Srivastava et al., 2019), the patients in all treatment groups (FCL vs. IL Triamcinolone vs. IL Verapamil) reported a reduction in height, vascularity, pliability, pain, and itching during each follow-up evaluation in all three groups, except pigmentation, which persisted in all of the treatment groups. There was no report on whether the three different treatments were statistically significant or not. Tawfic et al. (2020) compared FCL, Nd: YAG, and FCL + Nd: YAG, and there was a significant improvement in both VSS and POSAS in all three treatments, and pliability was the greatest improvement among scar characteristics. No significant difference among the three treatments was seen. However, they reported that FCL had better results with hypertrophic scars, and both FCL and Nd: YAG lasers had comparable results in keloids.

On the other hand, El-Hamid El-Azhary et al. (2022) compared FCL, FCL + IL triamcinolone, and FCL + 20% trichloroacetic acid (TCA) application and stated there was a statistically significant reduction in VSS of each group ($P < 0.001$) and the largest reduction was seen in FCL + IL triamcinolone group followed by FCL alone where minor reduction was seen with FCL + 20% trichloroacetic acid. Patient satisfaction score was highest in FCL alone and FCL + IL triamcinolone group. Alhamzawi (2021) performed research with FCL + IL 5-FU on 44 keloids and resulted in a significant reduction of VSS scores, which was more pronounced in pliability and height associated with a reduction in itchiness. The majority of patients responded with excellent results, and the study highlighted those keloids of < 3 years duration had more satisfactory responses. Tawaranurak et al. conducted a randomized controlled trial on 22 patients with keloid where the outcomes of FCL + topical triamcinolone and IL triamcinolone were compared. There was a marked reduction in the mean VSS score, but no significant difference was seen between the two groups ($P = 1.000$). Mean scar volume was significantly decreased in both groups ($P < 0.001$). Even though the VAS (visual analog scale) score was higher in the IL triamcinolone group, recurrence seemed to be higher in this treatment population.

Soliman et al. (2021) compared FCL, Nd: YAG, and FCL + Nd: YAG showing that FCL combination with Nd: YAG had the greatest improvement both in POSAS and patient satisfaction level which was followed by FCL alone group. This study also stated that FCL + Nd: YAG worked better together to control keloids than the laser alone therapy. Wang et al. (2020) treated 41 patients with refractory keloids by using FCL and topical triamcinolone and stated that all components of POSAS declined with the most significant decreases in pain, itchiness, thickness, stiffness, pliability, and color (all $P < 0.05$).

There were two studies where hypertrophic scars and keloids were treated with FCL + IL triamcinolone in one group and IL triamcinolone only in another group. The outcomes were measured by modified MQS in one study (Alexander et al., 2019), and measured by overall average improvement score including hypertrophy, texture, and color improvement using a 4-point scale in another study (Sahib et al., 2020). In Alexander's comparative study, there was a statistically significant decrease in length ($P = 0.025$)

and height (P = 0.003) of scars and no improvement in breadth (P = 0.902). Compared to the IL triamcinolone only group, the FCL + IL triamcinolone group exhibited statistically significant improvements in each of the four modified MQS parameters. Moreover, statistical analysis revealed that the FCL + IL triamcinolone group had higher patient satisfaction than the IL triamcinolone group (P = 0.003). Sahib reported that texture and hypertrophy were improved in their treatment, and the overall improvement score in combination therapy was 2.8 out of 3 and the dyschromia improvement score in IL corticosteroid alone was 2.2 out of 3.

4.2 Discussion

In this systematic review, the efficacy of 585-595 nm pulsed dye laser (PDL), 1064 nm Nd: YAG laser, and 10600 nm fractional CO_2 laser in treating keloid scars was studied, and it was found that all three lasers are safe and effective in treating keloid scars, especially in combination with other therapies. Based on 21 included studies, a combination of laser and intralesional corticosteroid/verapamil/bleomycin/ 5-FU is more effective than laser alone or topical corticosteroid treatments in terms of statistical reduction in scar characteristics on VSS, POSAS, and other validated scar scales. The optimum strategy for achieving the intended overall outcome of scar reduction is probably a multimodal approach to scar rehabilitation.

All three lasers improved the scar characteristics, particularly pliability and vascularity, with a high patient satisfaction rate. In terms of vascularity, the improvement rate from PDL was slightly greater than that of other lasers, where pliability was the most prominent category to improve with a fractional CO_2 laser. Al Mohamady and Koike stated that Nd: YAG laser was more effective in hypertrophic scars when compared to keloids. On the other hand, Akaishi found that Nd: YAG lasers performed better in treating keloids, which might be due to the combined action of topical corticosteroids. Since no trials were conducted comparing these three lasers, it was difficult to conclude which laser was superior in improving scar pliability. Pain and itchiness were reduced by all three lasers. When injectable treatment alone showed low satisfaction, the majority of patients were content with both combination therapy and laser alone therapy.

The studies included in this review stated that most of the side effects were tolerable and transient, subsiding after a week. Tawfic mentioned that using two lasers in the same session did not significantly increase benefits in addition to having a greater side effect profile.

While this study provided comprehensive coverage of the efficacy of three different lasers in treating keloid; there were several research limitations. A statistical meta-analysis comparing treatment methods was not possible due to heterogeneity in laser therapy regimens, and the scar assessment used by researchers also differed significantly from trial to trial. Moreover, all trials had brief follow-up periods. Therefore, greater sample sizes and longer follow-up periods are needed to identify possible clinical outcome variations and risks.

5. Conclusion

When comparing treatment categories, the combination of laser and intralesional therapy was most likely to provide notable changes when compared to laser alone or injection monotherapy. All three laser types showed great improvement in scar scores, especially in scar pliability and vascularity. Recurrence was higher in Nd: YAG laser, but this needed to be studied with a longer follow-up period to support this statement. In terms of side effects, all three lasers had tolerable, minor side effects. It is essential to keep developing treatment plans to meet the challenge of scar rehabilitation.

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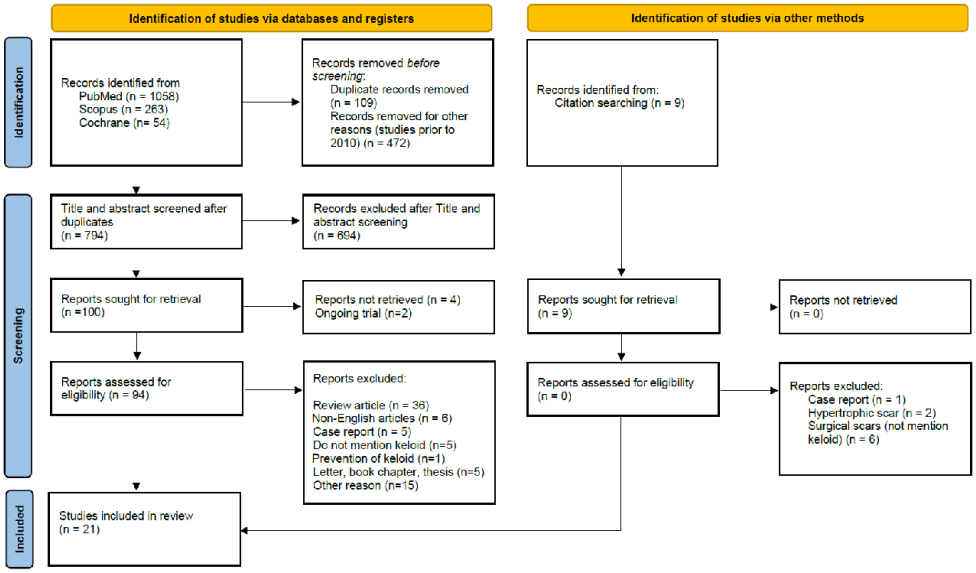

Figure 1 A PRISMA flow diagram describing the selection process of the studies included in this research

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