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PRACTICE, ATTITUDE, AND KNOWLEDGE OF PRESCRIBING GLUTATHIONE AMONG DERMATOLOGISTS IN SAUDI ARABIA

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ABSTRACT

Objectives: To assess practice, attitude, and knowledge of prescribing glutathione among dermatologists in Saudi Arabia. **Methods:** A cross-sectional study was conducted in 9 cities of Saudi Arabia to evalute knowledge, attitude and practice of prescribing glutathione among dermatologists. The study collected data from 243 dermatologists at public and private hospitals of the studied cities. Data about dermatologists' socio-demographic characteristics and their knowledge, attitudes and practice of prescribing glutathione were collected through predesigned structured self-adminsted questionnaire. The collected data were analyzed using appropriate statistical methods. **Results:**The study analysed data from 243 dermatologists. Their mean age was 37.2 ± 9.8 years, and 46.1% of them were male and 53.9% were female. 14.4% of dermatologists were found to practice prescription of glutathione to their patients particularly those with hyperpigmantation (63%). The level of good knowledge among the dermatologists was very low (4.1%). The level of knowledge was found to signficantly increase among senior, high educational degree dermatologists, and those working at private hospitals. **Conclusion**: The present study revealed that small percent of dermatologists (14.4%) prescribe glutathione for their patients. 63.6% of the dermatologists stated that there is no strong evidences supporting the usefulness of glutathione. This might be the reason behind not prescribing glutathione for their patients. The level of good knowledge among the dermatologists was very low (4.1%). Dissemination of this study findings is as important as for the dermatologists all over the Kingdom to know their current background about glutathione. Random controled trials regarding the use of glutathions for dermatological indications are crucial.

INTRODUCTION

Glutathione (GSH) is the most abundant low-molecular weight intracellular thiol in mammals. Glutathione, a tripeptide of cysteine, glycine, and glutamate, is primary antioxidants in the body and plays important roles in maintaining intracellular thiol status and in detoxification.[1,2] Glutathione is naturally synthesized in the body, and involved with numerous biochemical pathways and may have some role in different diseases.[3,4]

There have been preliminary recent studies for glutathione uses for a number of diseases; such as Parkinson's disease ,[5,6], cataract.[7], glaucoma.[8],asthma.[9] primary idiopathic male infertility.[10] and with cancer therapy to reduce its side effects.[11].In dermatology, glutathione is frequently used in skin lightening through its anti-melanogenic effects. There have been some study trials conducted on the oral version and on a topical lotion. These trials have been small sample sized but generally with positive results.[12-15]

The aggressive media campaigns all over the world about the magic and exaggerated effects of glutathione as a skin lightening agent, and over-the-counter availability of this drug, have resulted in random and false consumption. The consumers, as well as dermatologists who prescribe oral glutathione for general skin lightening or as an adjuvant for disorders of hyperpigmentation, are often oblivious about its efficacy, dosing and adverse effects. Moreover, dermatologists may encounter patients who are inclined to self-medicate with glutathione, enticed by the manufacturers' claims, without any previous knowledge about this treatment. The present research aimed to intelligently answer all these queries through the assessment ofknowledge, attitude and practice of prescribing glutathione in patients attending dermatology clinics among dermatologists in the Kingdom of Saudi Arabia.

OBJECTIVES: To assess practice, attitude, and knowledge of prescribing glutathione among dermatologists in Saudi Arabia.

METHODS AND MATERIALS

This cross-sectional study analyzed data from 243 dermatologists at dermatology clinics from public and private hospitals in Saudi Arabia during the period from 1 December to 30 December 2016. A multistage,

stratified cluster sampling procedure was employed, in which 9 cities (Abha, Khamis Mushayt, Jeddah, Hail, Riyadh, Al-Hassa, Arar, Jazan, and Makkah) were chosen randomly from the defined five regions of Saudi Arabia (Northern, Western, Southern, Eastern and Central). From each chosen city, public and private hospitals were randomly chosen. Finally, within each selected hospital, all dermatologists were invited to participate in the study. The participation in this study was voluntary. The privacy and confidentiality of data were considered as the data were collected and manipulated anonymously. The study aim and scope were carefully explained to the dermatologists and their informed consent was obtained.

Dermatologists who agreed to participate in this study were asked to click and fill a predesigned structured self-administerd questionnaire (Appendix 1). The questionnaire was developed, reviewed and validated by dermatology experts and an epidemiologist. The study questionnaires were distributed manually to the participated dermatologists by the researchers.

Assessment of attitudes

Attitudes towards glutathione use was assessed using modified Likert response scale from 1-3 (1= agree; 2= neutral; 3= disagree). The attitude items was included 5 statements represnting all aspects concerning glutathione use. Item and scale score are reported in the range + 1 to -1. The midpoint zero corresponds to the neutral Likert scale rating of 0, +1 corresponds to agree, and -1 corresponds to disagree.

Assessment of knowledge

The knowledge was assessed by14 questions. The correct ansewer for all questions is yes. Three answers for each question (yes, no and do not know) were proposed. For simplicity, "no" and "do not know" answers were categorized as "no". Each knowledge item was scored as follows: correct answer = 1, and incorrect answer = 0. Total knowledge were then assessed and categorized into good, fair and poor according to the sum of knowledge score given for each studied item. Good knowledge was defined if the respondents' correct answers was more than 75%, fair knowledge (50-75%), and poor knowledge if less than 50%.

STATISTICAL ANALYSIS

The collected data were entered and analyzed using Statistical Analysis System (SAS) software pakage (16). Data were presented using frequencies, means and standard deviation (SD). The dermmatlogists' knowledge, attitude and practice were assessed, analyzed and compared by their identification data using unpaired Student's t-test (for continuous data) and chi squared tests (for categorical data). P values ≤ 0.05 were used as a level of statistical significance.

RESULTS

Table 1. Characteristics of the dermatologists

Characteristics*	**N= 243**
Age in years, mean ±SD (range)	37.2 ± 9.8 (26, 66)
Sex	
Male	112 (46.1)
Female	131 (53.9)
Higher education certificate	
M.B, B.Ch.	50 (20.6)
M. Sc	45 (18.5)
Ph. D or MD	76 (31.3)
Saudi Board	72 (29.6)
Current job title	
Resident	109 (44.9)
Specialist	94 (38.7)
Consultant	40 (16.4)
Years of experience mean ±SD (range)	8.9 ± 8.2 (1,36)
Hospital	
Public	129 (53.1)
Private	114 (46.9)

*Data are presented by mean ± SD or by n (%).

Table 2. Distribution of the dermatologists by their characteristics and practice of prescribing glutathione

Characteristics	**Glutathione prescribing practice**		**P. value**
	Yes (n= 35)	**No (n= 208)**	
Sex			
Male	15 (13.3)	97 (96.7)	
Female	20 (15.3)	111 (94.7)	0.68

Higher education certificate			
M.B, B.Ch.	6 (12.0)	44 (88.0)	
M. Sc	12 (26.7)	33 (73.3)	
Ph. D or MD	15 (19.7)	61 (80.3)	
Saudi Board	2 (2.8)	70 (97.2)	**0.001****
Current job title			
Resident	10 (9.2)	99 (91.8)	
Specialist	18 (19.2)	76 (81.8)	
Consultant	7 (17.5)	33 (82.5)	0.10
Hospital			
Public	4 (3.1)	125 (96.9)	
Private	31 (27.2)	83 (72.8)	**0.0001****
Saudi city			
Abha	3 (60.0)	2 (40.0)	
Khamis mushayt	5 (33.3)	10 (66.7)	
Jeddah	8 (16.0)	42 (84.0)	
Hail	5 (23.8)	16 (76.2)	
Riyadh	2 (5.7)	44 (94.3)	
Al-Hassa	4 (8.0)	46 (92.0)	
Arar	2 (10.5)	17 (89.5)	
Jazan	2 (11.1)	16 (88.9)	
Makkah	4 (11.4)	15 (88.6)	**0.01****

* Significant at 0.05
** Significant at 0.01

Table 4. Frequency distribution of the dermatolgists by glutathione attitude scale

Attitude items*	Agree	Neutral	Disagree
1. Glutathione is a magic treatment for skin lightening (whitening)	12.7	33.3	54.0
2. Glutathione achieves the improvement that you and your patient desire	9.8	49.6	40.6
3. Taking glutathione in diet is better than taking it as medication	46.7	36.8	16.5
4. The price of glutathione in pharmacies satisfy all economic levels of patients	7.0	34.0	59.0
5.No strong evidences supporting the usefulness of glutathione	63.6	31.8	4.6

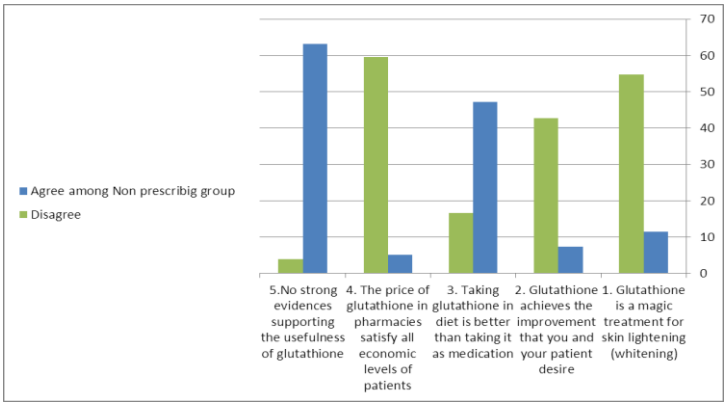


Figure 5. Frequency distribution of the dermatolgists by glutathione attitude scale

Table 5. Frequency distribution of the studied dermatolgists by glutathione attitude scale and their practice

Attitude item*	Prescribing n =35			Non prescribig n= 208			P value
	Agree	Neutral	Disagree	Agree	Neutral	Disagree	
1. Glutathione is a magic treatment for skin lightening (whitening)	7 (20.0)	11 (31.4)	17 (48.6)	24 (11.5)	70 (33.7)	114 (54.8)	0.32
2. Glutathione achieves the improvement that you and your patient desire	9 (25.7)	16 (45.6)	10 (28.6)	15 (7.3)	103 (50.0)	88 (42.7)	**0.002****
3. Taking glutathione in diet is better than taking it as medication	15 (42.9)	14 (40.0)	6 (17.1)	98 (47.2)	75 (36.1)	35 (16.7)	0.88

4. The price of glutathione in pharmacies satisfy all economic levels of patients	6 (17.1)	9 (25.7)	20 (57.1)	11 (5.2)	73 (32.2)	124 (59.6)	**0.03***
5.No strong evidences supporting the usefulness of glutathione	23 (65.7)	9 (25.7)	3 (8.6)	131 (63.2)	68 (32.8)	9 (4.0)	0.37

* Significant at 0.05
** Significant at 0.01

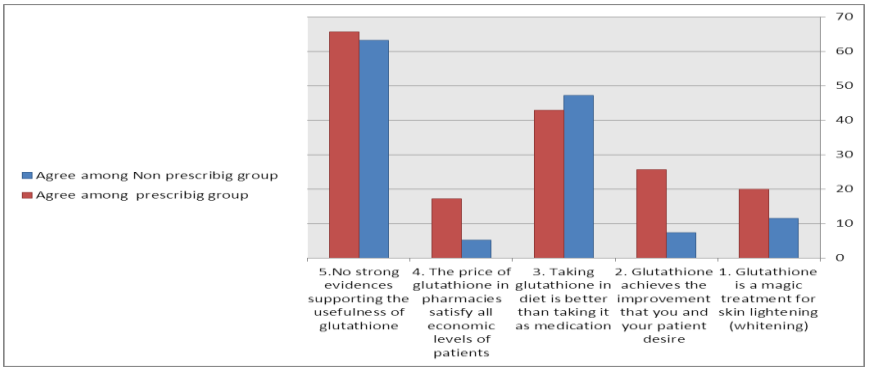
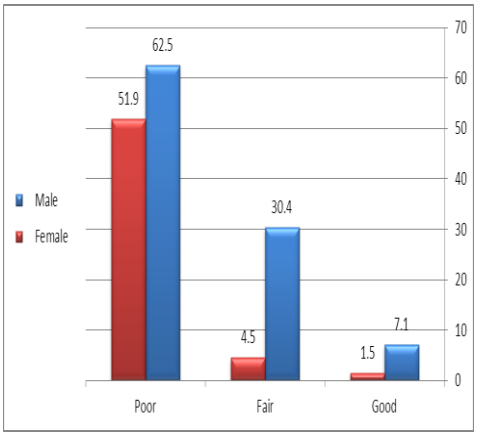


Figure 6. Frequency distribution of the studied dermatolgists by glutathione attitude scale and their practice

Table 3. Knowledge of the dermatologists about all studied items of glutathione according to their characteristics

	Level of knowledge			P. value
	Good n (%)	**Fair n (%)**	**Poor n (%)**	
All subjects	10 (4.1)	96 (39.5)	137 (56.4)	-
Sex				
Male	8 (7.1)	34 (30.4)	70 (62.5)	
Female	2 (1.5)	61 (4.5)	68 (51.9)	**0.01****
Higher education certificate				
M.B, B.Ch.	0 (0.0)	9 (18.0)	41 (82.0)	
M. Sc	0 (0.0)	22 (49.0)	23 (51.0)	
Ph. D or MD	7 (9.2)	27 (33.5)	42 (57.3)	
Saudi Board	3 (4.2)	37 (51.4)	32 (44.4)	**0.002****
Current job title				
Resident	2 (1.8)	40 (36.7)	67 (61.5)	
Specialist	6 (6.4)	40 (42.5)	48 (51.1)	
Consultant	2 (5.0)	15 (37.5)	23 (57.5)	0.50
Hospital				
Public	5 (3.9)	48 (37.2)	76 (58.9)	
Private	5 (4.3)	47 (41.3)	62 (54.4)	0.80
Practice of prescribing glutahione				
Yes	3 (8.5)	15 (42.9)	17 (48.6)	
No	7 (3.3)	85 (40.9)	116 (55.8)	**0.02***

* Significant at 0.05
** Significant at 0.01
*Significant. Fischer exacts tests were used. P value was done at 0.05.



P Value = 0.01

Figure 1. Knowledge of the dermatologists about all studied items of glutathione according to the gender

P Value = 0.002

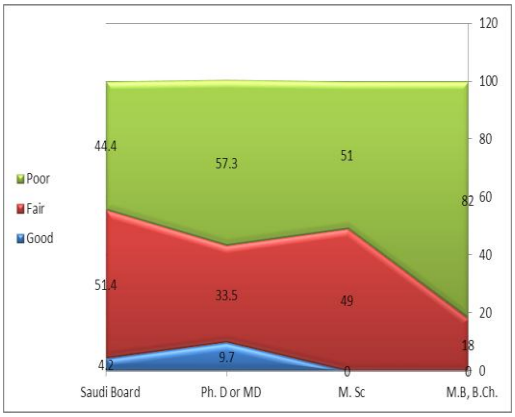


Figure 3. Knowledge of the dermatologists about all studied items of glutathione according to the Current job title

P Value = 0.50

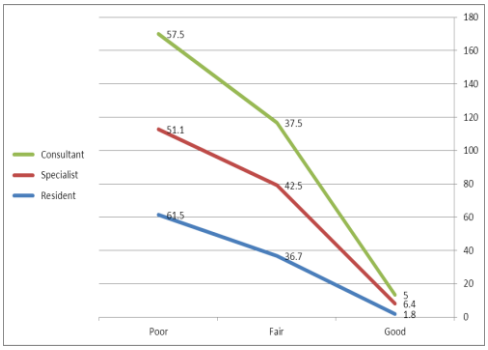
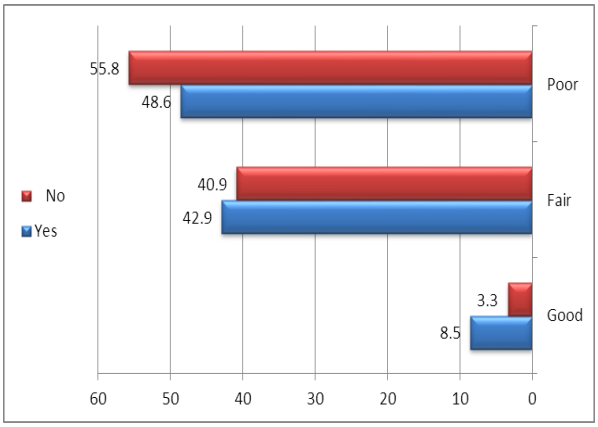


Figure 4. Knowledge of the dermatologists about all studied items of glutathione according to the Practice of prescribing glutahione

P Value = 0.02



THE RESULTS

A cohort of 243 dermatologists (112 male and 131 female) were participated in this study. These dermatologist were from (Abha (n= 5), Khamis Mushayt (n= 15), Jeddah (n= 50), Hail (n= 21), Riydh (n= 46), Al-Hassa (n=50), Arar (n= 19), Jazan (n= 19), and Makkah (n= 19)).

Table 1 shows the characteristics of the studied dermatologists. The mean age (±SD) of the studied dermatologists was 37.2 ± 9.8 years, of them 46.1% were male and 53.9% were female. More than half of the studied dermatologists(53.1%) were from public hospital and about one third of them (31.3%) have had Ph.D. degree. Their current job title was 44.9% residentss, 38.7% specialists, and 1.4% consultants. The mean experience years was 8.9 ± 8.2.

The prevalence of glutathione prescription among the studied dermatologists was 14.4% (35 out of 243). Of these 35 dermatologists, 22 (63%) were reported that they prescribe glutathione for hyperpigmentation cases, 7 (20%) prescribe it for skin whitening, and 6 (17%) for pregnancy induced hyperpigmentatin (PIH). Almost all of those 35 dermatologists have reported that they prescribe glutathione in the form of pills and cream. Only one of them has reported skin rashs as a side effect of glutathione. Table 2 displayed the result of distribution of the studied dermatologists according to their charcteristics and practice of prescribing glutathione. The practice of prescibing glutathione was among dermatologists with M.Sc (26.7%) and Ph.D (19.7%) degrees, working in private hospital (27.2%) in Abha (60%), Khamis Mushayt (33.3%), Hail (23.8%) and jeddah (16%). The lowest proportion of practice of prescibing glutathione was found among dermatologists in Riyadh city (5.7%). Although not significant, there have also been differences in dermatologists practice of prescribing glutathione by their sex where the higher proportion of practice was detected among female dermatologists (15.3%) comared to 13.3% among male dermatologists.

Table 3 showed the result of level of knowledge of dermatologists about all studied items of glutathione according to their characteristics. The level of good

knowledge was detected in only 10 of the dermatologists (4.1%). The level of good knowledge was signifcantly higher among males (7.1%) compared to females (1.5%), and those reported to have Ph.D (9.2%) and saudi board (4.2%) degree. A statistically significant difference was also found among dermatologists regarding the knowledg of prescribing glutathione where the highest level of good knowledge was found among those prescribing glutathione compared to those not prescribing glutathione (8.5% vs. 3.3%). Although not statistically significant, the level of good knowledge was higher among specialists, consultants and those working in private hospitals.

Table 4 showed the distribution of attitude scale among the studied dermatologists. High percent of dermatologists agree that the absence of strong evidence that support the usefulness of glutathione, as well as absence of good knowledge about glutathione hinder its medical use. 12.7% of dermatologists agreed that glutathion is a magic treatment for skin lightening. About half of the studied dermatologists (46.7%) agreed that taking glutathione in diet is better than taking it as medication. Less than one fifth of the studied dermaologists agreed that glutathione achieves the improvement that dermatologists and patient desire (9.8%), and that the price of glutathione in pharmacies satisfy all economic levels of patients (7.0%)

Table 5 presented the distribution of the studied attitude items among dermatologists by their practice of prescribing glutathione. Taking glutathione in diet is better than taking it as medication showed high precent of agree among non practicising dermatologists, although not signficant. For other studied attitude items, there have been high percentsof favorable attitude among practicising dermatologists. There have been statistically signficant differences between practicising and non practicising dermatologists regarding the attitude items concerning glutathione to achieve the improvement that the dermatologists and his/her patient desire (p= 0.002), and that the price of glutathione in pharmacies satisfy all economic levels of patients (p= 0.03).

DISCUSSION

The present study has evaluated knowledge, attitude and practice of prescribing glutathione among dermatologists in Saudi Arabia. The practice of prescribing glutathione among the studied dermatologists was found to be low (14.4%). The higher proportion of dermatologists reported practice of glutathione was observed among females (15.3%), dermatologists with M.Sc (26.7%) and Ph.D (19.7%) degrees, those working in private hospital (27.2%) and among dermatologists working in Abha (60%), Khamis Mushayt (33.3%), Hail (23.8%) and Jeddah (16%). The lowest proportion of of prescibing glutathione was found among dermatologists in Riyadh City (5.7%). The overall low practice of prescribing glutathione among the studied dermatologists observed in this syudy might be contributed to low level of good knowledge detected among them. These findings have appeared consistent with the reports suggesting the importance of knowledge and sharing information in medical practice.[17-19]

The majority of dermatologists prescribing glutathione reported that they prescribe glutathione for pigmentation and hyperpigmentation (63%), and skin whitening (20%). The use of glutathione for treatment of melasma was also reported by 8.5%. Most of previous stuy trials were conducted to evalutae the effect of glutathione in skin lightening on oral version and on a topical lotion.[12-15] Although these trials were of small sample size, they reported positive results.

The role of glutathione as a skin-lightening agent was an accidental discovery when skin lightening was noticed as a side effect of large doses of glutathione.[20] Various mechanisms for the hypopigmentary effect of glutathione have been proposed, with inhibition of tyrosinase being the most important. Glutathione can reduce tyrosinase activity in three different ways.[21] Tyrosinase is directly inhibited through chelation of the copper site by the thiol group. Secondly, glutathione interferes with the cellular transfer of tyrosinase to premelanosomes, a prerequisite for melanin synthesis.[21] Thirdly, tyrosinase inhibition is effected indirectly via its antioxidant effect. Glutathione shifts melanogenesis from eumelanin to phaeomelanin synthesis by reactions between thiol groups and dopaquinone leading to the formation of sulfhydryl-dopa conjugates.[22] Glutathione is known to have potent antioxidant properties. The free radical scavenging effect of glutathione blocks the induction of tyrosinase activity caused by peroxides (22). Glutathione has also been shown to scavenge ultraviolet radiation induced reactive oxygen species generated in epidermal cells.[23] A recent study on melasma patients noted significantly higher levels of glutathione-peroxidase enzyme in patients compared to controls, confirming the role of oxidative stress in melasma.[24] Based on these observations, the potential of glutathione in management of melasma and hyperpigmentation seems plausible.[25] Also, a recent randomized, double-blind, placebo-controlled, matched-pair study including 30 women has demonstrated that topical glutaione application to the face whitened the skin and improved skin condition in healthy women.

In our study, 3 out of 35 practicising dermalogists (8.5%) were found to prescribe glutathione for pregnancy induced hyperpigmrntation. The effect of multivatimens and antioxidents use in normal preganancies and in cases of pre-eclampsia has been evalutaed.[26] The authors reported that there were no significant differences in normal pregnancy group with and without multivitamin supplementation. However, the levels of creatinine, urea, cystatin, malondialdehyde (MDA) were significantly lower in pre-eclampsia cases with vitamin supplementation.

The current study demonstrated a very low percent of good knowledge (4.1%) about glutathione among the studied dermatologists. However, the level of good knowledge was slightly increased among male dermatologists, those with Ph.D degree, specialists, consultants, those working in private hospitals, and those prescribing glutathione. Due to lack of similar studies, results cannot be directly compared and discussed with other studies. However, we have tried to discuss some aspects of our results the study data and with other studies. The low level of knowledge about glutathione in this study might be attributed to the years of experiences among the studied dermatologists. For example, the mean years of experience showed statistically signficant differences (p<.0001) among the studied dermatologists by their job title and educational degree and working hospital. It was 10.9 among specialists, and 17.5 among consultants, 12.1 among dermatologists in private hospital. On the other hand, however, the mean experience years was 5.9 among public hospital dermatologists, 3.5 among dermatologists with M.B,B.Ch degree, and 2.9 among residents. In our sample, the residents and M.B,B.Ch subjects were representing more than one half of the sample. In a previous study.[27] assessed the awareness and knowledge regarding bisphosphonates related osteonecrosis of the jaw (BRONJ), in a sample of 222 physicians and dentists in Riyadh Military Hospital (RMH), Saudi Arabia, there have been statistically significant associations between knowledge and qualification (p=0.01), years of experience (p=0.002), and specialty (p=0.03).

Awareness about glutathione was evaluted in a cross-sectional study in Pkistan on 100 pharmacy undergraduate students.[28], and reported that 33 % of the studied students knew the function of glutathione, 25 % knew about the consequences of its deficiency and 12 % about its treatment approach. In another recent cross-sectional study conducted in Solapur, India.[29] to assess knowledge attitude of physicians regarding their use of antioxidants in patients with hypertension and to assess prescribing practices of antioxidants amongst these physicians. The authors in this study reported that 24 of the studied physicians (80%) were aware of the role of oxidative stress in hypertension and 70% believed in prescribig antioxidants and its positive results on blood pressure, and 33.3% were actually prescribing antioxidants.[26] However, the objectives and methodology and of this study have appeared to be out of our study scope as this study has evaluated the KAP of antioxidents, in general, and only evaluted its role in hypertension. Moreover, It was included very small sample size of physicians and cardiologists (n= 30) and it was used a questionnaire including only 10 questions.

The present study findings have also revealed a high percent of favorable attitude among studied dermatologists towards the absence of knowledge about glutathione hinders its medical use (71.4%) and no strong evidences supporting the usefulness of glutathione (63.6%), and there were no ststistically significant differences between practicising and none preacticising dermatologists regarding these studied attitude items.Although of these findings, however, the use of glutathione have been reported in treatment of many diseases including;Parkinson's disease.[5,6], cataract.[7], glaucoma.[8], asthma.[9], primary idiopathic male infertility.[10], autism.[30], cystic fibrosis.[31], and with cancer therapy to reduce its side effects.[11]

In our study, about one half of dermatologists have preferred taking glutathione in diet is better than taking it as medication. Glutathione is better to be taken in diet and it is found in fresh fruits, vegetables, and nuts are natural sources of glutathione. Also, tomatoes, avocados, oranges, walnuts and asparagus are some of the most common edibles that help to increase levels of glutathione in the body.[32]

The present study appeared to have a number of strengths. The study questionnaire was comprehensive and addressed almost all items related to glutathione. Also, the study questionnaire has been validated by an epidemiologist and dermatology professors. To the best of the available literature, this study is the first to evaluate knowledge, attitude and practice of prescribing glutathione among dermatologists in Saudi Arabia. Moreover, the study was national and has colleted data from public and private hospitals in 9 Saudi cities representing different regions of the Kingdom. The current study evaluated not only the awareness and practice of prescibing glutathione, but it also compared knowledge, attitude and practice of the studied dermatologists by their sex, higher education certificate, hospital, and current job title. However, the limitation of this study was that the study results cannot be directly compared and discussed with other studies because of the lack of similar studies in Saudi as well as in global literature.

In conclusion, the present study revealed small percent of dermatologists prescribe glutathione for their patients. This is not because it is not FDA approved but because of the low lvel of awareness among the studied dermatologists in Saudi Arabia regarding glutathione. Dissemination of this study findings is as important as for the dermatologists all over the Kingdom to know their current background about glutathione. Random controled trials regarding use of glutathions for skin is crucial.

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COMPETING INTERESTS
The authors declare that there have no competing interests regarding the publication of this manuscript. No funding was taken from any institutons to conduct this study.

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