

Kligman's formula misuse among the general population in Saudi Arabia

Faisal Hassan Tobeigei¹, Ibrahim Hassan Najmi², Ahmed Hussain Almutlaq³, Khalid Hussein Almutairi⁴, Mohammed O. Shami⁵, Mona Yahya Alqarni⁶

1. Assistant Professor of Dermatology, Department of Dermatology, King Khalid University, College of Medicine, Abha, Saudi Arabia. E-mail: ftobeigei@kku.edu.sa
2. Consultant dermatology, Department of dermatology, Khamis Mushait general hospital
3. General practitioner, Ministry of health ,Abha, Saudi Arabia. E-mail: dr.ahmedMutlaq@gmail.com
4. General Surgery Resident, Ministry of health, Saudi Arabia. E-mail: K.mm2030@gmail.com
5. Medical Intern, Jazan University, Jazan, Saudi Arabia. E-mail: Medm.shami@gmail.com
6. pharmaD, King Khalid University, Abha, Saudi Arabia. E-mail: Monna21q@gmail.com

***Corresponding author:**

Faisal Hassan Tobeigei

PO Box 641, Abha 61421, Saudi Arabia

E-mail: ftobeigei@kku.edu.sa

Abstract

Background:

Kligman's formula (Triple Combination) or modified Kligman's is a topical drug for that combines fluocinolone acetonide 0.1 %, hydroquinone 4%, and tretinoin 0.05%, and is now the only US FDA-approved medication for the treatment of melasma topically. It has recently gained widespread popularity among the general public for a variety of uses. When used incorrectly, it might produce negative consequences and undesirable side effects.

Methods:

A cross-sectional, observational study was performed using Kligman's formula misuse questionnaire in a convenient sample of 2634 participants. The statistical analysis included descriptive analysis, and tests of association (chi square and Fisher's exact test).

Results:

knowledge regarding triple combination cream is poor. 2% of the respondents correctly chose skin melasma, 1.3% chose hyperpigmentation, and 10.3% chose acne post pigmentation, however, as these conditions are all approved indications for using triple combination cream, only 18% chose at least two of them. Acne post pigmentation was the most common reason for using triple combination creams (42.5%), followed by other causes of pigmentation (21.1%), inflamed acne (13.8%), melasma (12.3%), and other non-reported causes (10.3%). Social media was the most prevalent source of cream-related information among non-users (23.1%) and the second most common source among users (35.9%).

Conclusions:

knowledge regarding triple combination cream is poor. Kligman's formula misuse and its adverse reactions is a concern in Saudi Arabia. The diversity in sources of informations of using Kligman's formula is negatively affecting the correct use of it. Therefore, we

recommend using social media websites, malls, and television to raise awareness for the correct way to use Kligman's formula and how to avoid its misuse.

Introduction

Kligman's formula (Triple Combination) or modified Kligman's is a topical drug for melasma treatment that combines fluocinolone acetonide 0.1 %, hydroquinone 4%, and tretinoin 0.05%, and is now the only US FDA-approved medication for the treatment of melasma topically [1]. Kligman's formula is FDA-approved for another hyperpigmentation disorders, and it is effective in treating post-inflammatory hyperpigmentation, was studied over an 8-weeks treatment period, the percentage of patients who were rated as clear from treatment with Kligman's formula cream was higher than with any of the comparators [2]. Furthermore, trending graphs suggest that Kligman's formula cream provides a more rapid response than the comparators and suggests that a longer treatment period may provide even better results [3]. In the last years many dermatologists spoke out on the efficacy of Kligman's formula on the treatment of acne post-inflammatory pigmentations, and melasma. As a result, many people used the treatment without knowing the correct way to use it and without referring to a dermatologist. Therefore, the aim of our study is to explore the Kligman's formula misuse among the general population in the kingdom of Saudi Arabia.

Materials & Methods

Study Design/Sample

A cross-sectional, observational study was designed between June 2021 and April 2022. A convenient random sampling technique was used in this study. The Raosoft sample size calculator was used to calculate the sample size (Raosoft Inc., Seattle, WA, USA) (<http://www.raosoft.com/samplesize.html>) based on the total population (35,013,414) according to General Authority for statistics in the kingdom of Saudi Arabia, with a 95% confidence interval, 5% margin of error, 50% response distribution; thus, a minimum sample size was set to be 377 . However, we increased the sample size to include 2634 participants to reduce sampling bias in our method as this study was based on an online questionnaire distributed by using social media (Facebook, Twitter, and WhatsApp). Inclusion criteria was population residing in Saudi Arabia at the time of the study who aged more than 18 years. Exclusion criteria was people less than 18 years.

Measures

Socio-demographic Variables

The first section contained demographic information such as age, gender, marital status, employment status, education level, monthly income, and area of residency.

Kligman's formula misuse questionnaire

The purposely constructed questionnaire was used for this research. The Kligman's formula misuse questionnaire was constructed by the panel of experts in the field, Language experts, dermatologists, doctors and subject specialist was there in the team. Internal consistencies of the questionnaire was measure through cronbach alpha.

Statistical analysis

After data collection, data were verified manually, and then coding was carried out within an excel sheet, then all data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS version 25). Data was analyzed using descriptive and comparative statistics. Descriptive statistics were calculated for study variables, i.e., frequency and percentage for qualitative variables and mean and standard deviation for quantitative variables. Tests of association (chi square and Fisher's exact test) were applied as appropriate. P-value of less than .05 or .01 was set to indicate statistical significance level.

Ethical consideration

All the necessary official permissions were obtained before data collection. All participants were informed about the objectives of the study. They were assured that no harm is expected to occur if they decide to participate in the stud, and also were assured about the anonymity and full confidentiality of their data. Their consent to participate was requested. No personal information such as name, phone number, and others were included in the questionnaire. Moreover, all collected data has been kept confidential and has not been used except for research. Ethical approval has been taken from The Research Ethics Committee at King Khalid University (approval number ECM#2022-502, dated 17/02/2022).

Results

The study enrolled 2634 participants from the 13 regions of Saudi Arabia; 56% were female, and 47.6% were aged 20-30 years. A total of 262 (9.9%) used triple combination cream. The use of triple combination cream was more prevailing among female subjects (82.4%, $P < .01$), subjects aged 20-30 years (51.1%, $P < .05$), subjects with a college degree of education (71.4%, $P < .05$), subjects residing in Makkah region (25.6%) followed by Aseer region (20.6%, $P < .01$), students (20.6%, $P < .01$) followed by employees in the health sector (33.2%, $P < .01$). The main characteristics of the respondents and the prevalence rate of triple combination cream use are shown in Table 1.

Characteristics	All subjects (N=2634)		Users (n=262)		χ^2 /Fisher's test	P value
	Frequency	Percent	Frequency	Percent		
Age (years)						
< 20	289	11.0	27	10.3	8.938	.030
20-30	1254	47.6	134	51.1		

31-40	578	21.9	67	25.6		
> 40	513	19.5	34	13.0		
Sex						
Male	1158	43.9	46	17.6	82.348	.000
Female	1476	56.0	216	82.4		
Education						
Primary school	15	.6	2	.8	17.373	.000
Middle school	70	2.7	3	1.1		
High school	569	21.6	35	13.4		
College level	1724	65.4	187	71.4		
Higher study	256	9.7	35	13.4		
Monthly income (Saudi Riyals)						
<5000	1257	47.7	123	46.9	.934	.817
5000-10000	486	18.4	49	18.7		
10000-15000	444	16.9	49	18.7		
> 15000	447	17.0	41	15.6		
Marital status						
Single	1415	53.7	139	53.1%	1.107	.775
Married	1140	43.3	113	43.1%		
Divorced	57	2.2	8	3.1%		
Widowed/widower	22	.8	2	0.8%		
Region of residence						
Riyadh	268	10.2	22	8.4	50.569	.000
Makkah	722	27.4	67	25.6		
Aseer	356	13.5	54	20.6		
Baha	21	.8	4	1.5		
Jazan	46	1.7	3	1.1		
Madinah	516	19.6	34	13.0		
Eastern	464	17.6	37	14.1		
Hail	76	2.9	18	6.9		
Tabouk	60	2.3	9	3.4		
Qassim	74	2.8	7	2.7		
Jouf	18	.7	3	1.1		
Northern	7	.3	3	1.1		
Najran	6	.2	1	.4		
Type of job						
None	341	12.9	43	16.4	14.225	.047
Student	959	36.4	87	33.2		
Military sector	52	2.0	3	1.1		
Education sector	262	9.9	33	12.6		

Health sector	473	18.0	54	20.6		
Private sector	288	10.9	16	6.1		
Field job (exposed places)	14	.5	2	.8		
Other	245	9.3	24	9.2		
Medical history						
None	2293	87.1	236	10.3	5.252	.386
Hyperthyroidism	32	1.2	2	6.3		
Hypothyroidism	92	3.5	11	12.0		
Diabetes	101	3.8	7	6.9		
Hypertension	90	3.4	5	5.6		
Heart disease	26	1.0	1	3.8		
^a Triple combination cream (i.e., Kligman's formula: Tretinoin (Acretin [®]), Hydroquinone (Hiquin [®]), fluocinolone acetonide (Differin [®]).						

A total of 262 (9.9%) used the triple combination cream, and 13.7% used products containing tretinoin (Acretin[®]). Although 84.7% of subjects visited a dermatologist, only 46.2% had a prescription for triple combination cream, and 51.5% used it over the counter. Most subjects used triple combination cream for less than four weeks (44.7%), 30.2% for 5-8 weeks, and 13.4% for more than one year. Use of triple combination cream during pregnancy was reported by 2.3% (Table 2).

Pattern	Frequency	Percent
Use of triple combination creams or one of their components ^a		
Tretinoin (Acretin [®])	361	13.7
Hydroquinone (Hiquin [®])	43	1.6
Fluocinolone acetonide (Differin [®])	21	.8
Triple combination cream	262	9.9
Other scrub products	94	3.6
Past dermatological assessment		
Yes	222	84.7
No	40	15.3
Use of triple combination creams or one of them as prescribed by a dermatologist		
Yes	121	46.2
No	135	51.5
Do not know	6	2.3
Duration of past use of triple combination creams		
Do not recall	12	4.6
< 4 weeks	117	44.7

5 to 8 weeks	79	30.2
9 to 12 weeks	19	7.3
> 12 weeks	35	13.4
Past use of triple combination creams during pregnancy		
Yes	6	2.3
No	150	57.3
Do not know	60	22.9
^a Analyzed for all subjects, other variables in the table were analyzed only for subjects with history of triple combination cream use.		

Figure 1 illustrates reasons for using triple combination creams among the study subject and shows that acne post pigmentation was the most common reason (42.5%), followed by other causes of pigmentation (21.1%), inflamed acne (13.8%), melasma (12.3%), and other non-reported causes (10.3%) (Figure 1).

As shown in Figure 2, almost one-third of subjects (32.4%) reported allergic reactions (redness and itching) after the application of triple combination creams, followed by dryness (29.8%).

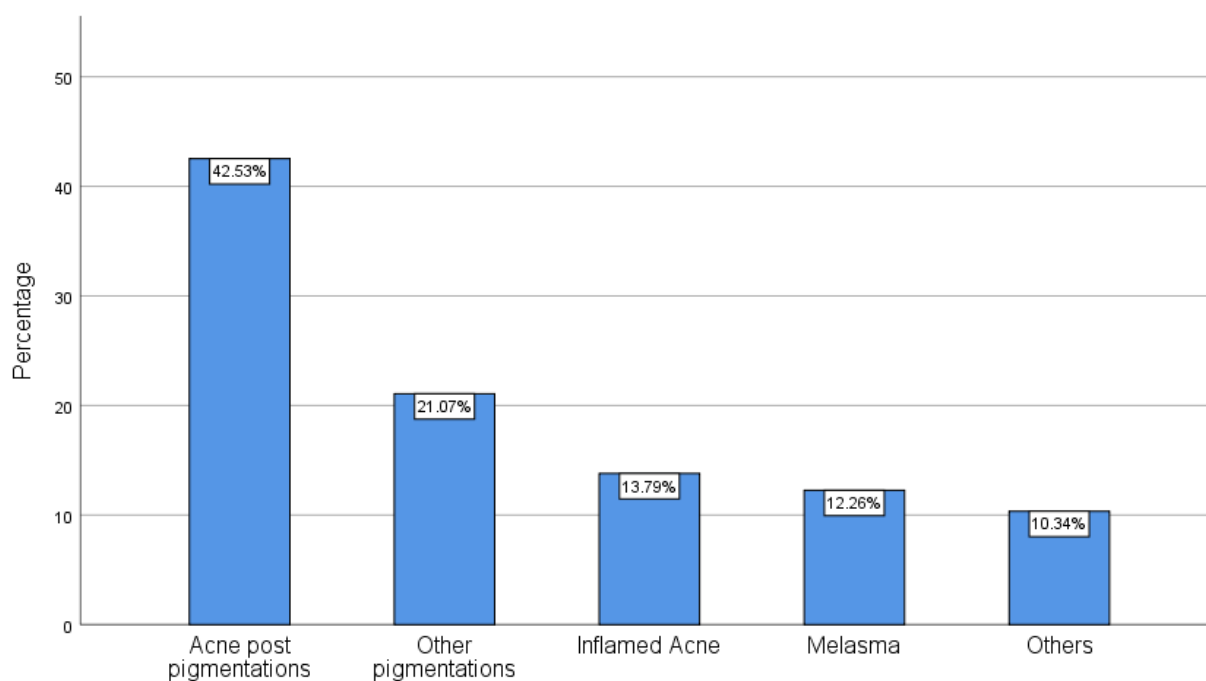


Figure 1 Reasons for using triple combination creams.

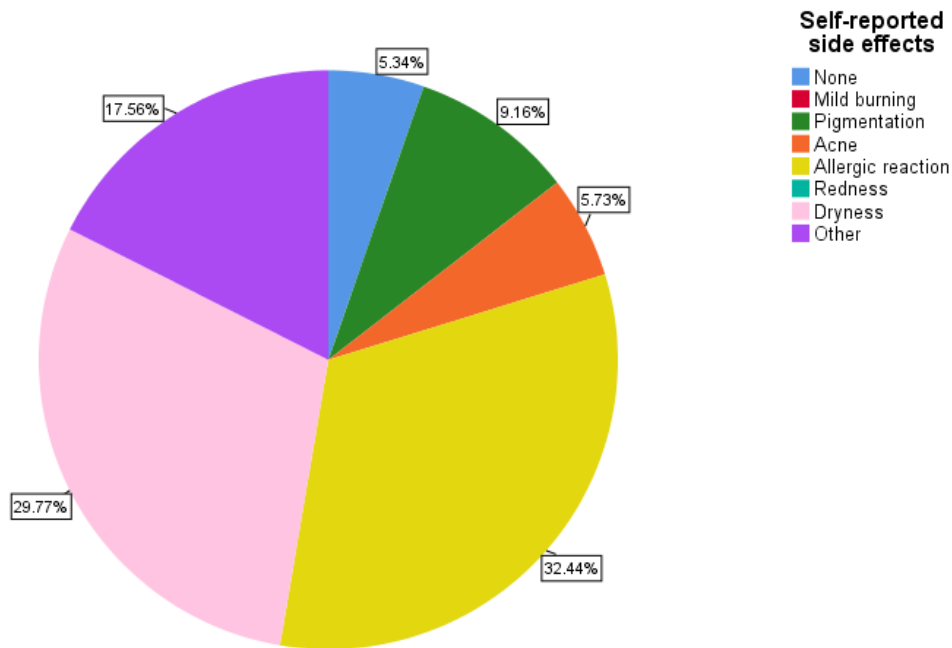


Figure 2 Self-reported side effects of triple combination creams.

Subjects were asked to select the most accurate choices based on their knowledge of triple combination cream, uncertain respondents could choose “I do not know,” and multiple choices were allowed in some questions. Respondents correctly chose either skin melasma (2%) hyperpigmentation (1.3%), or acne post pigmentation (10.3%). However, as these conditions are all approved indications for using triple combination cream, only 18% chose at least two of them. Regarding side effects of triple combination cream, correct answers included pigmentation (1.9%), acne (1.3%), allergic reaction (6.8), and redness (2%). Only 4% chose at least two correct combinations of the side effects. Regarding appropriate instructions for using triple combination cream, 36.4% chose bedtime for applying the cream, 48.6% thought users should avoid sun exposure and sunscreen, and 46.2% thought users should wash and dry affected areas before cream application. Furthermore, 23.7% were aware that users should avoid cream contact with eyes and lips, and 19.2% thought that cream application should be on the affected area only. A large proportion of subjects (92.7%) incorrectly identified the optimal period for clinical improvement when using triple combination cream (> 8 weeks) and the maximum period of using the cream for the same indication (96.1%) (Table 3).

Question/statement	Frequency	Percent
Approved uses of triple combination cream		
Melasma ^a	52	2.0
Skin Hypersensitivity	33	1.3
Skin Hyperpigmentation ^a	33	1.3

Acne post-pigmentations ^a	270	10.3
At least two correct	476	18.0
Incorrect answers	94	3.5
Do not know	1676	63.6
Side effects of triple combination cream		
Pigmentation ^a	51	1.9
Acne ^a	35	1.3
Allergic reaction ^a	179	6.8
Redness ^a	52	2.0
Dryness	103	3.9
At least two correct	102	4.0
Incorrect answers	571	21.6
Do not know	1541	58.5
Appropriate timing for using triple combination cream		
At bedtime ^a	959	36.4
Morning	48	1.8
Mid of the day	26	1.0
Anytime	67	2.5
Do not know	1534	58.2
Users should avoid sun exposure and use of sunscreen during the treatment period		
Yes ^a	1279	48.6
No	88	3.3
Do not know	1267	48.1
Users should wash and dry face before use the cream		
Yes ^a	1218	46.2
No	87	3.3
Do not know	1329	50.5
Which of the following is the correct way to use the cream?		
Apply the cream to the affected area ^a	505	19.2
Apply the cream on all over the face	113	4.3
Avoid putting the cream around the eyes and lips ^a	625	23.7
All above	2	.1
Do not know	1389	52.7
The optimal period for clinical improvement when using triple combination cream		
One week	88	3.3
Two weeks	204	7.7
Four weeks	388	14.7
Eight weeks	195	7.4
> 8 weeks ^a	192	7.3

Do not know	1567	59.5
The maximum period of continuous use of triple combination cream		
Three months	355	13.5
Six months ^a	104	3.9
One year	359	13.6
Do not know	1816	68.9
^a Correct response(s).		

As shown in Table 4, respondents reported different sources of their information about triple combination cream, and there was a significant difference in sources reported by users versus non-users ($P < .01$). Subjects with a history of triple combination cream use (38.2%) were more likely to rely on physicians to take related information as compared to those who never used the cream (15.3%). Social media was the most prevalent source of cream-related information among non-users (23.1%) and the second most common source among users (35.9%) (Table 4).

Source	All subjects (N=2634)		Users (n=262)		χ^2	P value
	Frequency	Percent	Frequency	Percent		
Social media	609	23.1	94	35.9	206.078	.000
Physicians	404	15.3	100	38.2		
Internet	373	14.2	30	1.5		
Friends	217	8.2	22	11.5		
Family	104	3.9	4	8.4		
Study materials	86	3.3	6	1.5		
Others	841	31.9	6	2.3		

Discussion

To gain a better understanding of the current discussion about Kligman's formula misuse, we decided to conduct this study to investigate the Kligman's formula misuse among the general population in the kingdom of Saudi Arabia. This is the first study investigating the Kligman's formula misuse in the kingdom of Saudi Arabia. The current study enrolled 2634 participants from the 13 regions of Saudi Arabia between the period June 2021 and April 2022. Out of the 2634 participants, a total of 262 participants used triple combination cream. Use of the triple combination cream was more prevalent among females and participants aged 20-30 years. This study has some limitations which should be considered when generalizing and interpreting its findings. The cross-sectional study may not provide a well-established casualty among the study variables. Such studies are subject to nonresponse bias, but the study has a good response rate, and we took every possible measure to eliminate systematic nonresponses. Furthermore, because the questionnaire used in this study was self-reported, future studies could apply different approaches, such as interviews. On the other hand, the

current study was valuable as it is the first study investigating the Kligman's formula misuse among the general population in the kingdom of Saudi Arabia. Additionally, This study included a large number of participants equal to 2634 participants.

Our results revealed that regarding to knowledge on triple combination cream, 2% of the respondents correctly chose skin melasma, 1.3% chose hyperpigmentation, and 10.3% chose acne post pigmentation, however, as these conditions are all approved indications for using triple combination cream, only 18% chose at least two of them. However, in Al Dhafiri study [4], participants had a poor attitude toward Kligman's formula which is contrary to India study [5] which found a considerable increase in awareness of the long-term usage of steroid creams including Kligman's formula, with 55.2% of medical students taking it without a prescription.

Reasons for using triple combination creams among the study subject showed that acne post pigmentation was the most common reason, followed by other causes of pigmentation, inflamed acne, melasma, and other non-reported causes which is similar to the findings in Al Dhafiri study [4] which revealed that skin lightening is the most common cause followed by acne scars. 84.7% of individuals who used Kligman's formula visited a dermatologist, only 46.2% had a prescription for triple combination cream, while 51.5% of them used it over the counter which is similar to Jha et al study [6] which showed that only 0.26% of the participants using TC formula based on the doctor's prescription. Furthermore, adverse reactions to TC formula, including Kligman's formula, may vary based on the type of cream used or the ingredients it includes. Adverse reactions include acne, hypopigmentation, pigmentation disorder, and cutaneous atrophy [6,7].

In our study, almost one-third of participants reported allergic reactions (redness and itching) after the application of triple combination creams, followed by dryness which is similar to Al Dhafiri study [4] which reported that the most prevalent side effects were skin redness, a burning sensation, and skin peeling and also reported face photosensitivity during sunlight exposure. Many studies reported cutaneous adverse effects after using the TC formula [4, 7, 8]. Adverse effects from using the combined formula can vary depending on the conditions being treated. Thus, it is necessary to get counseling before using it. In the current study, most of the participants used triple combination cream for less than four weeks representing 44.7%, 30.2% of them used it for 5-8 weeks, and 13.4% of them used it for more than one year. These findings is in agreement with Al Dhafiri study [4] and Dhanalakshmi et al. study [5] which both found that participants using the TC formula beyond the prescribed period.

In our study, there was a significant difference in information sources reported by users versus non-users for using Kligman's formula ($P < .01$). Users (38.2%) were more likely to rely on physicians to take related information as compared to those who never used the cream (15.3%). Social media was the most common source of cream-related information among non-users (23.1%) and the second most common source among users (35.9%) which is in agreement with Al Dhafiri study [4] which reported that electronic social network sites was

the most common sources of information. Our findings demonstrated that knowledge regarding triple combination cream is poor. Furthermore, these findings show that Kligman's formula misuse and its adverse reactions is a concern in Saudi Arabia. Moreover, the diversity in sources of informations of using Kligman's formula is negatively affecting the correct use of it. Therefore, we recommend using social media websites, malls, and television to raise awareness for the correct way to use Kligman's formula and how to avoid its misuse by implementing interventional strategies by dermatologists and by doing awareness campaigns targeting the community to decrease Kligman's formula misuse. Future studies needed to investigate the reasons behind Kligman's formula misuse by applying different methods and techniques like interviews.

Conclusion

Knowledge regarding triple combination cream is poor. Kligman's formula misuse and its adverse reactions is a concern in Saudi Arabia. The diversity in sources of informations of using Kligman's formula is negatively affecting the correct use of it. Therefore, we recommend using social media websites, malls, and television to raise awareness for the correct way to use Kligman's formula and how to avoid its misuse by implementing interventional strategies by dermatologists and by doing awareness campaigns targeting the community to decrease Kligman's formula misuse. Furthermore, because the questionnaire used in this study was self reported, future studies could apply different approaches, such as interviews.

Declaration of Competing Interest: The authors declare that there is no conflict of interests.

Acknowledgments: None.

Funding: None.

Submission declaration and verification: All of the authors confirms that this manuscript has not been previously published and is not currently under consideration by any other journal. Additionally, all of the authors have approved the contents of this paper and have agreed to the Journal submission policies.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

References

1. Torok, H.M. A Comprehensive Review of the Long-Term and Short-Term Treatment of Melasma with a Triple Combination Cream. *Am J Clin Dermatol* 7, 223–230 (2006).
<https://doi.org/10.2165/00128071-200607040-00003>
2. Torok H, Taylor S, Baumann L, Jones T, Wieder J, Lowe N, Jarret M, Rich P, Pariser D, Tschene E, Martin D, Menter A, Weiss J. A large 12-month extension study of an 8-week trial to evaluate the safety and efficacy of triple combination (TC) cream in melasma patients previously treated with TC cream or one of its dyads. *J Drugs Dermatol*. 2005 Sep-Oct;4(5):592-7. PMID: 16167418.
3. The comparison between modified kligman formulation versus kligman formulation and intense pulsed light in the treatment of the post-burn hyperpigmentation Amir Hossein Siadat, Fariba Iraj, 2016; 5: 125. Published online 2016 Jul 29. doi: 10.4103/2277-9175.186997
4. Al Dhafiri M, Almutairi M, Alutaibi H M, et al. (December 20, 2021) Attitude Toward Using the Triple Combination Bleaching Formula and Related Outcomes: A Cross-Sectional Study. *Cureus* 13(12): e20542. DOI 10.7759/cureus.20542
5. Dhanalakshmi K, Pious MT, Sudarvizhi A, Jennifer G: Awareness and attitude of medical students over the misuse of topical steroids- prospective study in 3rd year medical students in a medical college, Tamil Nadu. *IP Indian J Clin Exp Dermatol*. 2021, 7:115-9.
10.18231/j.ijced.2021.022
6. Jha AK, Sinha R, Prasad S: Misuse of topical corticosteroids on the face: a cross-sectional study among dermatology outpatients. *Indian Dermatol Online J*. 2016, 7:259-63.
10.4103/2229-5178.185492
7. Sendrasoa FA, Ranaivo IM, Andrianarison M, Raharolahy O, Razanakoto NH, Ramarozatovo LS, Rapelanoro Rabenja F: Misuse of topical corticosteroids for cosmetic purpose in Antananarivo, Madagascar . *Biomed Res Int*. 2017, 2017:9637083.
10.1155/2017/9637083
8. Majid I: Mometasone-based triple combination therapy in melasma: is it really safe? . *Indian J Dermatol*. 2010, 55:359-62. 10.4103/0019-5154.74545