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8 **Systematic review of single and combined treatments for different**
9 **types of striae:**10 **A comparison of striae treatments**11 **Running title: A systematic review of different therapies for all types of striae**

12

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57 **Abstract**

58 Striae Distensae (SD) or stretch marks are among the most common forms of atrophic scarring and
59 cosmetic problems, especially in women, that negatively affect quality of life. The main causes of SD
60 vary widely, but the most significant ones include obesity, pregnancy, high corticosteroid levels, weight
61 changes, endocrine disorders and genetic predispositions. Various modalities are available for the
62 treatment of SD; however, there is still no gold standard therapy for this condition. Given the many
63 questions concerning the preferred therapeutic modalities for SD or their overall cost-effectiveness, this
64 comprehensive systematic review discusses the most prevalent, recent and promising therapies for SD in
65 three main categories, including single therapy, therapeutic comparisons and combination therapy. A
66 systematic search was carried out in Medline, Scopus, Web of Science and Google Scholar for original
67 articles published on the treatment of SD by May 20, 2019. One hundred articles were reviewed and
68 divided into three categories. In the single therapy category, we found that laser and other light-based
69 devices and topical treatments are the most commonly-applied interventions. In the therapeutic
70 comparison category, we found that most of the common therapeutic modalities are equally effective and

71 there is no significant difference between them in side-effects and treatment duration. In the combination
72 therapy category, we found that the combination of two or more modalities is usually better than using
73 each one alone.

74 **Keywords:** Striae, Stretch Marks, Striae Alba, Striae Rubra, Striae Gravidarum, Striae Distensae, Scar, Atrophic
75 Scar, Treatment Modalities, Systematic Review, Single Therapy, Comparative Therapy, Combination Therapy,
76 Light, Laser, CO₂ Laser, IPL, Micro-needling, Needling, Abrasion Therapy, Topical Therapy, Radiofrequency, RF,
77 Platelet-Rich Plasma, PRP, Phototherapy, Tretinoin, Chemical Peeling, Peeling

78 **Abbreviations:** SD: Striae Distensae, CO₂ FS: Carbon Dioxide Fractional Laser Systems, IPL: Intense Pulsed Light,
79 Nd-Yag: Neodymium-Doped YAG Laser, PDL: Pulsed Dye Laser, RF: Radiofrequency, GCA: Glycolic Acid, TCA:
80 Trichloroacetic Acid, RCT: Randomized Controlled Clinical Trial, DLQI: Dermatology Life Quality Index, PRP:
81 Platelet-Rich Plasma, GAIS: Global Aesthetic Improvement Scale, DIS: Dermatologist Assessed Improvement
82 Scale, NM: Not Mentioned in References, PIH: Post-Inflammatory Hyperpigmentation, POSAS: Patient and
83 Observer Scar Assessment Scale, RCM: Reflectance Confocal Microscopy, TPI:
84 Transcutaneous Pneumatic Injection, DTS: Disk microneedle Therapy System, VAS: Visual Analogue Scale

85

86 Introduction

87 **Rationale:** Striae Distensae (SD), striae or stretch marks are one of the most common cosmetic
88 problems caused by the loss of collagen and elastin fibers in the dermis (1). Owing to its
89 aesthetic impact, this atrophic scarring can cause depression and psychological problems in
90 patients and affect their quality of life (2-4). With a prevalence of 11%-88% in the general
91 public, SD is more common in women. These scars are categorized into different types. Striae
92 rubrae are the early type of striae, presenting as erythematous to violaceous color lesions (4).
93 Striae rubrae lesions gradually become hypopigmented and atrophic due to reduced melanization
94 and turn into striae albae, appearing as white lines (4). Striae caerulea present as blue lines in
95 darker skins (5). Striae nigrae also appear in darker skins but have more melanin pigments and
96 appear as black lines (5). Striae gravidarum appear as red or violet lines, often on the abdomen
97 and breast skin of pregnant women due to mechanical stress on the skin and hormonal changes
98 (5).

99 SD have three main causes. First, they might develop during rapid weight changes, such as in
100 pregnancy, which is known as the most common cause of striae gravidarum (6), or during
101 adolescence as pubertal growth spurt (2). Second, they can appear when steroid levels increase.
102 Lastly, they can occur in patients with prolonged systemic or topical corticosteroid use, such as
103 Cushing's syndrome and Marfan syndrome (1, 2). According to literature, SD are also associated
104 with medical conditions like anorexia nervosa, typhoid fever, rheumatic fever, chronic liver
105 disease, augmentation mammoplasty, tissue expansion, tension-requiring skin sutures, organ
106 transplantation, cardiac surgery, HIV therapy, chemotherapy, tuberculosis therapy and
107 contraceptive or neuroleptic consumption (7). In addition, some environmental and genetic
108 factors, such as family history of SD, skin texture and color, malnutrition, age of pregnancy,
109 gestational age, fetal weight and gestational diabetes, can affect the incidence of SD (8).

110 In general, treating striae is difficult, especially chronic striae (9). Despite the various therapeutic
111 modalities for improving SD, there is no definitive treatment (10). The current modalities
112 improve SD by increasing fibroblast activity, collagen and fibronectin synthesis, anti-
113 inflammatory properties, skin elasticity and dermal thickness. These treatment options can

114 stimulate cell proliferation and improve skin blood perfusion and hydration (1). Since these
115 treatments only provide partial improvement, examining their effectiveness and possible side-
116 effects can help physicians choose the most effective treatment for patients.

117 **Objectives:** A comprehensive literature review to provide a critical analysis on which modality
118 is best for striae single therapy and examine the advantages of each modality and compare their
119 efficacy, costs and safety.

120 **Methods**

121 **Protocol and registration**

122 We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
123 statement.

124 **Information sources**

125 A search was carried out in Medline (PubMed) (<http://ncbi.nlm.nih.gov/pubmed>), Scopus
126 (<http://www.scopus.com>), Web of Science (<http://webofknowledge.com>) and Google Scholar
127 (<https://scholar.google.com>) for articles published by May 20, 2019, and all the English articles
128 on therapeutic modalities for SD were included.

129 **Search strategy**

130 The search keywords included "Striae Distensae" OR "Stretch Marks" OR "Striae Alba" OR
131 "Striae Rubra" OR "Striae Gravidarum" AND "Treatments" OR "Therapeutic" OR "Therapy"
132 OR "Treatment Outcome" OR "Treatment Failure" OR "Drug Therapy" OR "Radiotherapy" OR
133 "Surgery". There were no other limitations or filters. All the articles retrieved from PubMed,
134 Scopus and Web of Science were included; as for Google Scholar, only the 50 newest articles
135 were selected from a total of 4240 articles. All the articles published by 20 May 2019 were
136 included for data screening.

137 **Eligibility criteria**

138 For answering the first main question of this systematic review (i.e., What is the best single
139 therapy option?), all the articles that (1) Used only one therapeutic modality for SD and (2)
140 Reported the treatment outcomes and adverse effects, were selected for full-text screening. To
141 evaluate the advantages and disadvantages of each modality, all the studies comparing the results
142 of at least two different therapeutic modalities were included in the next phase. To assess the
143 effectiveness and safety of the combination therapies, all the articles that used a combination of
144 two or more treatment modalities and reported their results and adverse effects were accepted for
145 full-text screening. Only the English articles were included, while animal studies, in-vitro
146 studies, studies on preventive measures, review articles, case reports and studies on other types
147 of atrophic scars were excluded.

148 **Data collection**

149 Endnote® X8 (Clarivate Analytics, Philadelphia, USA) was used for study screening and data
150 extraction. In the first phase, from July 2 to August 23, 2019, two independent reviewers
151 screened and categorized all the extracted articles based on their titles and abstracts. Any

152 conflicts were resolved by consulting a third reviewer. In the second phase, full-text screening
153 was performed by all authors and the useful data of the articles were extracted.

154 **Results**

155 A total of 629 articles were retrieved, and after removing the 143 duplicates, 486 remained for
156 the title/abstract screening phase. Finally, a full-text screening was performed and 100 eligible
157 articles remained for data extraction. All these articles were reviewed and their extracted
158 information are separately shown in Tables 1 to 14 of Supplement 2 (T1-14, S2). Given the
159 impossibility of showing the entire retrieved data in this article, we included only three tables in
160 the main body of this manuscript, but the complete version of the data is available for review in
161 supplementary files. Based on our eligibility criteria, 57 articles were selected for the best single
162 therapy option, i.e., the single therapy category (T1, S2), 25 were selected to help identify the
163 advantages and disadvantages of each treatment modality over another, i.e., the therapeutic
164 comparison category (T2-3, S2), and 18 articles were selected for full-text review to evaluate the
165 effectiveness and safety of combination therapies, i.e., the combination therapy category (T7, 9
166 and 11, S2). The full text of these 100 articles were reviewed and any pertinent data to the main
167 research questions were extracted. The study phases (title/abstract screening and full-text review)
168 are summarized in the PRISMA flow diagram in Figure 1. To avoid giving excessive
169 information in the main article, only the data extracted from 27 studies focused on the most
170 prevalent, recent and promising therapeutic modalities and encompassing the best of the three
171 SD treatment categories are presented in the main manuscript (T1-3 in the main text).

172 The results of this comprehensive systematic review have been classified in three categories, as
173 summarized in Tables 1-3. These studies were focused on the most prevalent, recent and
174 promising therapeutic options and had the largest sample sizes and highest standards of evidence.
175 For evaluating the best single therapy options, the data from the most frequently-cited studies on
176 ablative fractional laser (often CO₂ fractional), non-ablative fractional laser, pulsed dye laser
177 (PDL), intense pulsed light (IPL), radiofrequency (RF), needling, abrasion therapies, and topical
178 therapies were extracted. For identifying the advantages and disadvantages of each treatment
179 modality (i.e., the therapeutic comparison category), the therapeutic modalities prevalently
180 discussed in the single therapy category were compared with each other. Finally, for assessing
181 the effectiveness and safety of combination therapies, the therapeutic results for using RF,
182 ablative fractional lasers (such as CO₂ and Erbium Yag), platelet-rich plasma (PRP), needling
183 and topical tretinoin were assessed in various combinations.

184

185 Insert Table 1 & Table 2

186

187 **Single therapies (T1, S2):**

188 This category contained studies investigating only one SD treatment modality; however, their
189 extracted data did not meet the criteria for meta-analyses due to differences in design, SD type
190 and outcome reporting format.

191 The category of light and laser therapies for SD had four sub-categories, including fractional
192 ablative CO₂ laser, fractional non-ablative laser, RF and other light and laser therapies. In the
193 fractional ablative CO₂ laser sub-category, the prospective studies had reported different rates of
194 improvement due to the different outcome measurement methods used; for instance, a significant
195 increase in thickness of the epidermal layer was observed by analyzing the collagen fibers and
196 epidermal thickness, but a minimal improvement was observed if the Cutaneous Resonance
197 Running Time was measured. This modality has minimal side-effects, which include swelling,
198 burning, erythema and post inflammatory hyperpigmentation (PIH). In the fractional non-
199 ablative laser sub-category, interventional studies proved that fractional photo thermolysis is an
200 effective treatment modality for all types of striae –with a potentially greater effectiveness for
201 striae albae. In general, it is a safe method with minimal side-effects, which include edema,
202 erythema, mild and transient pain and pigmentation. Based on interventional studies, 1565-nm
203 non-ablative fractional laser improves appearance, pigmentation, volume, and texture of SD and
204 is only associated with mild edema, erythema and pain as side-effects in some patients. Studies
205 on 1550-nm non-ablative fractional laser found this modality to be effective and safe for striae
206 albae and rubrae. Also, significant textural and pigment corrections were observed for this
207 modality. Likewise, edema, mild to moderate erythema, pain, itching, mild crusting, PIH and
208 mild to moderate acne were reported in some studies as the side-effects of 1550-nm non-ablative
209 fractional laser. In a randomized clinical trial, Erbium-doped non-ablative fractional laser caused
210 a significant improvement in the Dermatology Life Quality Index (DLQI) with an acceptable
211 safety profile and just a few cases of pruritus, scaling, and erythema. Both fractional and non-
212 fractional RF were effective and safe for striae albae and rubrae. They were associated with
213 transient and minimal side-effects, such as temporary rashes, ecchymosis, blister, pain, erythema,
214 edema and PIH, depending on the RF modality used. Tripollar RF seems to be the safest
215 modality, especially in the dark-skin phenotype. In the other light and laser therapies sub-
216 category, long-pulsed 1064-nm Nd:YAG showed an acceptable improvement in striae. PDL laser
217 seems to have moderate to good effectiveness in striae rubrae, but is not beneficial for striae
218 albae. IPL and low-level laser therapy showed an acceptable effect on SD, although their
219 histopathological improvement was higher than their clinical improvement. Diode 1450-nm laser
220 was not an effective modality. Excimer 308-nm laser had acceptable positive effects on scar
221 pigmentation. Side-effects were minimal and transient for these therapies.

222 Carboxytherapy seems to be an effective method of reducing stretch marks with moderate pain
223 and discomfort and hematoma in some patients. The pressure and dose-controlled transcutaneous
224 pneumatic injection of hypertonic glucose solution as mesotherapy was effective and safe for
225 treating atrophic skin disorders, such as SD, with little side-effects. Micro-needling was also safe
226 and effective and had minimal side-effects. Golden chemical peel showed clinically and
227 microscopically significant improvements in SD. Glycolic acid 70% was associated with little
228 improvement in patients. Abrasions, including derm or microderm-abrasion, are effective in the
229 treatment of striae rubrae in general. Nonetheless, microderm-abrasion is not effective for striae
230 albae. Naturally, derm-abrasion has greater side-effects. Galvano puncture and electroporation
231 demonstrated a significant improvement in striae albae without any side-effects.

232 **Therapeutic comparisons (T2-6, S2):**

233 Tables 2 and 3 compare the efficacy and safety of two or three SD treatment modalities with
234 each other qualitatively. Tables 4 and 5 present an analytical comparison of applying the

235 treatment modalities between two or three groups using mean scores and a 95% CI, and show the
236 improvement rate (usually assessed by the Dermatologist Assessed Improvement Scale (DIS),
237 Global Aesthetic Improvement Scale (GAIS) or Visual Analogue Scale (VAS)) and reduction in
238 SD surface area (usually assessed by DIS or GAIS). Table 6 summarizes comparative studies on
239 similar outcome measures (reporting the mean percentage of improvement) to enable better
240 clinical judgments. Compared to fractional CO₂ laser, some types of non-ablative fractional
241 lasers, needling, derm-abrasion and tretinoin apparently had the most optimal responses in proper
242 settings (23, 37, 38). Lasers: Fractional ablative lasers, mainly CO₂: The most prevalent and
243 seemingly effective and overall safe (with minor side-effects) modality for the treatment of SD
244 (both types), comparable to needling. Non-ablative fractional lasers: Favorable results in
245 comparison with fractional CO₂ laser. PDL and IPL are effective and safe for SD and rubrae,
246 with advantages for the rubrae type. PDL and short-pulse CO₂ laser: Not recommended for
247 darker skin tones. Microdermabrasion, dermabrasion and microneedling: Effective and safe
248 methods for SD; the efficacy of microderm-abrasion is less than the other two modalities.
249 Radiofrequency: Tripollar RF may deliver better results for striae albae. Carboxytherapy: Better
250 results for striae rubrae. PRP: Efficient treatment for striae rubrae, especially on the trunk (28).
251 Combinations: Er:YAG laser, carboxytherapy and PRP: Effective for both types of SD, but
252 Er:YAG laser is safer and more effective (39). Light therapies, especially IPL and UVB therapy,
253 are effective treatments for both striae types. Topical therapies, especially those containing
254 tretinoin, glycolic acid, L-ascorbic acid, succinylated collagen and herbal extracts, are
255 appropriate for SD treatment. Olive oil or Saj cream are not effective in preventing or improving
256 striae gravidarum (38, 40-42).

257 **Combination therapies (T7-14, S2)**

258 Tables 7 and 8 show the efficacy and safety of two different SD treatment modalities separately
259 and combined, and compare their results in groups, qualitatively and quantitatively. Outcome
260 was quantitatively defined as the patients' self-assessed scores, VAS score, decreased striae
261 surface area (usually assessed by the DIS or GAIS), 95% CI and improvement percentage
262 (usually assessed by the DIS or GAIS). Based on Table 9, the combination of two modalities is
263 usually better than using each one alone, but the efficacy of different regimens depends on the
264 types of therapies combined. For example, improvement in SD surface texture is significantly
265 greater with ablative fraction laser plus epidermal growth factor injection than with ablative
266 fraction laser plus topical aloe vera application. Also, needling is more effective than microderm-
267 abrasion plus sonophoresis. The combination of RF, micro-needling and CO₂ fractional laser is
268 an effective and safe option for SD that causes little, non-serious, early and transient side-effects
269 and may be better than applying each single therapy alone. The combination of PRP and
270 microderm-abrasion is more effective than each therapy taken separately too. Table 10 explains
271 the results of Table 9 quantitatively. Tables 11 and 12 compare the efficacy of different regimens
272 for treating SD qualitatively and quantitatively, respectively. Table 13 presents the qualitative
273 results of a five-arm clinical trial on SD. Table 14 summarizes studies reporting the same
274 outcome measures (mean percentage of improvement) to enable better clinical judgment.

275 **Discussion**

276 This review is a comprehensive analysis of different striae treatment approaches to find the most
277 efficacious therapies for each striae type (43-47). SD are one of the most common cosmetic
278 problems and most frequent subtypes of atrophic scars with various types and clinical

279 presentations that may affect different parts of the body (48). There are few systematic reviews
280 on SD treatment, and many questions remain unanswered, such as: What are the best therapeutic
281 modalities in terms of efficacy, safety, applicability, accessibility and cost-effectiveness? Based
282 on comparisons, which modalities work better? Regarding combination therapies, what are the
283 best available, effective and safe options? This systematic review study tries to answer these
284 questions.

285 **Single therapies**

286 Topical therapies and light/laser-based devices are the most common modalities used for SD (17-
287 21, 49-61). In the topical therapies category, water-in-oil creams containing Argan oil, Bio-Oil
288 and gels are effective, especially in the early phase of SD (49, 51). Tretinoin 0.025 is not
289 effective, but tretinoin 0.1% is an effective clinical treatment in the active and early stages of
290 stretch-mark development, especially pregnancy-related stretch marks (18, 50). Topical
291 medications containing herbal extracts are also effective overall. Meanwhile, cocoa butter, olive
292 oil and bitter almond oil are not effective (21, 55). Ablative CO₂ laser is the most frequently-used
293 laser therapy, yielding satisfactory results, and fractional non-ablative lasers like 1550-nm, 1565-
294 nm and Erbium-doped lasers also have positive results (2, 3, 11, 62). Both fractional and non-
295 fractional RF are effective and safe for SD treatment (12, 63-65). Long-pulsed 1064-nm
296 Nd:YAG and IPL show acceptable improvements in SD patients (61, 66). PDL laser therapy
297 shows satisfactory results only for striae rubrae, and excimer 308-nm laser is effective for
298 lightening scar pigmentation (67, 68). Meanwhile, diode 1450-nm laser is not an effective
299 modality (69).

300 **Therapeutic comparisons**

301 Although there are many comparative studies with similar outcome measures, the results
302 obtained for similar treatment modalities varied widely between the studies, which may be
303 attributed to the different types of SD examined, study designs and tools used for outcome
304 assessment. Fractional CO₂ laser as a type of non-ablative fractional laser therapy, micro-
305 needling, derm-abrasion and tretinoin seem to have the most optimal responses when used in
306 proper settings.

307 Among the different topical modalities examined, tretinoin showed the best therapeutic response
308 (27, 70) and is thus the best topical therapy for SD, although it frequently causes irritative side-
309 effects (27). Neither olive oil nor Saj cream were effective in preventing the occurrence of striae
310 gravidarum or affecting its severity (71).

311 Among the procedural methods examined, ablative fractional lasers (mainly CO₂) were the most
312 commonly-applied treatments with favorable results and a good safety profile (side-effects were
313 minimal and transient). Non-ablative fractional lasers, needling (micro-needling or RF-needling),
314 derm-abrasion, carboxytherapy and PRP are other effective and safe therapies with acceptable
315 results. Modalities such as microderm-abrasion, IPL, topical therapies (glycolic acid, L-ascorbic
316 acid, succinylated atelocollagen, and herbal extracts), phototherapy (UVB therapy, and excimer
317 laser) and Galvano puncture have an acceptable efficacy and safety as well, and while some of
318 them are popular but less effective, others are highly effective but not popular.

319

320 **Combination therapies**

321 The combination of two or more modalities is seemingly often better than applying each one
322 alone, but the efficacy of different combination regimens depends on the type of therapies
323 combined, and some powerful single therapies are even better than combined therapies
324 consisting of different modalities with lower efficacies.

325 The combination of RF and autologous PRP might have synergistic benefits and fewer side-
326 effects. Also, the combination of 2940-nm Er:YAG laser with other modalities, such as bovine
327 basic fibroblast growth factor (rb-bFGF), light-emitting diode-red light (LED-RL) and a spatially
328 modulated ablative (SMA) module, is a safe and effective treatment for SD. A regimen
329 combining ablative fractional laser and PRP-induced rapid healing after ablative resurfacing is
330 effective too. Some articles have reported promising effects for combining micro-needling with
331 other modalities. Some of these combinations have improved SD by 70%-90% (72-76). In a five-
332 arm clinical trial on the efficacy and safety of SD treatments, ablative fractional laser was an
333 effective option and the succinylated collagen site also showed clinical improvements with an
334 acceptable safety profile (77). Ablative RF with topical retinoic acid cream and low-frequency
335 acoustic pressure ultrasound has an improved therapeutic efficacy of about 75%, and this
336 regimen could lead to optimal outcomes. The combination of fractionated microneedle RF with
337 fractional CO₂ laser could also improve the final outcome by about 25% and create a 75%
338 response rate (30, 36, 77, 78). Needling also leads to better outcomes compared to some
339 combination therapies that do not use needling systems.

340 **Conclusion**

341 Despite the lack of a gold standard treatment for SD, this comprehensive systematic review on
342 the most prevalent, recent and promising therapeutic options for SD classified the results in three
343 categories. In the single therapy category, laser and other light-based devices (e.g., IPL and RF)
344 and topical treatments were the most commonly-applied interventions. In the therapeutic
345 comparison category, most therapeutic modalities were almost equally effective and there was no
346 significant difference in their side-effects and durations of treatment, and the most popular were
347 ablative and non-ablative fractional lasers, topical therapy, needling and derm-abrasion. In the
348 combination therapy category, the combination of two or more modalities was usually better than
349 applying each one alone, but the efficacy of different combination regimens depends on the type
350 of therapies combined, although some powerful single therapies proved even better than
351 combinations of therapies with lower separate efficacies. Combinations of regimens such as RF,
352 ablative fractional lasers (such as CO₂ and Erbium Yag), platelet-rich plasma (PRP), needling
353 and topical tretinoin are the most effective and popular therapies used for SD. Larger prospective
354 studies, especially randomized clinical trials with equal or comparable outcome measures, are
355 recommended for more accurate judgments of the effectiveness of different therapies for SD.

356 **Limitations**

357 The data in this systematic review did not meet the criteria for a meta-analysis, mainly due to the
358 different designs of the reviewed studies, the various types of striae examined and the diverse
359 outcome measures applied. Also, there were few placebo-controlled RCTs to be included in this
360 systematic review.

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364 **Contributors**

365 A. G., F. S. and S. S. wrote the initial draft, B. H. and H. B. methodologically appraised the study, and P. P and S.
366 M. edited the document. All the authors made extensive contributions to the final draft of this manuscript.

367
368 **Declarations of Interest**

369 We declare no competing interests.

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373
374
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576 Figure legend:

577 Figure 1: PRISMA flow diagram

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Table 1 summarizing the original studies retrieved on striae treatment modalities, category1 (single therapies)

Reference	Title	Number of patients	Gender	Study Group			Treatment Duration	Method of Measuring Improvement	Type of Striae	Adverse Effects	Summary of Results
				Group 1	Group 2	Group 3					
(2)	Treatment of striae distensae using an ablative 10,600-nm carbon dioxide fractional laser: A retrospective review of 27 participants	27	100% f	Fractional ablative CO ₂ laser	-	-	One session	Before and after photographs and participant satisfaction	Distensae	Post-therapy erythema, PIH, transient pruritus, post-treatment crusting or scaling, and oozing	CO ₂ FS can significantly affect late-stage striae distensae.
(11)	Fractionated CO ₂ laser in the treatment of striae alba in darker-skinned patients: A prospective study	30	90% f	Fractional ablative CO ₂ laser	-	-	Two sessions with four-week intervals	Cutaneous Resonance Running Time (CRR _T) was measured by a reviscometer (MPA5 multi-probe adaptor)	Alba	Erythema, burns, PIH*	The treatment of striae alba with fractional CO ₂ laser therapy led to minimal improvements and caused only mild side-effects.
(12)	An efficacy and safety of nanofractional radiofrequency for the treatment of striae alba	33	84.8% f	Radiofrequency	-	-	Three sessions with four-week intervals	Measurement of total lesion surface area (using Pictzar™ digital software)	Alba	PIH*	Non-fractional RF is highly effective and safe for treating striae alba.
(13)	Treatment of striae distensae with fractional photothermolysis	22	100% f	Fractional non-ablative laser therapy	-	-	Two sessions with four-week intervals	Before and after photographs and skin biopsy samples	Distensae	Erythema and mild pigmentation	Fractional photothermolysis may be effective in treating striae distensae; the treatment outcomes were better in the patients with white rather than red striae.
(14)	Fractional non-ablative 1540-nm laser treatment of striae distensae in Fitzpatrick skin types II to IV: clinical and histological results	51	94% f	Fractional non-ablative laser therapy	-	-	Two to four sessions with four- to six-week intervals	Skin biopsies and before and after photographs	Rubra and alba	Transient erythema and edema, PIH	Significant textural and pigment corrections were observed for a wide range of striae rubra and striae alba cases after treatment with a 1540-nm fractional non-ablative laser.
(15)	Treatment of striae distensae using needling therapy: A pilot study	16	87.5% f	Micro-Needling	-	-	Three sessions with four-week intervals	Before and after photographs, skin biopsies, and patient satisfaction using the quartile grading scale	Alba and rubra	Mild pain, erythema, and spotty bleeding	Disk microneedle therapy system (DTS) can be safely and effectively used in the treatment of striae distensae.
(16)	Treatment of striae distensae with microdermabrasion: A clinical and molecular study	20	70% f	Microdermabrasion	-	-	Five sessions with weekly intervals	Skin biopsy samples were subjected to RT-PCR for the assay of type I procollagen mRNA levels	Rubra and alba	PIH*, transient edema,	Microdermabrasion is effective in treating striae distensae and more so in striae rubra than striae alba.
(17)	A double-blind controlled clinical trial assessing the effect of topical gels on striae distensae (stretch marks): A non-invasive imaging, morphological and immunohistochemical study	20	100% f	Topical therapy (chemical)	-	-	Daily for six weeks	Skin biopsy, tissue tonometry, full-field laser perfusion imaging, Spectrum TM, Spectrophotometric Intracutaneous Analysis, and subjective assessment	Rubra and alba	Erythema	The application of gels by topical massage had a significant effect on SD.

(18)	Topical tretinoin 0.1% for pregnancy-related abdominal striae: An open-label, multicenter, prospective study	20	100% f	Topical therapy (chemical)	-	-	Daily for 12 weeks	Evaluated by the analysis of one preselected target lesion; color photographs; patients completed a questionnaire	Gravidarum	Erythema and scaling	The topical application of tretinoin significantly improved the clinical appearance of pregnancy-related stretch marks.
(19)	The effect of Aloe vera gel and sweet almond oil on striae gravidarum in nulliparous women	160	100% f	Topical therapy (natural)	-	-	Twice a day for 20 weeks	The striae diameter was measured by calipers; patient satisfaction	Gravidarum	No side-effects either in the mother or fetus	Aloe vera and sweet almond oil reduce itching in striae and prevent their progression.
(20)	Effects of olive oil on striae gravidarum in the second trimester of pregnancy	70	100% f	Topical therapy (natural)	-	-	Twice a day for eight weeks	Observational approach	Gravidarum	NM*	Olive oil had no effect on reducing or preventing striae.
(21)	The effect of bitter almond oil and massaging on striae gravidarum in primiparous women	141	100% f	Topical therapy (natural)	-	-	Daily for 12 weeks	A questionnaire and the Fitzpatrick Classification Scale (FCS) were completed	Gravidarum	Without any adverse effects	A 15-min massage with almond oil during pregnancy reduced the development of striae gravidarum; however, using bitter almond oil had no effect by itself.

*PIH: post inflammatory hyperpigmentation, *RF: radiofrequency

Table 2: summarizing the original studies retrieved on striae treatment modalities, Category 2 (therapeutics comparison)

Reference	Title	Number of patients	Gender	Study Group			Treatment Duration	Method of Measuring Improvement	Type of Striae	Adverse Effects	Summary of Results
				Group1	Group2	Group 3					
(22)	<i>Fractional CO2 laser versus intense pulsed light in treating striae distensae</i>	20	100% f	<i>Fractional CO2 laser</i>	<i>Intense pulsed light</i>	-	<i>Mod. 1: Once-monthly for five months Mod. 2: Twice-monthly for five months</i>	<i>Before and after photographs + patient satisfaction rate</i>	<i>Distensae</i>	<i>Mod. 1 & 2: Erythema, feeling of heat, pruritus and hyperpigmentation</i>	<i>Comparing both modalities showed a significant improvement in striae width in those treated with laser vs. IPL, but there was no significant difference between the study groups in the improvement in the length of striae.</i>
(23)	<i>Treatment of striae distensae with nonablative fractional laser versus ablative CO2 fractional laser: a randomized controlled trial</i>	24	100% f	<i>Fractional CO2 laser</i>	<i>Non-ablative fractional laser</i>	-	<i>Mod. 1 & 2: Three sessions with four-week intervals</i>	<i>Before and after photographs, non-invasive suction, patient satisfaction score and skin biopsies</i>	<i>Distensae</i>	<i>Mod. 1 & 2: Transient mild erythema, PIP, crust formation</i>	<i>The study suggests that both modalities may be an effective and safe treatment option for striae distensae in Asian skin.</i>
(24)	<i>Efficacy of fractional carbon dioxide laser versus microneedling in the treatment of striae distensae</i>	33	85% f	<i>Fractional CO2 laser</i>	<i>Microneedling</i>	-	<i>Mod. 1 & 2: Three sessions with four-week intervals</i>	<i>Before and after photographs, patient satisfaction and skin biopsies using the quartile grading scale for clinical improvements</i>	<i>Alba</i>	<i>Mod. 1: PIH, transient mild edema Mod. 2: Transient mild erythema, pinpoint bleeding</i>	<i>Microneedling is an effective, safe and cheap method for treating striae distensae, but fractional CO2 laser is more effective and affordable as a first line of treatment.</i>
(25)	<i>Efficacy of microneedling versus fractional non-ablative laser to treat striae alba: A randomized study</i>	20	100% f	<i>Non-ablative Fractional laser</i>	<i>Microneedling</i>	-	<i>Mod. 1 & 2: Five monthly sessions</i>	<i>Before and after photographs, skin biopsies</i>	<i>Alba</i>	<i>Mod. 1: Erythema pruritus + crusting + hyper-pigmentation and post-procedure pain Mod. 2: Erythema and pruritus</i>	<i>Both modalities are effective, well-tolerated and comparable in treating SA.</i>
(26)	<i>Clinical and immunohistochemical comparative study of the efficacy of carboxytherapy vs platelet-rich plasma in treatment of stretch marks</i>	20	70% f	<i>Carboxytherapy</i>	<i>Platelet-rich plasma</i>	-	<i>Mod. 1 & 2: Four sessions with three- to four-week intervals</i>	<i>Clinical photographs, skin biopsies using the quartile grading scale for clinical improvements</i>	<i>Alba</i>	<i>Mod. 1 & 2: Ecchymosis and pain during injection</i>	<i>Both methods were effective. On the one hand, PRP is cheap and has minimal side-effects; on the other hand, carboxytherapy is an effective, safe and novel method for the treatment of striae that needs further research.</i>

(27)	<i>The comparative study of topical therapy on striae alba between a herbal extract cream and 0.1% Tretinoin cream in adolescence</i>	24	100% f	<i>Herbal extract cream</i>	<i>0.1% Tretinoin cream</i>	-	Mod. 1 & 2: <i>every night for 16 weeks</i>	<i>Clinical photographs, digital Vernier caliper, roughness was assessed by a UVA-light video camera, patient satisfaction, histological analysis</i>	Alba	Mod. 1: <i>Mild skin irritation</i> Mod. 2: <i>Skin irritation, redness and scaling</i>	<i>The two topical agents were equally effective; since tretinoin can cause skin irritation, the herbal extract can be a better alternative topical treatment for striae alba.</i>
(28)	<i>Platelet-rich plasma versus tretinoin in treatment of striae distensae: A comparative study</i>	30	90% f	<i>Platelet-rich plasma</i>	<i>Tretinoin</i>	-	Mod. 1: <i>Three monthly sessions</i> Mod. 2: <i>Every night for three nights</i>	<i>Digital photographs, skin biopsies and patient satisfaction</i>	Distensae	Mod. 1: <i>Mild pain and bruises</i> Mod. 2: <i>Mild itching</i>	<i>Both treatments were safe for treating SD, but PRP was more effective and had a better therapeutic response.</i>
(29)	<i>Efficacy of pulsed dye laser versus intense pulsed light in the treatment of striae distensae</i>	20	100% f	<i>Pulsed dye laser</i>	<i>Intense pulsed light</i>	-	Mod. 1 & 2: <i>Five monthly sessions</i>	<i>Digital photographs, skin texture, skin biopsies</i>	Distensae	Mod. 1 & 2: <i>Erythema, pain, itching, PIH</i>	<i>Both lines of treatment were a therapeutic option for striae, but striae rubra gave a better response to both PDL and IPL.</i>

*MOD: modality, *SA: striae alba, *IPL: *Intense pulsed light*

Table 3: summarizing the original studies retrieved on striae treatment modalities, Category 3 (combination therapies)

Reference	Title	Number of patients	Gender	Study Group			Treatment Duration	Method of Measuring Improvement	Type of Striae	Adverse Effects	Summary of Results
				Group1	Group2	Group3					
(30)	Use of combination therapy fractionated microneedle radiofrequency with fractional CO2 laser for the treatment of striae distensae in Korean patients	21	100% f	Fractional CO2 laser	Microneedle RF	Fractional CO2 laser+ Microneedle RF	Three treatment sessions with one-month intervals	Before and after photographs and skin biopsy (Global Improvement Scale)	Distensae	PIH (30%) pain (20%) pruritus (20%)	A combination therapy made up of fractionated microneedle RF and fractional CO2 laser is safe and has a positive therapeutic effect on striae distensae.
(31)	Clinical improvement of striae distensae in Korean patients using a combination of fractionated microneedle radiofrequency and fractional carbon dioxide laser	30	100% f	Fractional CO2 laser	Microneedle RF	Fractional CO2 laser+ Microneedle RF	Three treatment sessions with one-month intervals	Before and after photographs + skin biopsy (Global Improvement Scale)	Distensae	PIH (30%), pain, pruritus (20%)	Fractionated microneedle RF treatment could be an effective treatment for striae distensae, and its combination with fractionated CO2 laser could be a better choice.
(32)	Fractionated bipolar radiofrequency and bipolar radiofrequency potentiated by infrared light for treating striae: A prospective randomized, comparative trial with objective evaluation	22	95.5% f	Fractionated bipolar radiofrequency	Bipolar radiofrequency potentiated by infrared light	Fractionated bipolar radiofrequency+ Bipolar radiofrequency potentiated by infrared light	Three monthly sessions	Before and after photographs, skin biopsy	Rubra and alba	Crust formation, pruritus (13%) PIH	The combination of these two methods is an effective treatment option for SD in the abdomen.
(33)	Comparison between the efficacy and safety of platelet-rich plasma vs microdermabrasion in the treatment of striae distensae: clinical and histopathological study	68	79.4 % f	Intradermal PRP	Microdermabrasion	Intradermal PRP+ Microdermabrasion	Six sessions, every two weeks, for six sessions	Before and after photographs, skin biopsy (using the Quartile Grading Scale for improvement assessment)	Alba and rubra	Pain during injection, ecchymosis	The combination modality was more effective in the short term.
(34)	Transepidermal retinoic acid delivery using ablative fractional radiofrequency associated with acoustic pressure ultrasound for stretch marks treatment	16	100% f	Ablative fractional RF	-	Ablative fractional RF + retinoic acid cream + low-frequency acoustic pressure US distinct technology for two minutes	Every four weeks	Skin biopsies and before and after photographs (five-point analogue scale)	Alba	Erythema, edema, moderate burning	Ablative fractional RF and acoustic pressure US technology and retinoic acid cream resulted in a significant clinical improvement and a low incidence of side-effects.

(35)	Microneedling system alone versus microneedling system with trichloroacetic acid in the management of abdominal striae rubra: A clinical and histopathological study	30	100% f	Microneedling	-	Microneedling + trichloroacetic acid	Six sessions with three-week intervals	Before and after photographs, skin biopsies	Rubra	Transient erythema and edema	Both modalities were effective, but derma roller + TCA 15-30% showed better results, while derma roller alone had fewer side-effects.
(36)	Comparative study between microneedling alone and microneedling combined with platelet-rich plasma in the treatment of striae distensae using clinical and histopathological assessment	20	100% f	Microneedling	-	Microneedling+ platelet-rich plasma	Four sessions with two-week intervals	Before and after photographs, and skin biopsies	Distensae	Pain, bleeding, erythema and PIH	Microneedling combined with PRP is more effective in SD.

*PIH: post inflammatory hyperpigmentation, *RF: radiofrequency, PRP: *Platelet-rich plasma*,

Figure1: PRISMA Flow Diagram

