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Phytochemical and Pharmacological Effect of *Phoenix dactylifera L.* (Ajwa date) Seeds on Imiquimod-Induced Psoriasis Like Inflammation in Mice

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Abstract

Bioactive compounds present in date palm seeds that comprise varied secondary metabolites include phenolic acids, flavonoids and non-polar phytosterols with their different quantity were investigated in the current study as natural sources in determining the pharmacology effects of these bioactive compounds. The qualification and quantification of these bioactive compounds in date palm seeds had been done to be employed in an animal model for psoriasis. The extraction and fractionation is done for Phoenix dactylifera L. as using two important fractions. The phenolic/flavonoid and phytosterols fractions. Thirty albino mice were divided into 5 Groups including Group I healthy mice; Group II the psoriasis induction group with 5% imiquimod cream; Group III the psoriasis induction mice treated with the clobetasol 0.05% ointment; Group IV and V represent psoriasis induction mice treated with *Phoenix dactylifera* L. phenolic/flavonoid fraction 4% ointment and phytosterols fraction 4% ointment respectively. The treatments groups were applied once daily for five days. The seeds phytochemical screening showed the presence of tannins, polyphenols, flavonoids, and glycosides. Vanillic acid, Ellagic acid, Gallic acid, and others are detected as phenolic compounds. Rutin and Quercetin are detected as flavonoids in the ethanolic fraction, while β- Sitosterol and Stigmasterol detected as a phytosterols in the n-hexane fraction. The pharmacology effects showed that the IHC of IL-17, TGF-beta, and EGF are significantly decreased with phenolic/flavonoid fraction when compared to psoriasis induced group. For phytosterols fraction treated group, the Munro abscess, parakeratosis, and dermis lymphocytic infiltrate are significantly decreased with other changes compared to psoriasis induced group. Different bioactive compounds in *Phoenix dactylifera L.* suggest a synergistic effect of these components may indicate a benefit in the future therapy of psoriasis or other disease.

Key words: β- Sitosterol, Phoenix dactylifera, Phytosterols, Psoriasis, Stigmasterol.

Introduction

Different pharmacological actions such as anti-inflammatory effects, are found in many useful medicinal plants due to the effect of organic compound that they contain. This idea needs to be investigated furthermore and further steps toward clinical studies have to be done [(1)]. Starting with the investigation of plant product information like plant origin, characteristic, active compound, pharmacology of compound, dose related information and different safety studies [(2)]. Date palm (*Phoenix dactylifera L.*) is an important edible date in North Africa and the Middle East consumed as a good source of carbohydrates mainly glucose and fructose, beside minerals as potassium and magnesium and the dietary non-starch polysaccharides. Date carbohydrate intakes provide 10% of energy needed and provides about one-fourth of potassium recommended for daily need.

In spite of wide distribution of date palm around the world, *Phoenix dactylifera* is considered the most socioeconomically important tree, [(3)] and all types were differed in many phenotypic and genotypic traits including the morphological and nutritional importance. Date palm was considered to be a multipurpose uses plant as they utilized as active components with antioxidant property and other bioactive rich source beside being a raw material in a huge number of food products, for human and animals [(4)], with increase interests in their waste usage in the production of medicinal products, antibiotics, biopolymers and currently the beneficial in biofuels production [(5)].

Bioactive compounds are naturally present in date palm fruits and seeds that comprise varied

carotenoids, and flavonoids and their quantity were dendritic cell again to make a permanent inflammatory skin [8]. Collectively psoriasis includes many process like antigen presentation, transcription arrangement, cell immunity activation, cell and inflammatory cytokine signal networks association. Classically, it can be said it is a IL-23/IL-17 inflammatory and a Th1/17 cell dependent disease [9]. The use of corticosteroid even for short period have a light side effect that includes a topical effect, hyperglycemia, hypertension, pancreatitis, electrolyte abnormalities, immunologic, hematologic and neuropsychological side effects and those can occur sometime significantly. In addition to that, the use of corticosteroid for long period causes a more sever side effect like osteoporosis, avascular osteonecrosis, adrenal insufficiency, some congenital malformations, growth suppression, hyperlipidemia, liver, gastrointestinal and ophthalmological side effects [10].

The presence of the serious side effect of steroid and other drugs suggest the search for finding a safer and effective therapy for psoriasis and this research used to find a newer pharmacological effect of *Phoenix dactylifera* seeds on imiquimod mice model of psoriasis.The study was aimed to identify the important biological compounds present in the seeds of the Ajwa dates and then study the extract in terms of its biological effectiveness on imiquimod-induced psoriasis like inflammation in mice.

Materials and Methods

Kits and chemicals

Immunohistochemistry kits include epidermal growth factor (EGF) (Catalog number ab184265), and interleukin -17 (IL-17) (catalog number ab214588) purchased from Abcam company (USA) while transforming growth factor (TGF beta 1) kit (Catalog number SL0086R) purchased from Sunlong Biotech company (China). All chemicals and reagents used were of high-quality grade. All standards were from Sigma-Alidrich Company. The high-efficiency liquid chromatographic (HPLC)examination was carried out at the Ministry of Science and Technology/Baghdad – Iraq, the instrument origin was Shimadzu, Japan.

Plant collection

Date fruits of *Phoenix dactylifera L.* were purchased from AL-MADENA ALMUNORAH/Sudia markets at 2019, authenticated by Iraqi local Herbarium in Al-Razi center for alternative medicine as *Phoenix dactylifera L.*. Seeds were collected, washed, dried, and powdered with the aid of electrical industrial miller to get fine powder and to be kept in well tight dry containers.

Ethanolic Seeds Extraction for Total Phenolic compounds

For total phenolic compounds extraction from date seeds, a cold extraction method was employed. About 150 g powered seeds was macerated in 1000 ml ethanol 80% v/v, for a week in a dark place with shaking occasionally to be filtered and dried with the different at various stages of ripening. The date possessed different bioactive components, many of them considered to be effective as antioxidant compound specially the phenolic acids and Polyphenolic that the plant rich with [5]. Psoriasis is an inflammatory chronic autoimmune disease affecting the skin and related to different environmental and genetic factors. It is widely distributed in many countries and reach to about 125 million patients through the world [6]. Skin inflammation in psoriasis occurred by the immune activation of cell continuously [7].

Many cells affect the pathogenicity of psoriasis. Those are T cells, dendritic cells, and keratinocytes. The signals between those cells include IL-12, IL-23, Type I IFNs, INF-gama, IL-17, IL-22 and TNF- alpha which may be assisted with additional immune cell factors, lead to production of keratinocyte inflammatory precursors in addition to proliferation and differentiation of the epidermis cells synchronously. This cycle is repeatedly occurring lead to amplify the signal finally.The increase concentration of inflammatory mediators and change the homeostasis of the skin affecting the T cell and secondary metabolites include phenolic acids, aid of rotary evaporator apparatus at 45° C. The maceration process was carried out again on the marc twice and all filtrates were collected before drying. The residue was weighted and kept in a dark container for next steps [11].

Preliminary phytochemical screening

The preliminary investigation of a major active constituent in the palm seeds powder was done by suspending 150mg from ethanolic seeds residue in 50ml D.W, then filtered using (Whatman No. 1) filter paper. The filtrate was subjected to check the absence or the presence of different secondary metabolites as the following in Table 1.

Analysis the phenolic compounds by HPLC technique [15]

HPLC conditions for analysis of the phenolic compounds of the seed residue was shown in Table (2-a& b).

Extraction of Non-polar lipid compounds from seeds with n-hexane by Soxhlet

In general, Soxhlet extraction is the most common technique for non – polar components present in Ajwa seeds [16, 17]. Briefly, about 150 g from dried powdered seeds was put in the apparatus thimble to be extracted with 250 ml n-hexane for 8 hours. The hexane layer was evaporated by rotary evaporator at45 °C to get 6 g oily residue solidified by cooling that represent as 8.6% w/w dried seeds.

Analysis The n- Hexane Layer by HPLC Technique

HPLC conditions for the analysis of the non-polar compounds extracted by n- hexane solvent was estimated by HPLC apparatus according to the conditions in reference [18] shown in Table(3).

Table 1. phytochemical screening tests of *Phoenix dactylifera* L. Seeds extracts

Constituent class	Chemical Tests	Experimental procedure	Reference
Saponins	Foam test	2 ml of extract + 10 ml of distilled water, agitated in test tube for 5 minutes	12
Tannins	1%Lead acetate test	2ml of extracts + few drops of lead acetate (1%) solution	13
Polyphenols	Ferric chloride test	2 ml of extract + 2 ml 5% ferric chloride solution	14
Flavonoids	Alkaline reagent test	2 ml of extract + few drops of sodium hydroxide solution	14
Alkaloid	Dragendroff' test	5 ml of extract + few drops of Dragendroff' reagent (solution of potassium bismuth iodide)	14
	HCl test	2 ml of extract + 1 ml of HCl	14
	Mayer reagent	Few drops of acidified plant extract + few drops of Mayer reagent (solution of potassium iodide mixed with $HgCl_2$)	14
Reducing sugar	Benedict's test	5 ml of extract + few drops of Banedict's reagent + boiling on water bath	12

Table 2-a . HPLC conditions analysis for phenolic compounds

Parameters	Conditions	
Instrument	Shimadzu, Japan	
Mobile phase	A= 0.1% Acetic acid (20%) B= Methanol (80%)	
Column	ODS_{C18} (250× 4.6 Id) mm/5µm partical size	
Flow rate	0.8 ml / min	
Injection Volume	20 µl	
Concentration of sample	50 mg / 1 ml	
Detection wavelength	UV-Vis at λ 254nm for phenolic acids & 280nm for flavonoids	
Column Temperature	Room Temperature	
Phenolic acid Standards used	Phenolic acid	Injection concentration (ppm)
	Vanillic acid	1
	Ellagic acid	1
	Gallic acid	1
	Syringic acid	1
	Chlorogenic acid	1
	Caffeic acid	1
	Ferulic acid	1
	Sinapic acid	1
	Salicylic acid	1
	Benzoic acid	1

Table2-b. HPLC conditions analysis for flavonoid compounds

Parameters	Conditions	
Instrument	Shimadzu, Japan	
Mobile phase	Methanol (70%)	
Column	ODS_{C18} (250× 4.6 Id) mm/5µm partical size	
Flow rate	0.8 ml / min	
Injection Volume	20 µl	
Concentration of sample	50 mg / 1 ml	
Detection wavelength	UV-Vis at λ 254nm for phenolic acids & 280nm for flavonoids	
Column Temperature	Room Temperature	
Flavonoids Standards used	**Flavonoids**	**Injection concentration (mg/l)**
	Rutin	5
	Coumarin	5
	Quercetin	1
	Catechin	2.5
	Apigenin	5
	Kaempferol	1
	Naringin	2.5
	Luteolin	1

Table 3. HPLC conditions analysis for Non-polar compounds

Parameters	Conditions
Instrument	Shimadzu, Japan
Mobile phase	methanol and acetonitrile (9:1 v/v)
Column	reversed-phase C18 column (250 x 4.6 mm i.d.; 5 µm).
Flow rate	1.2 ml / min
Injection Volume	20 µl
Concentration of sample	4 mg / 1 ml
Detection wavelength	UV-Vis at λ 202 nm
Column Temperature	Room Temperature
Standard used	β- Sitosterol (5µg/ml)
	Stigmasterol (5µg/ml)

Pharmacological study of the Seeds Extract on Animal Model

Preparation The Ointment Dosage Form For Topical Treatment

In order to study the biological effect of Ajwa seeds extracts and investigate their pharmacological analysis on imiquimod-induced psoriasis like inflammation in mice. Both extracts were introduced in a topical dosage form as an ointment with aid of Vaseline as inert base to be mixed with the seed extract residue use weight of 4 g of the n-hexan seed extract residue and ethanolic seeds extract separately and mixing them first with a small amount of glycerin (about 1ml) to achieve homogenization per 100 g Vaseline base ointment, in concentration of 4%W/W by the incorporation method [19].

Study Design

The pharmacology part was done in the pharmacology and toxicology department, college of pharmacy, AL- Nahrain University was done. Six weeks thirty albino male mice used in this study. The animals were divided into five groups randomly (six mice in each group).

Group I: Six healthy mice with normal feeding without any treatment.

Group II: Six mice treated with imiquimod 5% (250 mg of cream) topically used once daily (Glenmark company) on the dorsal area of mice back skin for five days [20].

Group III: Six mice as treated group starting with imiquimod induction, then after three hours' application of the treatment with clobetasol 0.05% w/w ointment (SDI company) was used [21].

Group IV: Six mice as treated group starting with imiquimod induction, then after three hours' application of treatment with Phoenix *dactylifera* phenolic/flavonoid fraction 4% ointment topically was used [22].

Group V: Six mice as treated group starting with imiquimod induction, then after three hours' application of treatment with *Phoenix dactylifera* phytosterols fraction 4% ointment topically was used [22]. All treatments were applied once daily for five days.

Immunohistochemistry measurement (IHC)

The applied procedure of IHC was first evaluated and established with the aid of the consultant center, department of pathology, college of medicine, AL – Nahrain University. The applied procedure depends on the catalogs protocols.

Histopathology

Mice were sacrificed at the end of study after five days by using inhalant chloroform as anesthetic. The tissue of the mice was taken from the dorsal mice back and stored in buffered formaldehyde immediately [23]. Scoring system was used for mouse model evaluation histopathology (Munro abscesses (1.5), papillary papillae congestion (1), dermis lymphocytic infiltrate (0.5–1.5), acanthosis (1), length of rete ridges (0.5–1.5), parakeratosis (1), hyperkeratosis (0.5). Each score given number according to the authenticated scale by Baker [24] and the slides were reads by professional pathologist.

Statistical Analysis

The statistics are done using Statistical Package for the Social Sciences program 2016 to find the median and range. Mann Whitney test in addition to Kruskal Wallis test used where *p* value was less than 0.05 and considered significant, while when *p* value was less than 0.01 it is considering highly significant [25].

Results

The Yields of Ethanolic Extraction and Non-polar lipid compounds with n-hexane from Ajwa Seeds

The Yields from *Phoenix dactylifera* L. date seeds for the ethanolic extract and Non-polar lipid compounds of n-hexane extract residue were showed in Table (4).

The phytochemical screening of plant Ethanolic extract from seeds

Phytochemical screening of *Phoenix dactylifera* L. date seeds results were summarized in Table (5)

Table 4. The *Phoenix dactylifera* L. date seeds yields of alcoholic residue in 80% ethanol and fatty material in n-Hexane dried layer.

Plant name	Weight of Powdered seeds (g)	Weight of Ethanolic Residue (g)	Residue of 80% Ethanolic extract weight (%)	Weight of n-hexane Residue (g)	Residue of n-hexane extract weight (%)
Phoenix dactylifera L. date seeds	150	12.156	8	12.9	8.6

Table 5. Preliminary phytochemical screening of *Phoenix dactylifera* L. date seeds

Phytochemicals	Observation	*Results
Saponins	Formation of froth	-
Tannins	White precipitate	+
Polyphenols	Brown precipitate	+
Flavonoids	Bright yellow color	+
Alkaloids	Orange brown precipitate (Dragendroff's test)	-
	A white precipitate (HCL test)	-
	A white to yellowish precipitate ***(Mayer reagent)***	-
Glycosides	Reddish brown precipitate	+
***The symbols + means presence of that component , The symbols — means absence of that component**		

The phenolic compounds Analysis by HPLC technique

Figure (3) and (4) showed the HPLC chromatogram of phenolic standards and phenolic compounds investigated in the seeds of the plant respectively.

While figure (5) and 6) represented the HPLC chromatogram of standard flavonoids and that present in the seed ethanolic extract respectively.

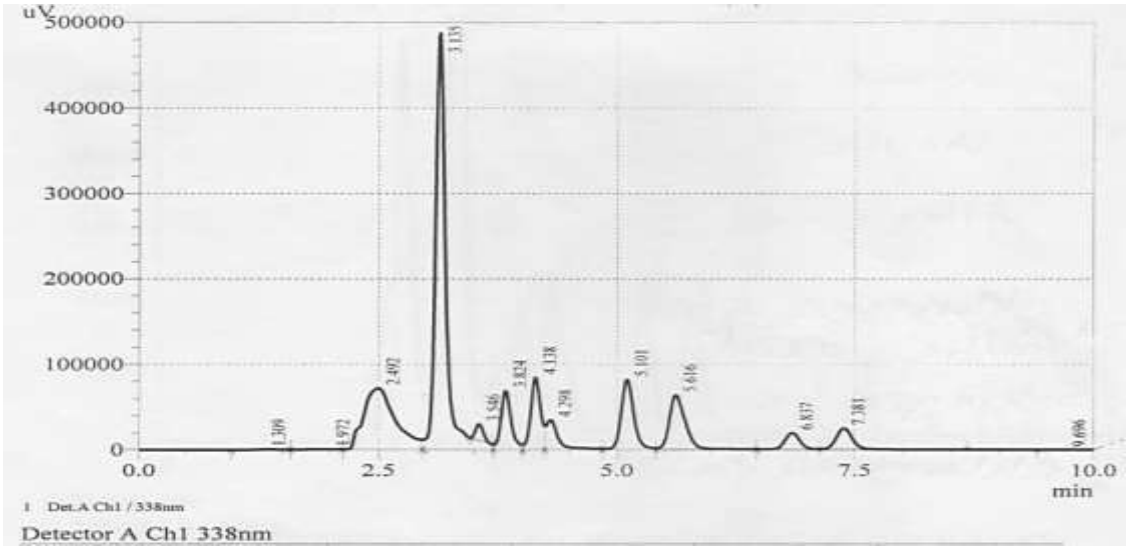

Figure 3. HPLC chromatogram of phenolic standards compounds

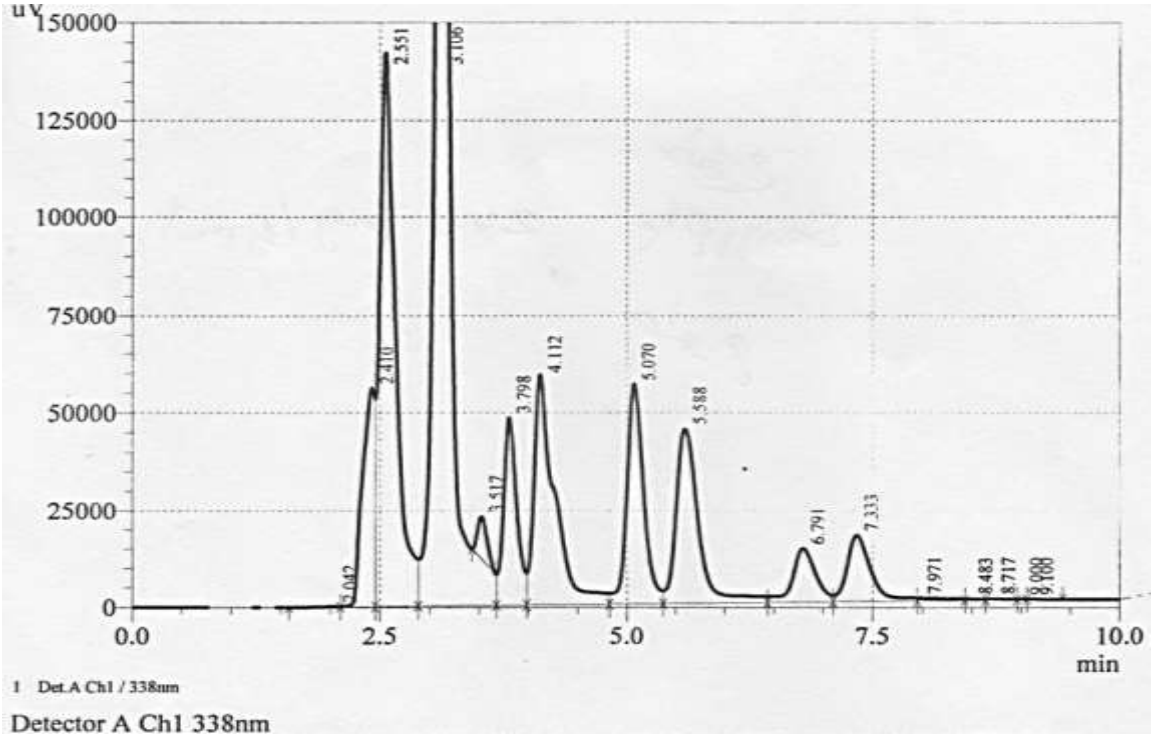

Figure 4. HPLC chromatogram of phenolic compounds investigated in the seeds

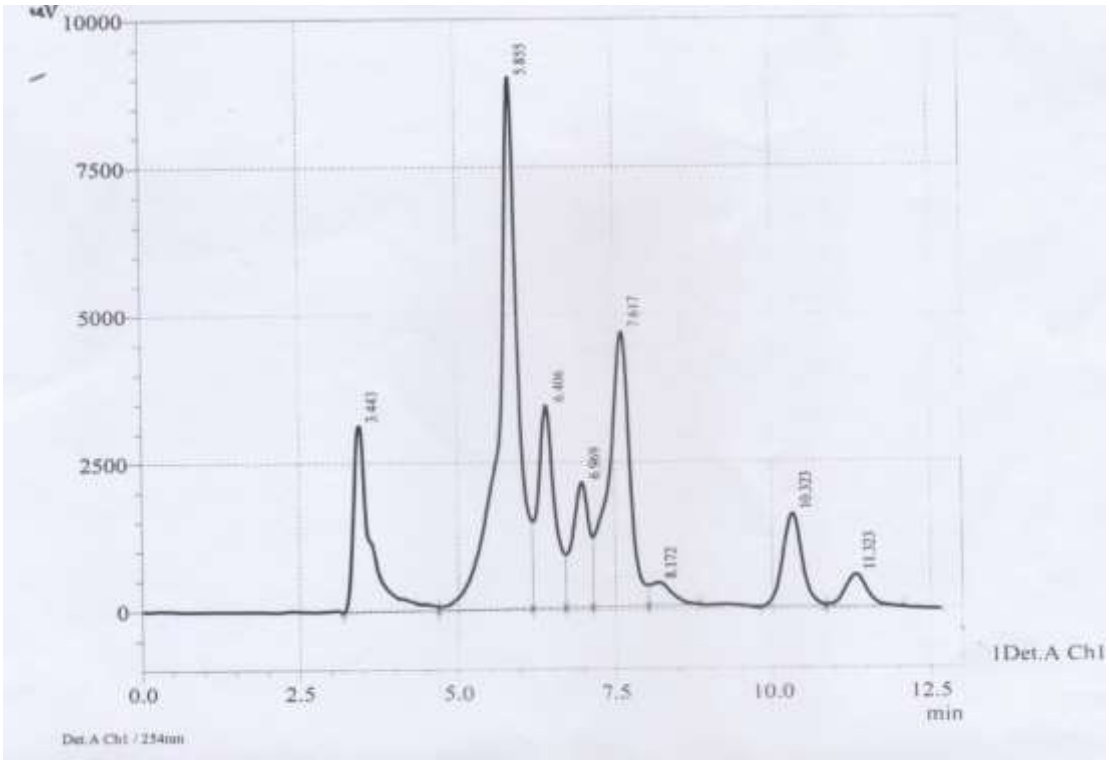

Figure 5. HPLC chromatogram of standard flavonoids

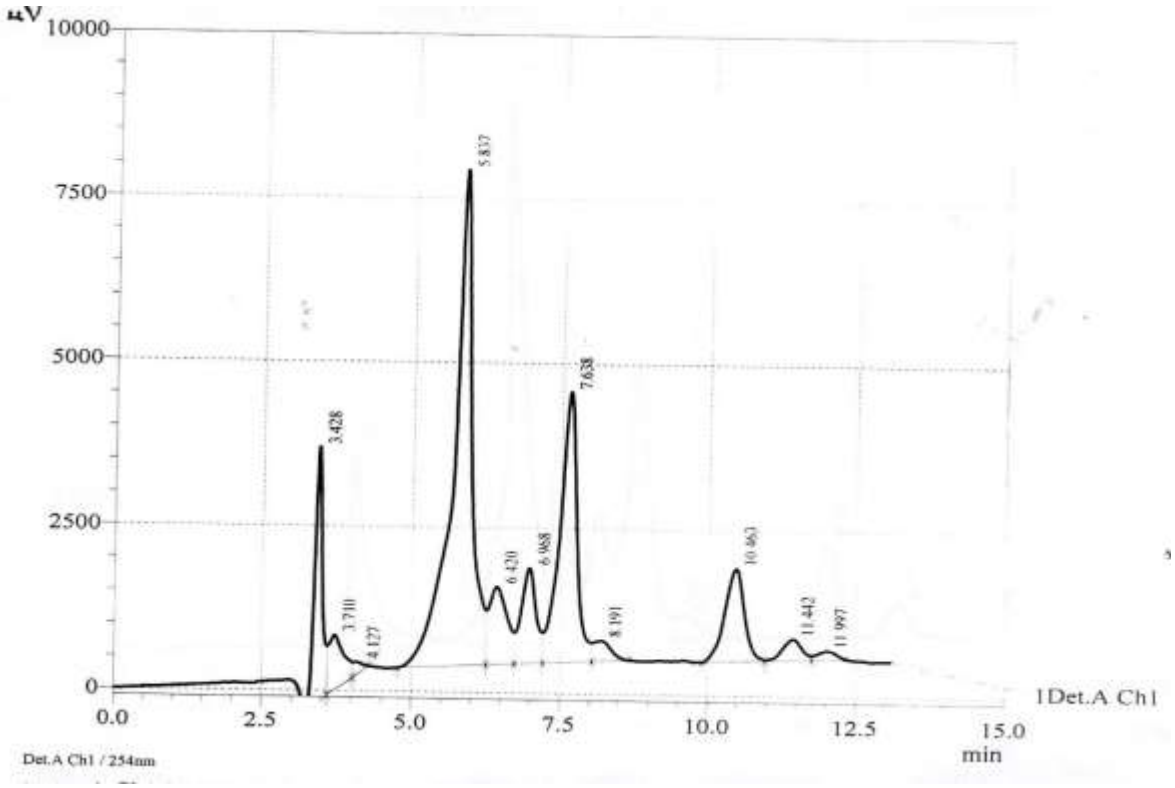

Figure 6. HPLC chromatogram of flavonoids present in the seed ethanolic extract

The quantitative amount of each phenolic and flavonoid compounds present in the seeds extract were investigated in Table (6) and Table (7) respectively in corresponding to standard compounds. Both Tables showed the concentration of each detected phenolic or flavonoid components in the ethanolic extract in corresponding to standard retention time.

Table 6. HPLC analysis results for standards and the extracted phenolic compounds

Phenolic compound	St. Conc. mg/ ml	Standard Rt (min)	Standard Area	Sample Rt (min)	Sample Area	Sample Conc. mg / ml	Conc. µg /g. plant
Vanillic acid	1	2.492	1668852	2.55	1578746	0.946	1.597
Ellagic acid	1	3.135	3733833	3.106	3216535	0.861	1.4544
Gallic acid	1	3.546	108466	3.517	73848	0.68084	1.15
Syringic acid	1	3.824	519704	3.798	464684	0.894132	1.51
Chloragenic acid	1	4.138	628481	--	---	Nil	nil
Caffeic acid	1	4.298	315876	---	---	Nil	nil
Ferulic acid	1	5.101	763955	5.076	678582	0.8882	1.4996
Sinapic acid	1	5.616	766132	5.588	709087	0.92554	1.5626
Salicylic acid	1	6.837	226221	6.791	224297	0.991495	1.6739703
Benzoic acid	1	7.381	310229	7.333	28742	0.92635	1.564

Table 7. HPLC analysis results for standards and the extracted flavonoid compounds

Phenolic Compound	St. Rt(min)	St. Conc. µg / ml	St. Area	Sample Rt (min)	Sample Conc. µg / ml	Sample Area	Concentration µg /g. plant
Rutin	3.443	5	60495	3.428	2. 8	34257	566.3
Coumarin	5.885	5	194917	5.837	4.21	164132	842
Quercetin	6.406	5	64184	6.420	1.98	25441	369.4
Catechin	6.969	2.5	39337	6.968	1.617	25441	323.4
Apigenin	7.617	5	111970	7.638	3.675	82302	735
Kaempferol	8.172	1	9530	8.191	0.676	6441	135.2
Naringin	10.323	2.5	33923	10.463	2.388	32402	477.58
Luteolin	11.323	1	13730	11.442	0.553	7592	110.59

As shown in Table (6) and (7), the ethanolic residue found to be rich with phenolic compounds and the flavonoids and the major phenolic components were arranged **Salicylic acid> vanillic acid > Benzoic acid > Sinapic acid > Syringic acid > Ferulic acid > Ellagic acid > Gallic acid**. While in case of flavonoids and polyphenols, the decreasing amount was arranged as: Coumarin > Apigenin> Rutin > Naringin > Quercetin > Catechin > Kaempferol > Luteolin, beside other unknown flavonoid components had been found in this fraction.

Assay by HPLC Technique for the n- Hexane Layer

HPLC chromatogram of the non-polar compounds extracted by n- hexane as phytosterols was shown in figure (7) and (8) for standard compounds and the plant extract respectively and the quantitative amount was investigated in Table (8).

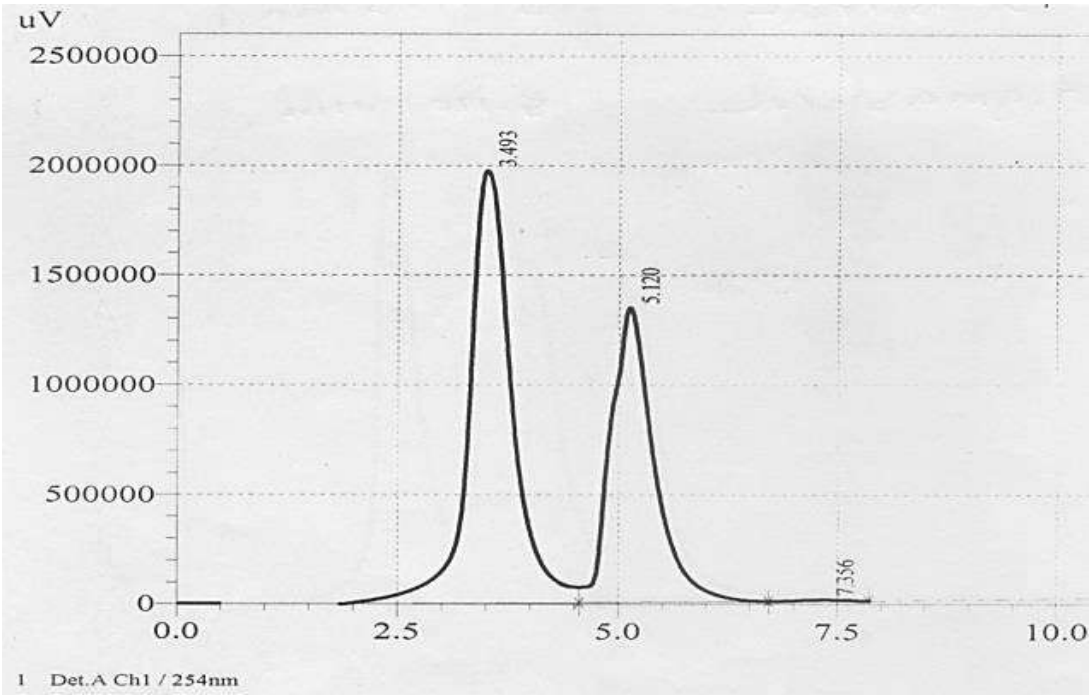

Figure 7 .HPLC chromatogram of the phytosterols standard compounds

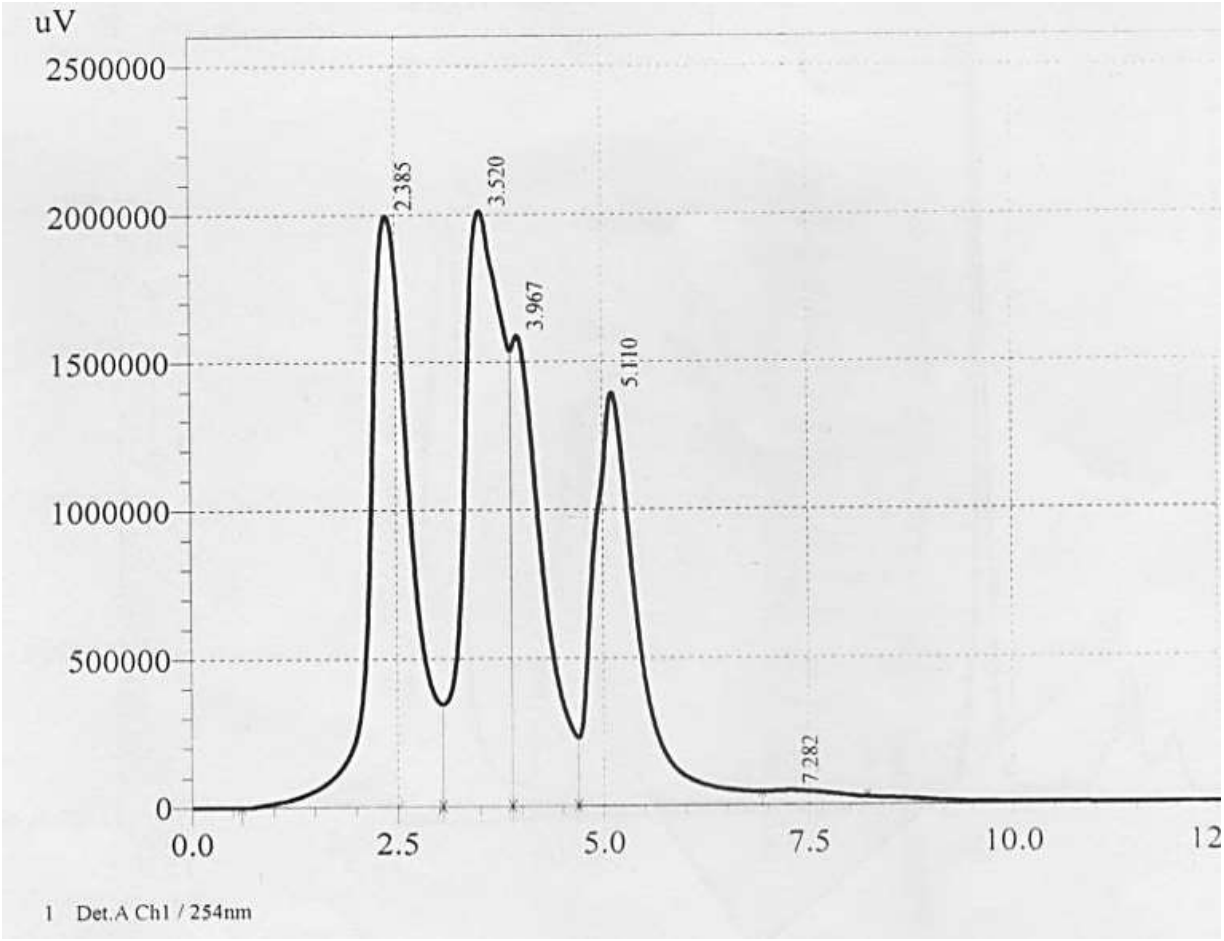

Figure 8. HPLC chromatogram of the n- hexane extracted as non-polar compounds represented as phytosterols in the seeds

Table 8. HPLC quantitative analysis results for the extracted phytosterols compounds in the seeds in

Sterols compound	Conc. µg / ml	Rt. in minutes For Standard sterols	Area For Standard sterols	Rt. min. For extracted sterols	Area For extracted sterols	Conc. µg / ml	Conc. µg /g. plant
β- Sitosterol	5	3.493	67428143	3.52	68419793	5.073	104
Stigmasterol	5	5.120	45929732	5.110	57279009	6.235	133.6

corresponding to standard phytosterols

Pharmacological study of the Seeds Extract on Animal Model

The pharmacological study of both seeds extracts residue; the ethanolic residue represented the phenolic and flavonoids, while the n-hexane residue represented the non-polar phytosterols in the seeds, on mice model with imiquimod-induced psoriasis like inflammation results were showed in the Table (9), represented as comparison between the groups in relation to IHC in mice skin; while Table (10) represented comparison between the groups in relation to histopathology parameters in mice skin. Figure 9 (groups I, II, III, IV, and V) represented Immunohistochemistry of IL-17, TGF-beta, and EGF beta of mice skin groups, while Figure 10 (groups I, II, III, IV,V) illustrated the histopathology slide sections of skin mice groups with munro abscess, parakeratosis, hyperkeratosis, lengthening of rete ridges, papillary papillae congestion, dermis lymphocytic infiltrate, and acanthosis.

Table 9. Comparison of immunohistochemistry parameters between the groups

Parameter		Healthy group N=6	Psoriasis induction group N=6	Clobetasol group N=6	Ajwa phenolic/flavonoid group N=6	Ajwa phytosterols group N=6
Skin IL-17	Median (Range)	0 (0-1)	3 (1-3)	2 (1-2)	1 (1-2)	2 (1-3)
	P value [a]		0.002	0.008	0.035	0.008
	P value [b]			0.041	0.026	0.093
	P value [c]				0.394	0.818
	P value [d]					0.310
	P value [e]			0.373		
Skin TGF-beta	Median (Range)	1 (1-1)	3 (2-3)	2 (1-2)	1.5 (1-2)	1 (1-2)
	P value [a]		0.001	0.051	0.138	0.366
	P value [b]			0.026	0.015	0.009
	P value [c]				0.699	0.394
	P value [d]					0.699
	P value [e]			0.533		
Skin EGF	Median (Range)	1 (1-1)	3 (3-3)	1 (1-2)	2 (1-3)	2 (1-2)
	P value [a]		0.001	0.366	0.051	0.051
	P value [b]			0.002	0.015	0.002
	P value [c]				0.310	0.394
	P value [d]					0.818
	P value [e]			0.373		

a: p value by comparison healthy with each other group by Mann Whitney test
b: p value by comparison psoriasis induction with each treatment group by Mann Whitney test
c: p value by clobetasol with each Ajwa group by Mann Whitney test
d: p value by comparison between two Ajwa groups by Mann Whitney test
e: p value by comparison among treatment groups by Kruskal Wallis test
significant difference when P value < 0.05
high significant difference when P value < 0.01

Table (10). Comparison of skin histopathology parameters between the groups

Parameter		Healthy group N=6	Psoriasis induction group N=6	Clobetasol group N=6	Ajwa phenolic/flavonoid group N=6	Ajwa phytosterols group N=6
Munro abscess	Median (Range)	0 (0-0)	2 (0-2)	0 (0-0)	0 (0-0)	0 (0-0)
	P value [a]		0.008	1.000	1.000	1.000
	P value [b]			0.015	0.015	0.015
	P value [c]				1.000	1.000
	P value [d]					1.000
	P value [e]			1.000		
Hyperkeratosis	Median (Range)	0 (0-0)	0.5 (0.5-0.5)	0 (0-0)	0.5 (0-0.5)	0.25 (0-0.5)
	P value [a]		0.001	1.000	0.008	0.138
	P value [b]			0.002	0.699	0.180
	P value [c]				0.015	0.180
	P value [d]					0.394
	P value [e]			0.018		
Parakeratosis	Median (Range)	0 (0-0)	1 (1-1)	0 (0-1)	0 (0-0)	0 (0-0)
	P value [a]		0.001	0.366	1.000	1.000
	P value [b]			0.065	0.002	0.002
	P value [c]				0.394	0.394
	P value [d]					1.000

	P value [e]			0.119		
Lengthening and clubbing of rete edges	Median (Range)	0 (0-0)	1.5 (1.5-1.5)	1.5 (0-1.5)	1.5 (0-1.5)	1.5 (1.5-1.5)
	P value [a]		0.001	0.051	0.051	0.001
	P value [b]			0.394	0.394	1.000
	P value [c]				1.000	0.394
	P value [d]					0.394
	P value [e]			0.297		
Acanthosis	Median (Range)	0 (0-0)	0.5 (0.5-0.5)	0.5 (0.5-0.5)	0.5 (0.5-0.5)	0.5 (0.5-0.5)
	P value [a]		0.001	0.001	0.001	0.001
	P value [b]			1.000	1.000	1.000
	P value [c]				1.000	1.000
	P value [d]					1.000
	P value [e]			1.000		
Papillary congestion	Median (Range)	0 (0-0)	0.5 (0.5-0.5)	0.5 (0.5-0.5)	0.5 (0.5-0.5)	0.5 (0-0.5)
	P value [a]		0.001	0.001	0.001	0.008
	P value [b]			1.000	1.000	0.699
	P value [c]				1.000	0.699
	P value [d]					0.699
	P value [e]			0.368		
Dermis lymph infiltrate	Median (Range)	0 (0-0)	2 (2-2)	0.75 (0.5-1)	0.5 (0.5-0.5)	0.5 (0.5-0.5)
	P value [a]		0.001	0.001	0.001	0.001
	P value [b]			0.002	0.002	0.002
	P value [c]				0.180	0.180
	P value [d]					1.000
	P value [e]			0.033		

a: p value by comparison Healthy with each other group by Mann Whitney test.
b: p value by comparison psoriasis induction group with each treatment group by Mann Whitney test
c: p value by clobetasol with each Ajwa group by Mann Whitney test
d: p value by comparison between two Ajwa groups by Mann Whitney test
e: p value by comparison among treatment groups by Kruskal Wallis test
significant difference when P value < 0.05
high significant difference when P value < 0.01

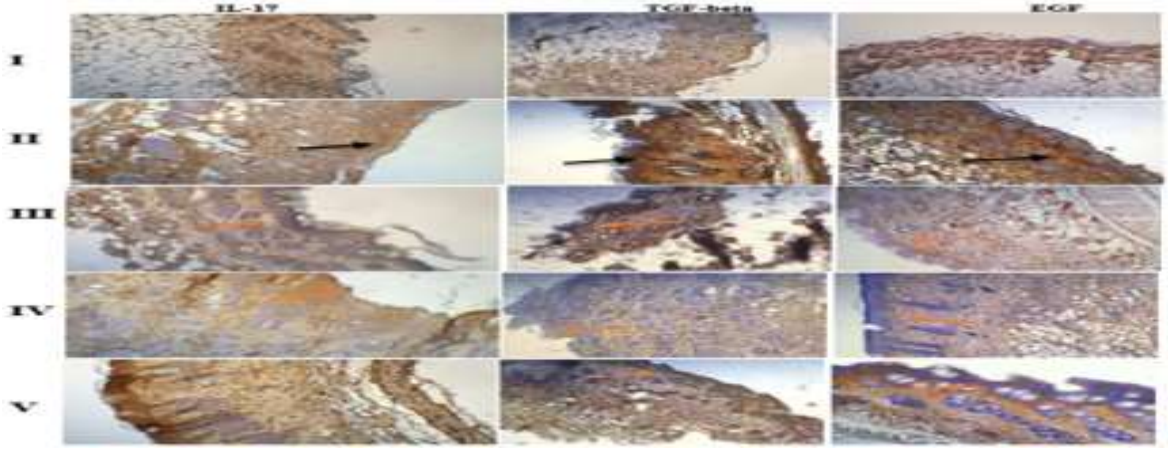

Figure 9. Immunohistochemistry of IL 17, TGF-beta, and EGF beta of mice skin groups. Group I: Healthy, Group II: Psoriasis induced group, Group III: Clobetasol group, Group IV: Ajwa phenolic/flavonoid group, Group V: Ajwa phytosterols group. Group II show dark brown color indicate positive cell reactions (Black arrow). Decrease intensity of color is seen with other groups indicates no or less reaction of the cells to the parameters (Orange arrow). Microscope lens of power 10.

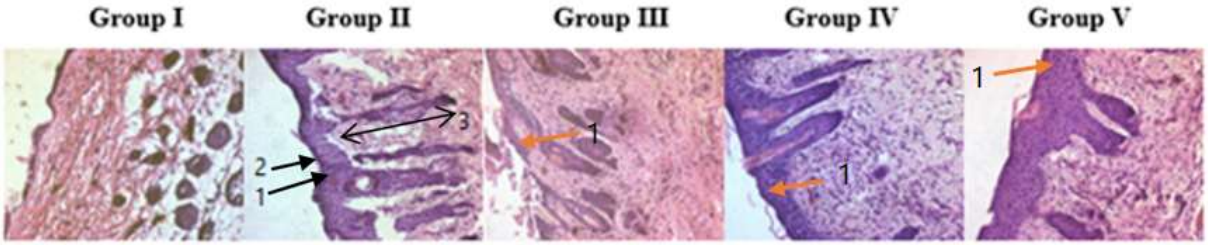

Figure 10. Histopathology slide sections of skin mice groups with munro abscess, parakeratosis, hyperkeratosis, lengthening of rete ridges, papillary papillae congestion, dermis lymphocytic infiltrate, and acanthosis. Group I: Healthy, Group II: Psoriasis induced group, Group III: Clobetasol group, Group IV: Ajwa phenolic/flavonoid group, Group V: Ajwa phytosterols group. Group II Black arrow show different histopathology changes like munro abscess (Black Arrow 1), parakeratosis, hyperkeratosis (Black Arrow 2), acanthosis, papillary papillae congestion, lengthening of rete ridges (Black Arrow 3), and dermis lymphocytic infiltrate. Better munro abscess seen in groups III, IV, and V (Orange arrows 1). Better hyperkeratosis seen in group III. Better parakeratosis seen in group IV and V. Decrease dermis lymphocytic infiltration seen in groups III, IV, and V. Microscope lens of power 10.

Discussion

Many studies had been improved for the pharmacological and the importance of different bioactive compounds such as plant phenolic compounds, flavonoids, terpenoids, alkaloids, and others that possessed medicinal effects against huge number of human diseases and boosting their health [26-30]. Date seeds seemed to be rich in phenolic compounds and both component β-sitosterol; and stigmasterol are phytosterol that seeds rich with have announced effects in medicine, thus the current work acted to high lightened the pharmacological effects for such components present in the seeds of the Ajwa dates extract in overcome the imiquimod-induced psoriasis like inflammation in mice in relation to steroidal traditional therapy. Starting with comparing the healthy and induced groups, it was found high significant increase of skin IHC of IL-17, TGF-beta and EGF. Interleukin-17 is a homodimeric main important cytokine that is secreted from Th-17 cell line. Interleukin-17 plays a major function in recruitment first and activation secondly of neutrophil cells [31].

Furthermore, IL-17 induce TNF-α and IL-1 β expression in psoriasis from monocytes [32]. For the histopathology parameters it was found that all of the parameters are highly significantly increased. A previous research showed that imiquimod can cause hyperplasia, hyperkeratosis and inflammation in mice skin of the induced group [33]. Date seed provide an important compound like phenolic acids, flavonoids, and others. Those have a beneficial biological effect like antioxidant that can be used in many formulations. The phenolic/flavonoid fraction as shown in this study contain the flavonoids rutin and quercetin which is identical with the previous study that proven to contain them [34].

When we compare this phenolic/flavonoid fraction with the psoriasis induced groups, it was found that the Skin IHC of IL-17, TGF-beta, and EGF are significantly decreased and the histopathology reading hyperkeratosis , parakeratosis , and dermis lymphocytic infiltrate are highly significant decrease while Munro abscess only significantly decreased. Chen *et al.* in 2017 showed in a study that quercetin may act as anti-psoriatic agent because quercetin pretreated mice showed better skin sores, like less parakeratosis, soft epidermis, and less serum IL-17 with decrease epidermal thickening in addition to its antioxidant capacity [35].

The current study gives a good idea about the histopathology inflammation level of the skin psoriasis like cells, while a previous study showed in addition to that the antioxidant capacity may be another underlying mechanism that it associated to improving anti-inflammatory and antioxidant status which may be associated with NF-κB signaling inhibition. In addition to that, IL-17 may shows different multiple effects acting on nonimmune cells, lead to induction of several pro-inflammatory cytokines like chemokines, matrix metalloproteinases, nitric oxide, and antimicrobial peptides [36], [37].The changes in the cytokine IL-17 was investigated as shown in the result that the levels of IL-17 were significantly decreased after administration of phenolic/flavonoid fraction, which mean that the inflammatory process had been improved better in the mice [38]. As showed from the result, this fraction contains different phenolic acid. It is similar to a study showed to contain gallic acid, syringic acid, chlorogenic acid, and caffeic acid phenolic compounds [39]. Those phenolic acid have a pharmacological effect in many other studies, where a previous study showed gallic acid mechanism of action in psoriasis through Nrf2 by inhibiting KRT 16 with KRT 17 significantly in vivo and in vitro. Moreover, epidermal hyperplasia is highly decreased in treated group of psoriasis – imiquimod like mice model [40]. In addition to that, it was found clinically that gallic acid can decrease IL-17 cell frequency producing within CD3+CD4+ (Th) and CD3+ (T) pathway [41].

In a study showed natural Chlorogenic Acid, when present in a mixture with other herbal substance, it suppresses inflammation and the proliferation process in keratinocytes leading to ameliorate lesion of psoriasis skin model [42]. There was a proposed mechanism of action to chlorogenic acid, the high fat diet to mice and using chlorogenic acid for those mice lead to highly decreased expression of the genes of adipose tissue macrophage markers. Those like pro-inflammatory related genes like TNF-α and MCP-1 in addition to F4/80, Cd11b, Cd11c, and Cd68 [43]. It was suggested also in another study that caffeic acid decrease nitrite levels and inflammatory symptoms relief [44]. In relation to Ellagic acid, it was found that it can reduce the epidermal thickness and parakeratosis [45]. Also for Ferulic acid, protection against psoriatic imiquimod skin model was found.

The interaction of IL-17A and its receptor IL-17RA was found to be the protection mechanism [46]. As with our study that contain salicylic acid in the fraction of phenolic acid, it was assumed previously in a study the advantage of salicylic acid in psoriasis. The keratolytic agent salicylic acid start the desquamation of skin stratum corneum. This effect increases the penetrations of other agent like corticosteroid. Evidence suggests that this keratolytic effect can enhance the penetration of other topical agents, such as corticosteroids [47].

This effect is very important due to double benefit of salicylic acid especially when present in a mixture of compound like this research phenolic/flavonoid fraction. Using phenolic/flavonoid fraction of various compounds could be giving an excellent product. This combination product could be more effective as a result of synergistic effect of those compounds. This synergistic effect of many compounds made this fraction may be more effective in decreasing more psoriasis parameters than the phytosterols fraction where IL-17 was non-significant in phytosterols group.

When we compare the phytosterols fraction with psoriasis induced group, the anti-proliferative parameter of skin IHC of TGF-beta, EGF, parakeratosis, and dermis lymphocytic infiltration are highly significant decreased, while Munro abscess is significantly decreased only, but also The β- Sitosterol containing fraction (n-hexane extract) show non-significant decrease in IL-17 parameters. A previous study showed sitosterol compound can suppressed expression cytokines of Th17-types like IL-17 and decrease the skin lesions in mice [48]. This is may be due to different concentration used between the two studies, the content is a combined of two identified compound in our study and different inducer used with different statistical tests used. A support for the similarity part, a previous early molecular docking studies technology suggesting that EGF molecule by the use beta –sitosterol, querctine and other compounds can be decreased [38]. A previous study found that stigmasterol significantly elevate superoxide dismutase, glutathione, and catalase enzyme when compared to a control group [49].

The Clobetasole group when compared to psoriasis induction group, it was found a highly significant decrease in skin IHC EGF and a significant decrease of skin IHC of IL-17, IHC of TGF-beta, munro abscess, hyperkeratosis, and high significant decrease in dermis lymphocytic infiltration. It was approved before that clobetasole can highly significantly decrease the IL-17 parameter [50].The none- significant difference between the ajwa each group with the clobetasol group indicate a good outcome of the benefit of those each group, where its effect may be similar to the steroid in the treatment of induction of psoriasis. When we compare all of the treatment group between each other, only a significant difference was found in hyperkeratosis and dermis lymphocytic infiltrate which may need farther studies to explain the cause.

Conclusion

Date palm *Phoenix dactylifera L.* fractions contain many useful compounds. Those fractions have anti-inflammatory effect by depression of IL-17 and anti-proliferative effect by depression of TGF-beta and EGF in addition to improvement of other histopathological readings, indicating a useful role in treatment of psoriasis in the future after more additional studies.

Recommendation

Further studies are needed by increase sample size, adding a vaseline use group in addition to investigate the mechanism of action of different isolated compound from Phoenix dactylifera L.

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Conflicts of Interest

There is no conflict of interest regarding the publication of this manuscript.

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Ethics Statements

The study protocol and authorization is approved by Biotechnology research center ethics committee, AL-Nahrain University (Animal application number 6, reference number P.B.6, Date 2.1.2023, Plant application number 7, reference number P.B.7, Date 2.1.2023).

Author Contribution

All authors confirm contribution to the paper as follows: study conception and design: Zainab, Y. and Mohammed, .F.; data collection analysis and interpretation of results by Zainab, Y, ; Mohammed, F

and Raghad, A,. All authors reviewed the results and approved the final version of the manuscript.

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دراسة كيمياء النبات والتاثير الدوائي لبذور تمر العجوة (*Phoenix dactylifera L.*) لالتهاب الجلد المشابه للصدفية في الفئران المستحثة بالايميكويمود

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الخلاصة

ان المركبات الفعاله حيويا في بذور تمر النخيل والتي تمثل مركبات ايض ثانوي تشمل الأحماض الفينولية والفلافونويدات والستيرولات النباتيه غير القطبية بكميات مختلفة تم فحصها في الدراسة الحالية كمصادر طبيعية في تحديد التأثيرات الصيدلانية لهذه المركبات. تم التحري نوعيا وكميا عن المركبات الفعالة في بذور نخيل التمر لاستخدامها في معالجة اصابة جلدية كنموذج حيواني لمرض الصدفية. تم الاستخلاص والتجزئة لمركبات بذور التمر حيث تم استخلاص المركبات الفينولية / الفلافونويد والستيرولات النباتية منها. تم تقسيم ثلاثين فأرًا ابيضا إلى ٥ مجموعات بما في ذلك الفئران السليمة من المجموعة الأولى. المجموعة الثانية: مجموعة استحثاث الصدفية في الفأرباستخدام كريم إيميكويمود ٥٪.دون علاج. المجموعة الثالثة للفئران استحث فيها الصدفية وتعالج مع مرهم كلوبيتاسول ٠,٠٥ ٪. المجموعة الرابعة والخامسة تمثل الفئران التي استحث فيها مرض الصدفية التي عولجت بالمستخلص يحوي مركبات فينولية / فلافونويدية بشكل مرهم تركيزه ٤٪ والاخرى بمرهم ستيرولات نباتية بتركيز ٤٪ على التوالي وتم استخدم العلاج مرة واحدة يوميًا لمدة خمسة أيام.

أظهر الفحص الكيميائي النباتي للبذور وجود التانينات والفينولات المتعددة والفلافونويد والجليكوسيدات في المستخلص. تم الكشف عن حامض الفانيليك وحامض إيلاجيك وحامض جاليك وغيرها كمركبات فينولية. تم اكتشاف Rutin و Quercetin على أنهما مركبات الفلافونويد في الجزء الإيثانولي ، بينما تم اكتشاف β- Sitosterol و Stigmasterol على أنهما ستيرولات نباتية في جزء الهكسان. أظهرت التأثيرات الصيدلانية أن قراءات الكيمياء الهستولوجية المناعية التي تخص IL-17 و TGF-beta و EGF قد انخفض بشكل ملحوظ مع المجموعات التي يسببها مرض الصدفية والتي تمت معالجتها بمرهم الفينول/ الفلافونويد. بالنسبة لمجموعة الستيرولات النباتية، انخفض خراج مونرو، التظليل، والتسلل اللمفاوي للادمة بشكل ملحوظ مع التغيرات الأخرى مقارنة بالمجموعة المحفزة التي يسببها مرض الصدفية. تشير الدراسة ان اختلاف المركبات الفعالة حيويا في Phoenix dactylifera L. إلى أن التأثير التآزري لهذه المكونات قد يكون ذو فائدة في العلاج المستقبلي للصدفية أو أمراض أخرى.

الكلمات المفتاحية: بيتا –سيتوستيرول, تمر العجوة, الستيرولات النباتية, الصدفية ,ستيغماستيرول.