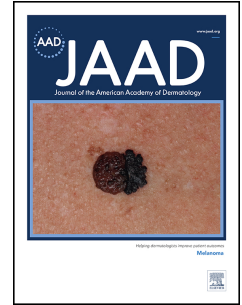


Journal Pre-proof

Comparative Long-Term Efficacy of Phenol-Croton Oil Chemical Peels for Persistent Melasma at Varied *Croton tiglium* Oil Concentrations

Mayra B.C. Maymone, MD, DSc, Fatima N. Mirza, MD, MPH, Denise Steiner, MD, PhD, Felipe Ribeiro, MD, Marina Landau, MD, Carolina Marçon, MD, MSc, Tereza C. Celidonio, MD, Seaver L. Soon, MD, Carlos G. Wambier, MD, PhD, for the International Peeling Society



PII: S0190-9622(24)00547-4

DOI: <https://doi.org/10.1016/j.jaad.2024.03.034>

Reference: YMJD 18499

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 17 December 2023

Revised Date: 15 February 2024

Accepted Date: 27 March 2024

Please cite this article as: Maymone MBC, Mirza FN, Steiner D, Ribeiro F, Landau M, Marçon C, Celidonio TC, Soon SL, Wambier CG, for the International Peeling Society, Comparative Long-Term Efficacy of Phenol-Croton Oil Chemical Peels for Persistent Melasma at Varied *Croton tiglium* Oil Concentrations, *Journal of the American Academy of Dermatology* (2024), doi: <https://doi.org/10.1016/j.jaad.2024.03.034>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2024 Published by Elsevier Inc. on behalf of the American Academy of Dermatology, Inc.

1 **Article type:** Research Letter

2

3 **Title:** Comparative Long-Term Efficacy of Phenol-Croton Oil Chemical Peels for Persistent
4 Melasma at Varied *Croton tiglium* Oil Concentrations

5

6 Mayra B. C. Maymone, MD, DSc¹, Fatima N. Mirza, MD, MPH,¹ Denise Steiner, MD, PhD,²
7 Felipe Ribeiro, MD,² Marina Landau, MD,³ Carolina Marçon, MD, MSc,⁴ Tereza C. Celidonio
8 MD,⁵ Seaver L. Soon, MD,⁶ Carlos G. Wambier, MD, PhD¹, *for the International Peeling*
9 *Society.*

10

11 ¹Department of Dermatology, The Warren Alpert Medical School of Brown University, Providence, RI, USA.

12 ²Department of Dermatology, University of Mogi das Cruzes, Mogi das Cruzes, Brazil.

13 ³ Arena Dermatology, Herzliya, Israel.

14 ⁴ Carolina Marçon Dermatologia, São Paulo, Brazil.

15 ⁵ Tereza Celidonio Dermatologia, São Paulo, Brazil.

16 ⁶ The skin Clinic MD, San Diego, California, USA.

17

18 **Corresponding author:**

19 Carlos Gustavo Wambier, MD, PhD

20 Department of Dermatology, Rhode Island Hospital

21 593 Eddy Street, APC building, 10th Floor.

22 The Warren Alpert Medical School, Brown University

23 Providence, RI, USA. 02903

24 X handle: @WambierMD

25

26 **Funding sources:** None

27 **IRB approval status:** N/A

28

29 **Patient Consent on File:** Consent for the publication of recognizable patient photographs or
30 other identifiable material was obtained by the authors and included at the time of article
31 submission to the journal stating that all patients gave consent with the understanding that this
32 information may be publicly available.

33

34 **Acknowledgement:** The authors are grateful for Carolina Morais, MD for the collaboration and
35 expertise of the histopathology evaluation.

36

37 **Conflict of interest:** Dr. Wambier advises Young Pharmaceuticals, Inc and is an inventor in the
38 USPTO patent #11,253,465 on methods of emulsification of Phenol-Croton oil formulas. The
39 other authors have no conflict of interest to declare.

40

41 Word count: 500

42 References: 5

43 Table: 1

44 Figure: 1

45 Supplement: Mendeley Data: doi: 10.17632/jf7k2g5cdy.2

46

47 **Keywords:** melasma; chloasma, photoaging; chemical peels; phenol-croton oil; croton oil; Hetter's
48 formula; Fintzi's formula; deep chemical peel; phytochemistry; rejuvenation; phorbol esters;
49 phenol; protein kinase C; PKC.

Journal Pre-proof

50 **To the Editor:** Patients with persistent melasma strive to achieve long-term remission despite
51 rigorous compliance to traditional dermatologic therapy such as topicals, and lasers.¹ Phenol
52 formulations have been used with success for melasma when mixed with castor oil (*Ricinus*
53 *communis* oil), but there is a dearth of literature regarding results with phenol-croton oil peels
54 (*Croton tiglium* oil, CO) at different concentrations for the treatment of melasma.^{2,3} In this
55 retrospective international cohort study, we aimed to compare the safety and efficacy in those
56 treated with medium concentration of CO (0.7–0.9%, CO<1%) versus at higher concentration
57 (1.1–1.6%, CO>1%) for the treatment of recalcitrant melasma.

58 The primary outcome was the relative improvement in the modified Melasma Area Severity Index
59 (mMASI) compared to baseline. Wilcoxon signed-rank test was performed with $P<0.05$
60 considered statistically significant. Secondary outcomes: proportion of remission (achieving
61 $mMASI \leq 1$ at the last follow-up), physician Global Aesthetic Improvement Scale (GAIS), and side
62 effects. Statistics were calculated using Stata/SE 17.0 (StataCorp, College Station, TX).

63 Twenty-six females (mean age 46 years) were included, 42% had skin type IV (range: II-IV), 92%
64 received full face treatment. Routine electrocardiographic screening and intraoperative monitoring
65 revealed no abnormalities. 65% of patients had CO>1% peels, baseline mMASI=6, interquartile
66 range (IQR) 5–8, with 8 (IQR:6–9) for CO<1%, and 6 (IQR:4–7) for CO>1%. The median follow-
67 up was 46 months, **Table 1**.

68 The relative improvement in mMASI was greater in CO<1%, median 100% (IQR:100-100)
69 compared to CO>1%, median 88% (IQR:83-100), $P<0.001$. For individual improvement see **Fig.1**.

70 There was a significant difference between baseline and post-treatment mMASI ($P<0.001$) for both
71 concentrations. The median physician GAIS was 5 (much improved) for both CO<1% and
72 CO>1%. Overall, 85% maintained remission, 78% for CO<1% and 88% for CO>1%, $P=0.591$.

73 Histology evaluation was obtained in 3 (12%) patients. The most common adverse event was
74 temporary post-inflammatory hyperpigmentation seen in 44% of patients for CO <1% and 30%
75 for CO >1%, which underwent spontaneous recovery with strict sun-protection. Such evolution is
76 also observed during periorbital dark circle treatment with phenol-croton oil peels.⁴ Extremely
77 relevant clinical-histopathological **Figures S1-6 and dataset** available (Supplement).

78 Limitations of our study include a modest number of cases, retrospective design, and the lack of
79 patients treated with lighter concentrations of croton oil, such as 0.1-0.4%. A careful selection of
80 patients, including those who failed previous treatments despite strict compliance, and
81 perimenopausal women who are no longer planning to become pregnant, might have contributed
82 to the favorable outcomes. This cohort study included 12 patients with skin type IV, adding to the
83 current literature of safety of phenol-croton oil peels in skin of color individuals.⁵

84 In conclusion, our study provides preliminary evidence to support deep chemical peel for the
85 treatment of melasma refractory to topical and oral treatments. Moreover, CO <1% had increased
86 relative improvement in mMASI compared to CO >1%, however both were effective and had
87 similar side effect profiles, suggesting that for melasma, contrary to the treatment of deep wrinkles,
88 higher concentrations of croton oil are not required to achieve a significant long-term clinical
89 improvement.

90

91 **References**

- 92 1. Ma W, Gao Q, Liu J, et al. Efficacy and safety of laser-related therapy for melasma: A
93 systematic review and network meta-analysis. *J Cosmet Dermatol*. 2023;22(11):2910-
94 2924. doi:10.1111/jocd.16006
- 95 2. Wambier CG, Lee KC, Soon SL, et al. Advanced chemical peels: Phenol-croton oil peel. *J*
96 *Am Acad Dermatol*. 2019;81(2):327-336. doi:10.1016/j.jaad.2018.11.060
- 97 3. Piamphongsant T. Phenol-croton oil: modified peel for dermal melasma. *Dermatol Surg*.
98 2006;32(5):611-617; discussion 617. doi:10.1111/j.1524-4725.2006.32131.x
- 99 4. Soon SL, Wambier CG, Rullan PR, et al. Phenol-Croton Oil Chemical Peeling Induces
100 Durable Improvement of Constitutional Periorbital Dark Circles. *Dermatol Surg*.
101 2023;49(4):368-373. doi:10.1097/DSS.0000000000003708
- 102 5. Paiva ML, Justo AS, Lemes BM, et al. Skin of color repigmentation after phenol-croton
103 oil chemical peel. *J Am Acad Dermatol*. 2023;89(5):1068-1070.
104 doi:10.1016/j.jaad.2023.06.053

105

106

107 **Tables and Figures**108 **Table 1.** Characteristics of 26 women with persistent melasma treated with phenol-croton oil
109 peel formulas.

Characteristics	Overall	Croton Oil <1%	Croton Oil >1%
Total, n (%)	N=26 (100)	n=9 (35)	n=17 (65)
Age median (IQR), y	46 (39–56)	44 (40–46)	46 (39–60)
Skin Type median (min-max)	3 (2–5)	4 (4–4)	3 (2–4)
Baseline mMASI median (IQR)	6 (5–8)	8 (6–9)	6 (4–7)
Histology confirmation, n (%)	3 (12)	1 (11.1)	2 (12)
Previous Treatments[†]			
Peelings			
Superficial, n (%)	12 (46)	-	12 (71)
Medium-Depth, n (%)	2 (8)	-	2 (12)
Lasers			
1,064nm nanosecond	6 (23)	-	6 (35)
1,064nm picosecond	1 (4)	-	1 (6)
2,940nm	2 (8)	-	2 (12)
10,600nm	2 (8)	-	2 (12)
Microneedling	2 (8)	-	2 (12)
Oral isotretinoin	1 (4)	-	1 (6)
Phenol-croton oil peel			
Year of Procedure \bar{x} (SD), year	2017(4.7)	2015 (6.1)	2019 (3.4)
Follow-Up Time median (IQR), months	46 (23–87)	144 (24–168)	44 (11–77)
Facial surface treated, %			
Full Face	24 (92)	9 (100)	15 (88)
Segmental peels	2 (8)	-	2 (12)
Croton oil, % (volume/volume)			
0.7	8 (31)	8 (89)	-
0.8	1 (4)	1 (11)	-
1.1	1 (4)	-	1 (6)
1.2	12 (46)	-	12 (71)
1.6	4 (15)	-	4 (23)
Outcomes			
Post mMASI median (IQR)	0 (0–1)	0 (0–0)	1 (0–1)
Relative mMASI improvement, %(IQR)	100% (84–100)	100% (100–100)	88% (83–100)
mMASI median improvement (IQR)	6 (5–8)	7 (6–8)	5 (4–7)
Remission (Achieved mMASI \leq1), n(%)	22 (85)	7 (78)	15 (88)
Baseline versus Post mMASI*	p<0.001	p=0.009	P<0.001
Physician GAIS median (IQR)	5 (5–5)	5 (5–5)	5 (4–5)
Side Effects, %			
Post-inflammatory hyperpigmentation	9 (35)	4 (44)	5 (30)
Acne	1 (4)	-	1 (6)

[†] Percentage of patient cohort receiving each treatment. Percentages does not add to 100 as patients may have received multiple treatments. IQR= Interquartile range, expressed as 1st Quartile – 3rd Quartile.

* Two-tailed Wilcoxon signed-rank test was applied.

110
111
112
113

114 **Figure Legend**

115

116 **Figure 1.** Persistent Melasma. Relative improvement (% difference in mMASI scores) among 26
117 patients treated with phenol-croton oil chemical peeling, per croton oil concentration (<1% and
118 >1%).

Journal Pre-proof

