ORIGINAL ARTICLE

Reporting Adverse Reactions of Skin Whitening Products in Wad-Medani Dermatology Hospital, Sudan

Wegdan Yousif Mahgoub[1], Abdelraheem Adam Ibrahim[2], Jehan Yousif Mahgoub [3], Rana Ahmed[4], Elmustafa M[5]

1. Department of Pharmacy Practice, Faculty of pharmacy, University of Gezira, Sudan
   Department of Dermatology, Faculty of Medicine, University of Gezira, Sudan
2. Head of Dermatology Department, Faculty of Medicine, University of Gezira, Sudan
3. Head of Health informatics department, The Association of Public Health Research (Epilab)
4. Department of Pharmacology, Faculty of pharmacy, University of Gezira, Sudan

Correspondace:Email:wijdany@gmail.com

Abstract:

Background: There is growing concern about skin whitening both worldwide and in Sudan where there is no specific reporting system for the adverse reactions to whitening products.

Objective: To identify adverse reactions associated with whitening products use through implementing an adverse reactions reporting system at the dermatology hospital in Wad -Medani, Sudan.

Methods: A cross sectional study of patients presenting at the dermatology hospital in Wad-Medani, with adverse reactions (ARs) associated with the use of whitening products was done between October 2017 and September 2018.ARs reporting forms (containing socio-demographic characteristics, whitening products details and the detected ARs) were filled by the doctors attending both referral and out-patient clinics.

Results: The study included 1000 patients aged 15- 48 years old, 98.5% of which were females. About 58% of patients had skin type VI, 32% skin type V and 10% skin type IV. More than 80% of the population used Hydroquinone and/or Clobetasol propionate or unlabeled mixtures of several whitening products bought from street vendors. Most patients (52%) used these products for more than 6 months. Acne, inflammation, ochronosis, hyperpigmentation, bacterial and fungal infections were the most reported ARs. The latter occurring in more than 42% of included patients. More than 68% of reported ARs were classified as severe by the

treating doctors.

Conclusion: Serious ARs of whitening products are prevalent and urgent measures are needed to address their irrational use. Vigilance ARs reporting systems are applicable and feasible which was evident since whitening products ARs reporting was continued even after the study was completed. The development and implementation of these systems should be adopted and encouraged by health authorities.

Keywords: Adverse reactions (ARs), reporting system, skin whitening products, -Pharmacovigilance, hydroquinone, clobetasol

Introduction:

The use of products containing whitening compounds is a growing trend in several parts of the world, including Sudan especially among females [(1)]. Women face pressure to lighten their skin due to the widespread social perception that light skin is considered more attractive, beautiful, and reflective of high social status [(2)]. This has led to increase the use of these products which threatens to increase the incidence of adverse reactions associated with their use [(1-3-4)].

Most whitening products contain hydroquinone, corticosteroids with high potency and mercury salts as active ingredients [(1)]. These chemicals could be extremely harmful in some concentrations; therefore, they are banned in many countries over the world. However, unlabelled skin whitening products containing hydroquinone are commonly sold over the counter at concentrations above the permissible 2% [(1-5-6)]. The adverse reactions of skin whitening have increased greatly in recent years [(1-2-3-4)]. They pose a risk to patient safety and adversely affect their quality of life and increase the cost of health care [(7)]. Different dermatological adverse reactions and consequences have been recorded with the use of different whitening products for examples: ochronosis, skin infections as erysipelas and dermatophytes, straie, telangiectasia and acne [(8)]. Also, prolonged use of corticosteroids has always been associated with Cushing's syndrome and renal impairment [(9)]. Moreover, serious neurological complications have been associated with using mercury compounds as whitening creams [(10)].

Despite the widespread use of these products, the rate of detection of ARs associated with their use is relatively low. Lack of information concerning the

type, the number, and the severity of these ARs could partly be due to the absence of a reporting system [11-12] or the under-reporting associated with spontaneous ARs reporting systems [7].

In Sudan, in spite of the prevalent use of cosmetics- particularly skin whitening products- there is no formal cosmetic surveillance system. Also, doctors working in dermatology hospitals in Sudan speak of staggering numbers of hospital visits related to ARs of skin whitening products. This study will attempt to determine the prevalence of these ARs using a spontaneous reporting system. It also aims to create awareness among health professionals about "cosmetovigilance" and promote ARs reporting.

Methods:

A cross sectional study was conducted at Dr. Ahmed Abdullah Hamadain Dermatology Hospital in Wad-Medani the capital of Gezira State, Sudan. This took place between October 2017 and September 2018 through implementing a reporting system for ARs associated with the use of whitening products. All patients included in this study gave a verbal consent before an ARs report was filled by the treating doctor. Patients presenting at the hospital seeking medical care of ARs associated with the use of whitening products were included in this study, whether they were using whitening products at the time of study or had used it previously. Patients denying using whitening products were accepted if reporting doctors would be certain about associated ARs. Any products known to contain hydroquinone, corticosteroids or mercury were reported if used by the included individuals. Patients with hyperpigmentation, melasma, chloasma, acne, inflammation, or other adverse reactions due to dermatological conditions far from using whitening products were excluded from this study. Adverse reactions of whitening products were reported using an adverse reactions reporting form adapted from the "Suspected Adverse Reaction (AR) Reporting Form" used officially by the Pharmacovigilance Centre/ National Medicines and Poisons Board-Sudan. The collected data included; the demographic characteristics of the patients (gender, age, occupation, income and skin type), brand and generic names of the used whitening products, frequency of use, pharmaceutical form of the whitening product, duration of use, type and severity of ARs seen with their use,

and management steps taken by the doctors.

Statistical Analysis:
Data were analyzed using the Statistical Package for Social Sciences; IBM SPSS Statistics 24.0, (IBM Corporation, New York, USA). Descriptive statistics were used to summarize data. Chi square analysis was used to test the association between all variables. A bivariate analysis using logistic regression was used to test the association of study variables and different ARs. All variables with a p value <0.05 was entered in the multivariate analysis using binary logistic regression. Age and sex were forced in all models.

Results:

Out of the 1000 adverse reactions reporting forms filled, 985 were for females (98.5%) and 15 for males (1.5%). The whitening products were used twice a day by (47.8%), while 30.2% and 22.1% used them once or three times a day respectively.

Many included patients (42.7%) were aged 26-35 years (mean=31.18±2.9). Most of them were employees or self –employed (35.8%) and (30.1%) respectively. Around half of them (51.8%) earned 12.5-62.5$ monthly, while (26.9%) earned more than 62.5$ monthly. The predominant skin photo-type found in 586 (58.6%) of the study sample was VI (dark brown), while skin type V (brown skin) was found in 319 (31.9%), and the least was skin type IV (light brown skin) seen in 95 patients (9. 5%) see Table 1. The modal duration of the use of skin whitening products was more than six months in 51.8% of patients.

Table (1): Demographic characteristics of the study population (n= 1000)

Characteristics	**Frequency(%)**
Sex	
Female	985 (98.5%)
Male	15 (1.5%)
Age group *(Mean=33 years*)	
16-25	169 (16.9%)
26-35	427 (42.7%)
36-45	355 (35.5%)
>45	49 (4.9%)
Monthly Income	
12.5$	213 (21.3%)
12.5-62.5	518 (51.8%)
>62.5$	269 (26.9%)
Skin Type	
IV (Light brown skin)	95 (9.5%)
V (Brown skin)	319 (31.9%)
VI (Dark brown skin)	586 (58.6%)
Occupation	
Student	134 (13.4%)
Self-employed	301 (30.1%)
Employee	358 (35.8%)
Housewife	207 (20.7%)

Twelve different brands of whitening products were identified as being used by the included sample population as shown in Table 2. Unlabelled extemporaneously prepared products obtained mainly from vendors in small beauty shops and street vendors were the top reported products used by 25.1% (n= 251) of them. The top 3 combinations were (Orannovate[1] + civic[2]+Amalico[3]) used by 13.6% (n=136) of the study population, (Amalico[3]+Movate[4]), used by 12.2% (n=122) and (Lucocid R[6] + Orannovate[1]) used by 5.4% (n=54). The active components of each of these brands are shown in the footnote of Table 2.

Table (2): Brand names of whitening products used by the study population (n= 1000)

Whitening product(s) used	Frequency	Percent
Extemporaneously prepared product[1]	251	25.1
Orannovate[1]+Civic[2]+Amalico[3]	136	13.6
Amalico[3]+Movate[4]	122	12.2
Melanofree[5]	108	10.8
Amalico[3]	66	6.6
Kenza[1]	63	6.3
Carotone[1]	57	5.7
Lucocid R[6]+Orannovate[1]	54	5.4
Top gel[1]+Lucocid R[6]	45	4.5
Dodo[7]	41	4.1
Civic[2]	32	3.2
Al Amira[1]	18	1.8
Dr.clear[1]	7	0.7
Total	1000	100%

[1]Un known active ingredient(s) (not declared on container or leaflet),

[2 ‘4] Clobetasol propionate 0.05%,

[3] Hydroquinone4.4%+Retinoic acid 0.025%

[5] Hydroquinone 4%+Flucinolone acetonide 0.01%+Tretinoin0.05%

[6] Hydroquinone 3%+Retinoic acid 0.025%

[7] kojic acid

[8] Others

Males in this study although small in numbers, tended to use only one whitening product at a time. Eleven males used Mealnofree[5] cream while 4 used Al Amira[1] soap. On the other hand, 377 females used one whitening product. These were as follows; 97 females used Melanofree[5] cream alone, 66 used Amalico[3] cream, 63 used Kenza[1] cream, 57 used Carotone[1] cream, 41 used Dodo[7] cream, 32 used Civic[2] cream, 14 used Al Amira[1] soap and 7 females used Dr. Clear[1] cream.

Factors associated with the reported ARs of the whitening products:

Hyperpigmentation: Using multivariate analysis, whitening products were highly associated with having hyperpigmentation. Al Amira[1] cream had the higher odds in having hyperpigmentation compared to using Top gel[1]+Lucocid R[6] (OR 8.1, 95%CI 1.4-45.3). Whitening products (Extemporaneously prepared product[1], Melanofree[5] , Amalico[3]+Movate[6] and Oranovate[1]+Civic[6] +Amalico[3]) seemed to be protective against having hyperpigmentation. Those who used whitening products for 2-4 weeks had significantly higher odds of having Hyperpigmentation+ acne (OR 70.6, 95%CI 6.7-741.2). In addition, participants with skin type IV were more likely to have both Hyperpigmentation and acne (OR 2.7, 95%CI 1.0-7.1). See Table 3

Acne with inflammation:A duration of < 2 weeks of using whitening had the higher odds of causing inflammation alone compared to a duration of > 6 months (OR 6.1, 95% CI 3 -11.9). Frequency of using whitening products twice had the higher odds of causing inflammation compared to using products more frequently (OR 11.9, 95% CI 3.2-11.1). Kenza[1] and Al Amira[1] creams were significantly associated with having acne as an AR. The odds of having acne using these products were higher compared to using Top gel[1]+Lucocid R creams[6] (OR 11.5, 95%CI 2.6-49). In addition, duration of using whitening products for <2 weeks and between 2-4 months were highly associated with having acne (P<0.05).

Fungal infection with straie and telangiectasia: In multivariate analysis, patients who used Al Aamira[1] cream had the higher odds of having fungal infection (OR 9.3, 95%CI 1.5-57.5). Only age group of (36-45) were associated with straie. This group had a higher odds compared to > 45 years (OR 25.7, 95%CI 1.7-382.2).

Severity of ARs: In bivariate analysis severity of ARs was associated with age, skin type, duration, frequency, and whitening products' name. Using multivariate analysis, severity of ARs was highly associated with using AL Amira[1] cream (OR 33, 95% CI 3.3-304.3). In addition, the duration of using whitening products for < 2 week as well as using whitening products once were significantly associated with the severity of ARs (OR 6.5 ,95%CI 2.9-14.8 & OR 4.8 ,95%CI 2.8-8.1 respectively). Moreover, those with skin type IV ranked the higher odds of having severity (OR 1.8, 95%CI 1.1-3.0).

Table (3): Highly associated factors with skin whitening products ARs

	Frequency(%)	P-value	Odd ratio(OR)	Confidence Interval(CI)
Acne				
AL amira[1] cream	8(11.8%)	0.001	11.53	2.69-49.45
Kenza[1] cream	28(41.2%)	0.039	6.97	1.11-43.92
<2weeks usage	17(25%)	0.000	15.25	4.88-47.71
2-6weeks usage	28(41.2%)	0.008	3.11	1.39-7.23
Inflammation				
twice/day usage	54(62.8%)	0.0001	11.86	3.19-44.13
Acne + inflammation				
2-6months usage	7(6.08%)	0.001	0.25	0.11-0.59
once/day usage	25(21.7%)	0.0001	0.15	0.07-0.33
twice/day usage	49(42.6%)	0.0001	0.26	0.15-0.45
Hyperpigmentation				
AL amira[1] cream	7(6.5%)	0.017	8.09	1.45-45.26
Extemporaneously prepared product[1]	23(21.3%)	0.025	0.39	0.17-0.89
Melanofree[5]	4(3.7%)	0.009	0.19	0.05-0.65
Amalico[3]+Movate[6]	2(1.6%)	0.001	0.07	0.01-0.33
Oranovate[1]+Civic[6]+Amalico[3]	13(12.03%)	0.026	0.35	0.14-0.88
Straie				
36-45 age group	5(18.51%)	0.018	25.78	1.74-382.21
Severity of ARs				
AL amira[1] cream	1(0.15%)	0.003	31.92	3.35-304.35
<2weeks usage	40(12.7%)	0.0001	6.59	2.93-14.84
once/day usage	134(42.7%)	0.0001	4.78	2.83-8.09
skin type IV	43(13.7%)	0.027	1.80	1.07-3.04

Discussion:

The aim of our study was to implement an adverse reaction reporting system in a dermatology hospital so as to identify ARs associated with the use of skin whitening products. We have chosen this setting as more serious ARs would finally reach hospital seeking treatment [(20)]. Hamadain dermatology hospital is the only dermatology hospital in Gezira state so our chances to report many ARs were great. The first difficulty we had run into was to get doctors accustomed with reporting practice, despite their knowledge of the importance of adverse reactions reporting. Hamadin dermatology hospital had a shortage in dermatologists at the time we began this study (only one consultant and 2 registrars and 1medical officer were available per day). This highly affected the filling of the reporting forms due to lack of time and clinical workload. Filling the reporting forms in our study was done manually. This drawback made the reporting practice time consuming and has discouraged some dermatologists from participating in filling the forms. This matches the study of Sportiello et al, as absence of fax machines in the dermatology surgery or close to it was problematic to the procedure of reporting in terms of time[(18)]. Although Hamadain hospital has a pharmacy, reporting by pharmacists was not considered in this study as pharmacists at Hamadian hospital were not deeply involved in patient care along with dermatologist. Their only role was to dispense prescriptions, which will not add to spontaneous reporting. However, notification system at the clinical pharmacist level helps the economic aspects of therapeutics [(23)] and community pharmacists, as suggested by others could effectively contribute in the reporting of ARs, although their role is controversial [(19)].

During reporting, some of the data requested in the forms for example (gender, age, occupation, income, skin type, brand and generic name of the whitening product) was not accurately filled or kept blank due to hurry in filling the forms , inaccurate answers by users or due to a certain carelessness of the users, who often did not give correctly the name of the suspected whitening product[(18)] or even drastically deny their use, this directly led to many incomplete forms which have been excluded from final analysis. The final number of reports analysed in this study (n=1000) during a period of I year is in line with other studies concerning formal cosmetovigilance systems [(11)] considering the obstacles to reporting doctors faced in our study that fully agreed with the few studies that

have analysed the problems of spontaneous reporting in hospitals [20-22]. The large number of females (98.5%) reported using skin whitening products in our results agree to previous studies, as in Lagos, Nigeria 27.6% of males and 72.4% of females' traders used skin-lightening cosmetics [24]. These results were very close to another study of which 73.3% women, and 27.6% men of four hundred and fifty Nigerians declared the use of bleaching creams [9]. The Sudanese studies related to our study scope were exclusively among females and concerning only the use of bleaching creams, for example the study in Gezira University among undergraduate's females [13], and the study among students of 19 higher secondary girls' schools in Wad Medani locality, capital of central Sudan [1]. Like other women all over the world, Sudanese women face pressure as the social perception that light skin tone is a title of beauty, attractiveness and high socioeconomic status [13] and the belief that it is the gate to self-confidence, youth, marriage and business [1] all these facts heighten the practice of skin whitening which has become a trend all over the country and was given the name "Fasikh". Moreover, Similar to what has been detected by other studies, 35.7% whitening products users included in our study tended to use two or three whitening products at the same time [14]. Many of these users preferred to mix two or more whitening products as they believed this combination would enhance and accelerate the bleaching effect plus their ability to counter act the ARs of these products [9].The predominant combination used in our study was Hydroquinone plus the very potent corticosteroid Clobetasol at 31.3% which was the common combination in related studies too[2].However of a particular concern in this study is the high use of extemporaneously (unlabelled) products at 25.1%, which were either concoctions obtained from vendors in small beauty shops or some skin whitening products with undeclared active ingredients on their labels. In Wad –Medani, Sudan, large numbers of vendors competitively work to supply unlabelled concoctions to women seeking skin whitening "Fasikh". Ironically, many of these vendors are men and concoctions are named after them [EZZO concoction, Donglawi concoction, Jedo concoction, etc.]. The containers of these concoctions never have labels of their active ingredients plus they are sold according to the customer's need where they can get just one spoon of the concoction up to a full container. In this study Ezzo concoctions were the top reported ones (analysed as extemporaneously (unknown) products). Add to that users struggled to obtain their whitening products regardless of their income or the product price. This was

evident as "Fasikh" was prevalent among all income ranges in this study. Previous socio-economic findings revealed that, the majority of participants believed that these cosmetics were economically expensive, but they insist to buy them even through their own saving financial sources [(1)]. This is in agreement with the finding that skin whitening products were easy to access and affordable from informal markets [(10)]. One concerning matter in our results is that Al Amira[1] cream, which is a skin whitening brand with no declaration of its active ingredient on its label, had the higher odds in having hyperpigmentation compared to using the combination of Top gel[1]+Lucocid R[6] (OR 8.1, 95%CI 1.4-45.3). Moreover, fungal infections were also highly associated with the use of AL Amira cream[1]. Hence, further studies to analyse the ingredients of un-labelled skin whitening products are urgently needed and will be valuable in identifying causes of whitening products related ARs. A recent paper investigating the contents of the top 10 skin lightening creams on the market in Durban, South Africa, revealed that nearly half of the analysed products contained mercury as an active ingredient (banned for use in cosmetics). Although this was neither declared on the ingredient listing nor the packaging label [(12)]. Furthermore, the concentrations of chemicals on the labelled products were largely found to be inaccurate on analysis as most products exceeded the concentrations displayed on the product [(9)]. Efficient cosmetovigilance systems would have allowed the identification of the causative ingredients and consequently the adoption of appropriate measure to counteract harmful ones [(18)].

Among those reported ARs, acne accompanied with inflammation was the highest reported AR in 11.5%. However, fungal infections (tinea incognito) were predominant in our study as they were reported alone or accompanied by striae and telangiectasia in 9.3% and 10.6% respectively. The dermatophyte infections are especially common with the use of topical corticosteroids as observed in other studies [(9-16)]. This finding is also consistent with the study that detected a change in the pattern of whitening ARs in the last 10–15 years as more steroid-actuated cutaneous side effects were seen than exogenous ochronosis due to shifting from hydroquinone to potent steroids [(17)]. This study showed that searching for beauty through whitening practice can lead to devastating complications that need further whitening treatment such as hyperpigmentation that was reported in 10.5% of the study population. However, ochronosis which is directly related to the long use of Hydroquinone was seen in only 4.9%, and only age was associated with having

this AR. Contrary to Hardwick who found that the age group (40-49) years was the highest group associated with ochronosis [15], we observed that ochronosis was prevalent among age group (20-35) years at 46.9%, and only at 12.2% for those aged more than 45 years This may have many reasons: Firstly, denying the practice of whitening and giving an inaccurate duration of using whitening products. Secondly much other dermatological pigmentation may be misdiagnosed as ochronosis. Finally, many whitening products and cosmetics contain phenol which is known to cause ochronosis [15].

With regard to categories of the whitening products certainly involved and to type of ARs observed, our results are limited by the absence of severity scales or clinical investigations to assess the severity of ARs caused by these products. However, 68.6% of patients were categorised as having severe ARs as per each doctor's own assessment and evaluation. Uncertainty of some whitening products ARs and the thought that only severe ARs should be reported were wrong ideas related to spontaneous reporting among hospital doctors [20] may have reduced the number of reports filled. Improving the reporting of whitening products ARs among healthcare professionals and the general public can help find out more accurately the numbers and extent of severity of these complications.

Conclusions and Recommendations:

This study demonstrated a high incidence of whitening products related ARs indicating the serious health effects of these products. There is an urgent need for regulations and restricted inspection to different selling channels of skin whitening products. Banning unscrupulous concoctions and extemporaneously (unknown) products is needed to avoid the damaging consequences of these products and their vague ingredients which were highly associated with whitening ARs reported in this study.

A proper vigilance system to report the adverse reactions of cosmetics (cosmetovigilance), particularly whitening products would highlight more ARs and complications of this practice. It will also increase our knowledge of their types, incidence, and severity. National education and training on different reporting tools and vigilance methods should be considered not only to different health care professionals but also to the public.

Ethical approval:

This study was granted ethical approval from the Research Department, Ministry of Health, Gezira State, Sudan (44/T/K/A/2017)

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References:

1. Yousif AK, Ahmed AA, Idris AE, Elmustafa MO, Ahmed EH. The use of bleaching creams among Central Sudan Students, 2010. Pharmacology & Pharmacy. 2014 May 13;2014.
2. Del Giudice P, Yves P. The widespread use of skin lightening creams in Senegal: a persistent public health problem in West Africa. International journal of dermatology. 2002 Feb;41(2):69-72.
3. Rusmadi SZ, Syed Ismail SN, Praveena SM. Preliminary study on the skin lightening practice and health symptoms among female students in Malaysia. Journal of environmental and public health. 2015 Jan 1;2015.
4. Kuffour RA, Dartey E, Owusu W, Dabuoh PM. Level of awareness of effects of the use of cosmetic bleaching products among women: a case study of Bolgatanga Municipality of Ghana. Res Humanit Soc Sci. 2014;4:57-62.
5. Al-Ashban RM, Barratt DA, Shah AH. Mercury Contents of Skin-Lightening 9 Marketed in Saudi Arabia. Journal of Saudi Chemical Society. 2006;10:383-8.
6. Obuekwe IF, Ochei UM. An epidemiological survey on the presence of toxic chemicals in soaps and cosmetics used by adolescent female students from a Nigerian university. Journal of International Women's Studies. 2004;5(5):85-92.
7. Bisht M, Singh S, Dhasmana DC. Effect of educational intervention on adverse drug reporting by physicians: a cross-sectional study. International Scholarly Research Notices. 2014;2014.
8. Ajose FO. Consequences of skin bleaching in Nigerian men and women. International journal of dermatology. 2005 Oct;44:41-3.
9. Olumide YM, Akinkugbe AO, Altraide D, Mohammed T, Ahamefule N, Ayanlowo S, Onyekonwu C, Essen N. Complications of chronic use of skin lightening cosmetics. International journal of dermatology. 2008 Apr;47(4):344-53.
10. Dlova NC, Hamed SH, Tsoka- Gwegweni J, Grobler A. Skin lightening practices: an epidemiological study of South African women of African and Indian ancestries. British Journal of Dermatology. 2015 Jul;173:2-9.
11. Sautebin L. A cosmetovigilance survey in Europe. Pharmacological research. 2007 May 1;55(5):455-60.

12. Ashique KT, Chandrasekhar D. Role of clinical pharmacist in cosmeto-vigilance of misuse and abuse of topical corticosteroids. Indian J Dermatol. 2017 Mar 1;62(2):213-4.
13. Ahmed AE, Hamid ME. Use of skin-whitening products by Sudanese undergraduate females: A survey. Journal of racial and ethnic health disparities. 2017 Apr 1;4(2):149-55.
14. Lartey M, Krampa FD, Abdul- Rahman M, Quarcoo NL, Yamson P, Hagan PG, Tettey Y, Gyasi R, Adjei AA. Use of skin- lightening products among selected urban communities in Accra, Ghana. International journal of dermatology. 2017 Jan;56(1):32-9.
15. Hardwick N, Van Gelder LW, Van der Merwe CA, Van der Merwe MP. Exogenous ochronosis: an epidemiological study. British Journal of Dermatology. 1989 Feb;120(2):229-38.
16. Ladizinski B, Mistry N, Kundu RV. Widespread use of toxic skin lightening compounds: medical and psychosocial aspects. Dermatologic Clinics. 2011 Jan 1;29(1):111-23.
17. Dlova NC, Hendricks NE, Martincgh BS. Skin-lightening creams used in Durban, South Africa. ETHNIC SKIN AND HAIR DISORDERS IN KWAZULU-NATAL. 2012 Nov 1:37.
18. Sportiello L, Cammarota S, de Portu S, Sautebin L. Notification of undesirable effects of cosmetics and toiletries. Pharmacological research. 2009 Feb 1;59(2):101-6.
19. Berne B, Bostrom Å, Grahnen AF, Tammela M. Adverse effects of cosmetics and toiletries reported to the Swedish Medical Products Agency 1989–1994. Contact dermatitis. 1996 May;34(5):359-62.
20. Vallano, A. *et al.* (2005) 'Obstacles and solutions for spontaneous reporting of adverse drug reactions in the hospital', *British Journal of Clinical Pharmacology*, 60(6), pp. 653–658. doi: 10.1111/j.1365-2125.2005.02504.x.
21. Kligman AM, Willis I. A new formula for depigmenting human skin. Archives of dermatology. 1975 Jan 1;111(1):40-8.
22. McGettigan P, Golden J, Conroy RM, Arthur N, Feely J. Reporting of adverse drug reactions by hospital doctors and the response to intervention. British journal of clinical pharmacology. 1997 Jul;44(1):98-100.
23. Sautebin, L., 2008. Understanding the Adverse Effects of Cosmetics. Drug safety, 31(5), pp.433-436.
24. Adebajo, S., 2002. An epidemiological survey of the use of cosmetic skin lightening cosmetics among traders in Lagos, Nigeria. Mercury, 5(7), pp.43-8.