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Review

Insights on Phytochemistry and Pharmacological Properties of *Argania spinosa L. Skeels:* A Comprehensive Review

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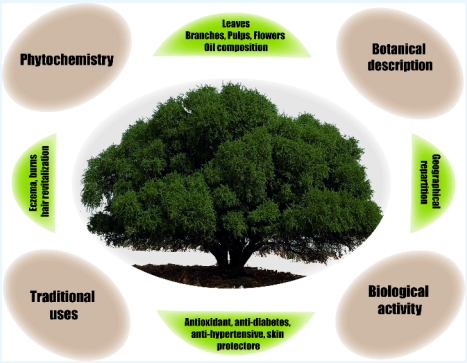
ABSTRACT: Across civilization, medicinal and aromatic plants have occupied an important place due to their extensive use in the treatment of different diseases. This review aims to summarize the existing knowledge about *Argania spinosa L. Skeels* by bridging traditional herbal knowledge with scientific investigations performed since 1957. Also, this review has shed light on the plant's botanical description and its partition in Morocco, followed by its traditional usage in southwestern Morocco and its socioeconomic importance for the local population. Furthermore, the present comprehensive review reported exhaustively the chemical composition of native and introduced *Argania spinosa L. Skeels* found in fixed oil, such as fatty acids, tocopherols, and phytosterols. Moreover, the bioactive compounds identified in other plant parts are also highlighted. Also, this review reports also techniques adopted in extraction, isolation, and purification and identification of biocompounds found in *Argania spinosa L. Skeels*. This review also sheds light on the pharmacological properties of this endemic plant of Morocco, such as antioxidant, antidiabetic, antibacterial, antiobesity, nanotechnology, and toxicity. Furthermore, a section of clinical trials performed on the plant products is also reported. Finally, this comprehensive review forms the backbone for future research on argan and its bioproducts, leading to improved health conditions and addressing future challenges.



INTRODUCTION

Argan, scientifically known as *Argania spinosa*, is an endemic plant of Morocco that belongs to sapotaceae family.[1] This plant presents an important role in Moroccan forest alongside with green oak and cedar.[2] In southern Morocco, the zone covered with Argan trees was designated a UNESCO biosphere reserve in 1998.[3] On the other hand, this plant plays an important socioeconomic and ecological impact.[4,5]

As noted by Emberger (1925), argan tree distribution is highly influenced by climate.[6] Similarly, it was found that this plant is highly concentrated in southwestern Morocco, while it is found as a relic in the north of the country especially in Beni-Snassen, Oued-Cherrat, Plaine Bou-Areg which is explained by the existence of favorable bioclimatic conditions that promotes *Argania spinosa* growth.[7]

Currently, and due to its strong exploitation in forestry and overgrazing, this Moroccan endemic plant faces a continuous regression. The production of seedlings remains a reliable process with high potential for plant regeneration.[8] In order to increase the diversity of the genetic heritage, sexual reproduction was used for better adaptation to the different climatic changes that Morocco is facing.[9] However, the current trend of extending the cultivation of Argan in modern management requires not only the selection of efficient clones with reference to ecophysiological, sanitary, and agronomic criteria, but also the development of vegetative propagation techniques to stabilize these performances.

Argan oil is considered as one of the main products from the plant's almonds, which is famous worldwide with its nutritional value[10] and with numerous health benefits.[11]

The known medicinal virtues of the plant is attributed to the oil richness with tocopherols, unsaturated fatty acids, and with phenolic compounds.[12] Additionally, the other parts of the plant (leaves, pulp, flowers, ...) are no less active that the oil, in fact the population of southern Morocco were accustomed to use these different parts in traditional medicine to treat various illnesses which with the modern techniques were reported to be rich with different bioactive components such as rutin, myricitrin, hyperoside).[13] On the other hand, research projects on Argan have confirmed scientifically these different reported virtues which has led to its use in traditional medicine. These reported

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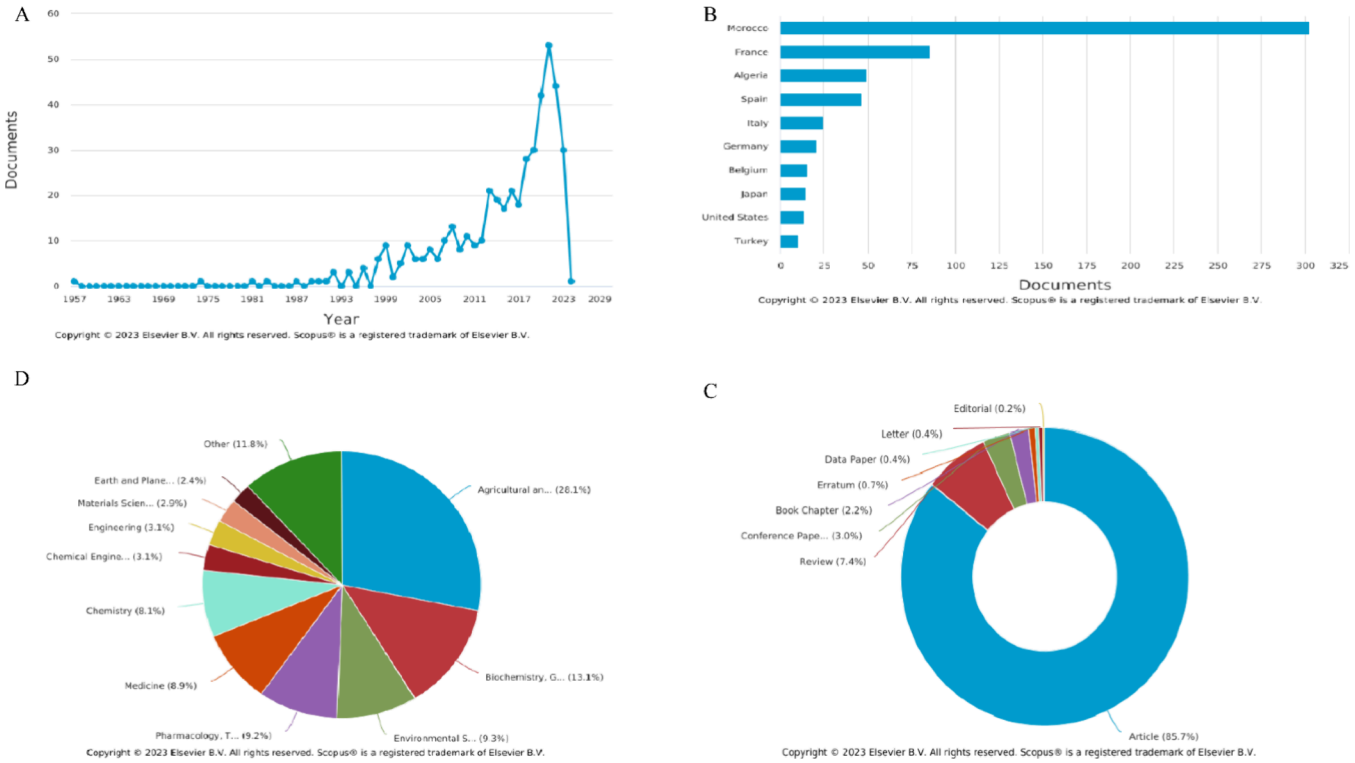

Figure 1. Research trends in *Argania spinosa*. (A) Published papers per year. (B) Ranking of countries publishing papers on *Argania spinosa*. (C) Papers types. (D) Papers according to research areas. Data were retrieved from Scopus database October 2023.

studies have indicated that Argan is endowed with a large spectrum of biological properties for example, the antidiabetic and anti-inflammatory potential,[14] antihypertensive and antioxidant effects[15] which gives this plant a promising future in the field of phytotherapy https://doi.org/10.1007/s13596-024-00766-x.

The aim of this review is to highlight the botanical description and geographical partition of native and introduced *Argania spinosa L. Skeels* in different regions of Morocco. Followed by traditional usage and its socioeconomic impact on the local population. Furthermore, the various bioactive compounds identified in different plant parts, such as leaves, branches, and flowers, using techniques such as liquid chromatography and gas chromatography, were reported along with the extraction, isolation, and purification methods adopted. Also, this review shed light on the pharmacological properties of *Argania spinosa L. Skeels* including its antioxidant, antidiabetic, antibacterial, antiobesity, nanotechnology applications, and toxicity. Moreover, clinical trials conducted using argans were also reported in this review. Therefore, an extensive review was conducted in the field to provide better guidance for future research aimed at improving health conditions.

METHODOLOGY OF RESEARCH

Along the formulation of this comprehensive review, the authors followed a specific methodology of research for better understanding of *Argania spinosa* utilization in traditional medicine by providing an insight into its traditional utilization. Furthermore, this review highlighted the research trends on Argan and its main bioactive compounds, phytochemistry, and pharmacological activities. The data used was collected from different online databases (Scopus, ScienceDirect, and Web of Science). The terms used were "*Argania spinosa*", "Phytochemistry", "Traditional use", "Antioxidant", "Antidiabetic", "Anticancer", "Antibacterial", "Anti-obesity", "Dyslipidemic", "Antiparasitic" in order to collect the different relevant papers related to the main goal of the manuscript. All collected research articles were exhaustively verified and were filtered according to their quality and relevance to the topic. All research papers published articles published both in English and French until 2023 on *Argania spinosa* and its pharmacological properties.

RESEARCH TRENDS

Argania spinosa first article appeared online in the literature for 66 years. Since first published article in 1957 argan an interest was observed in fact by 1999, nine articles were published while by 2021 about 53 articles were published (Figure 1A). This observed leap in published papers justifies the increasing interest in the exploration of argan virtues among the scientific community for possible application in different domains. Morocco has ranked in first place with about 302 documents, followed by France with 85 documents, while Algeria is in third place by 49 documents despite this plant is considered an endemic plant of Morocco (Figure 1B). When analyzing the various documents published, it was noticed that research articles had the largest share with 85.7% (394 documents), followed by review articles that were represented by a percentage of 7.4% (34 documents), while conference papers represented 3% (14 documents) (Figure 1C). The conducted analysis by subject has revealed that agricultural and biological sciences was represented by 244 documents (28.1%), biochemistry, genetics, and molecular sciences by 114 documents (13.1%), while pharmacology, toxicology, and pharmaceutics area was represented by 80 documents (9.2%) which provide significant proof about the importance and the potential use of the plant in the clinical care (Figure 1D).

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BOTANICAL DESCRIPTION AND GEOGRAPHICAL REPARTITION

Argania spinosa (L.) Skeels (formerly *Argania sideroxylon Roem et Schult, Sideroxylon spinosum L.*)] belongs to the tribe Sideroxyleae of the family Sapotaceae (Table 1),[16] is a very hardy, 2.5 to 4.5 m high, semievergreen tree species,[17] which can reach up to 11 m,[18] and can live from 150 to 200 years. The Argan tree is characterized by an upright, spreading or more rarely weeping habit[19] with a crown that is widely spread and a tormented trunk consisting of several intertwined stems. This species is characterized by a hard and heavy wood.[17,20]

Table 1. Botanical Classification of Argan

Name:	*Argania spinosa L. (skeels)*
Phylum:	Phanerogams
Sub-branch:	Angiosperms
Class:	Dicotyledons
Subclass:	Gamopetales
Order:	Ebenales
Family	Sapotaceae
Genus	Argania
Species	Spinosa

Argan have spiny branches and rarely inerminous, with attenuated leaves into a short petiole, alternate,[1] simple on newly formed branches and fasciculate on lignified branches.[21] Leaves are presented in different forms such as obtuse spatulate, obtuse obovate, mucronate lanceolate, or acute lanceolate.[22] The tree is monoecious with flowers in the form of axillary glomerules and each glomerule has up to 14−15 flowers, hermaphroditic with allogamous, anemophilic, or entomophilic fertilization.[23,24]

The fruit is a drupe, fleshy and characterized by a green color that becomes yellow at maturity,[25,17] other authors consider it a false drupe or berry[1,26] and is presented in different forms: oval, globular, fusiform, and elliptical enclosing inside a nucleus which is characterized by a lignified shell, hard and smooth, of light to dark brown color and which can contain up to 3 whitish almonds.[17]

GEOGRAPHICAL REPARTITION

Regarding its distribution, this unique species covers an area of 871,210 ha (Figure 2), mainly located in southwestern Morocco,[7] which makes the Argan tree one of the main forest species in Morocco, along with the holm oak and the cedar.[2] In eastern Morocco, this species covers an area of 700 ha (Figure 2) in the mountain massifs of Beni-snassen. Isolated feet have been located in the plain of Bou-Aareg (Nador) testifying to the former existence and extent of the Argan tree in the eastern region of Morocco.[6,8,27−29]

Currently a large area of the Morocco surface is bioclimatically suitable for the development of *Argania spinosa*. However, due to climate change, the actual suitable lands located in the southern part of the country will no longer be suitable in the

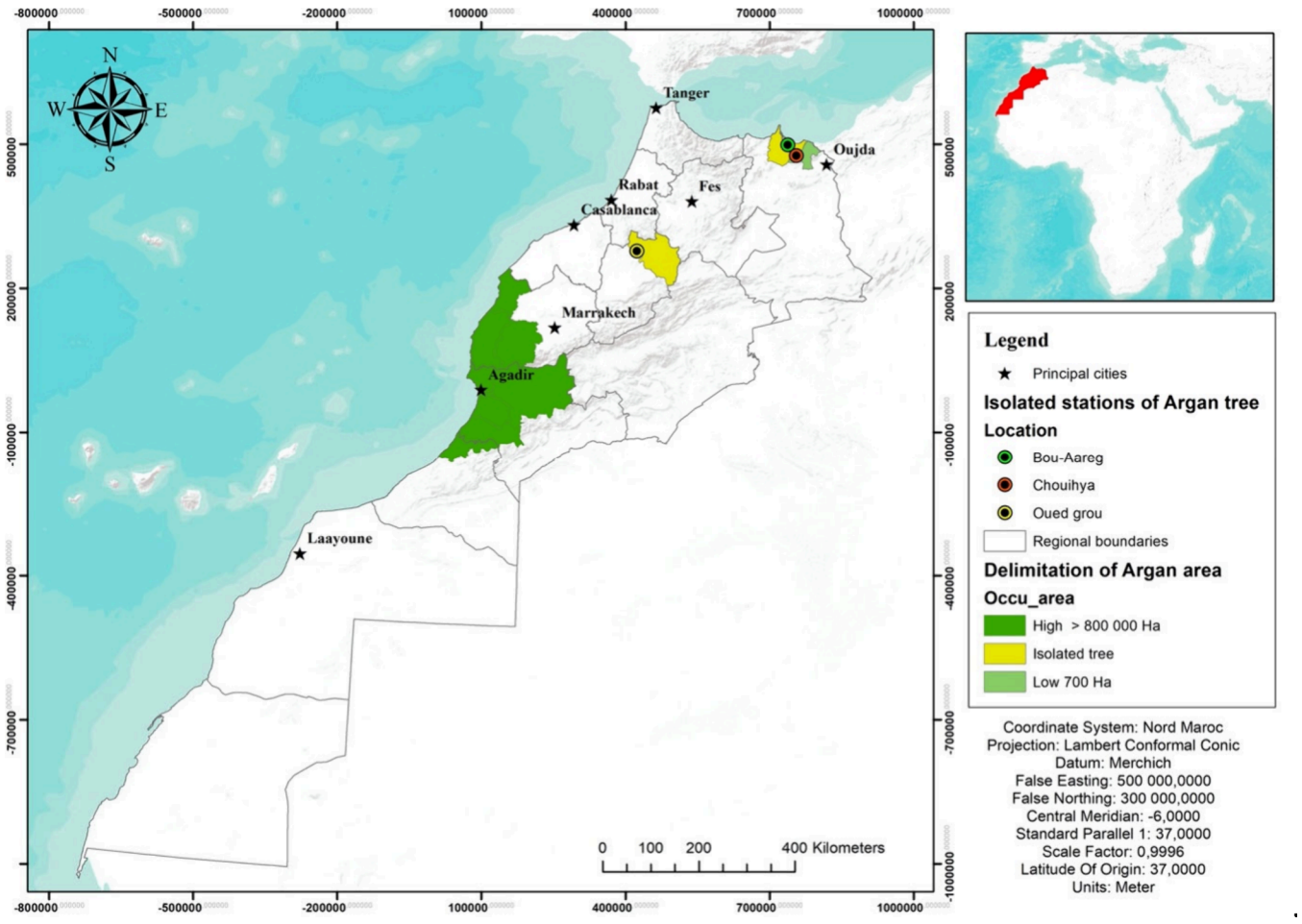

Figure 2. Repartition of *Argania spinosa* in Morocco.

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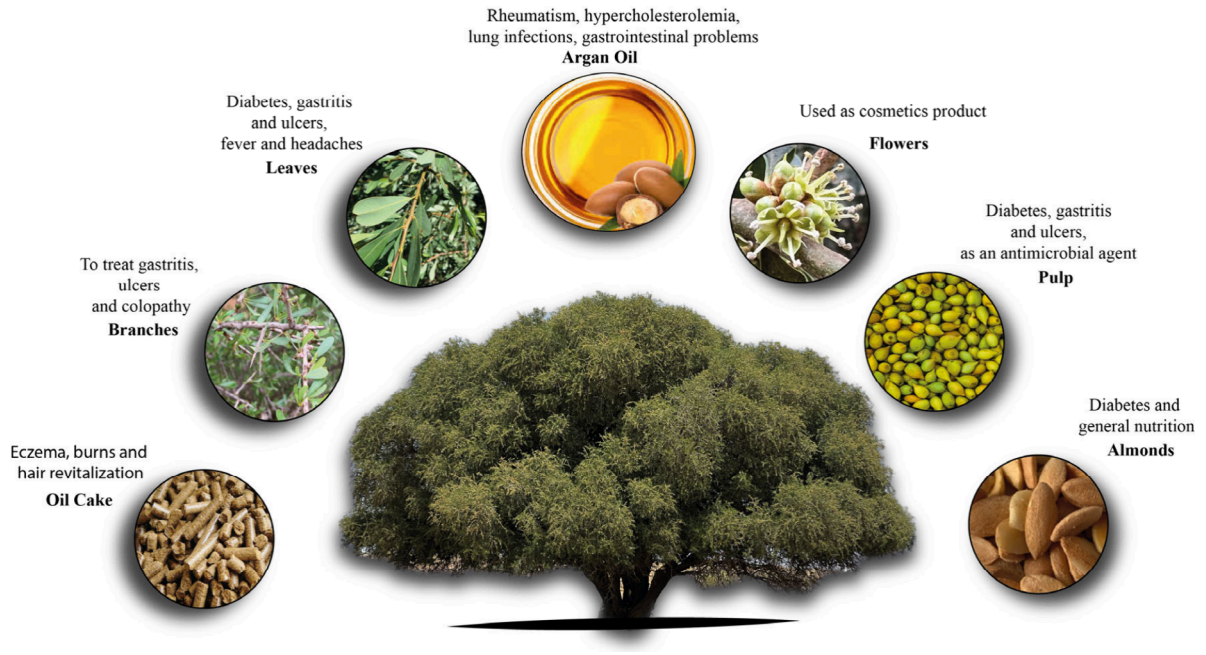

Figure 3. Traditional uses of Argan part and product.

Table 2. Traditional Usage of *Argania spinosa L. Skeels*

Plant parts	Administration mode	Traditional usage	References
Trunk bark	Oral administration	Gastritis, ulcers and colopathy	41
Leaves	Oral administration	Diabetes, gastritis and ulcers, fever and headaches	38, 39
Flowers	External application	Dermal product	41
Pulp	Oral administration	Treat diabetes, gastritis and ulcers, as an antimicrobial agent	40, 41
Fixed oil	Oral administration	Rheumatism, hypercholesterolemia, lung infections, gastrointestinal problems and the prevention of cardiovascular disease, and as an antioxidant and hepatoprotective agent	36
	External application	Skin care and aesthetics	
Almonds	Oral administration	Diabetes and general nutrition	34, 35
	External application	External application for the treatment of eczema, burns and hair revitalization	

future;[7,30] hence, the conservation of this valuable species remains necessary since it contributes to the local economy and ecological wealth of the country.[22]

SOCIOECONOMIC IMPORTANCE

The argan tree (*Argania spinosa*) holds significant socio-economic importance, especially in southwestern Morocco where this tree is considered a vital source of income for the local population. The production of argan oil, extracted from kernels of the argan tree, has a major economic impact on the local population. Worldwide, Argan oil is highly valued for its culinary and cosmetic usage. Cooperatives founded by women play a crucial role in this industry, allowing rural women to generate a stable income and thereby promoting economic and social empowerment, which helps in preserving cultural traditions and supports the local community. According to Charrouf and Guillaume (2009), the sustainable development of the argan forest provides a model for other regions to adopt. The same authors highlighted that the economic benefits derived from argan oil production have helped improve the living conditions of local populations while also promoting gender equality.[31] These cooperatives have also contributed to the preservation of traditional knowledge and practices related to Argan extraction and usage.[31] Moreover, the fruits are primarily used to produce oil, which is sold locally and has seen significant development and commercialization in the international market. On the other hand, Argan nut shells are typically used as a source of bioenergy and to produce eco-friendly biochar. Additionally, due to its rich composition of terpenoids and saponins, Argan pulp is used as a biopesticide.[32] Also, argan press cake which is the result of argan oil production is used to produce bioplastics and as a livestock for goats and cows due its high energy value.[33]

TRADITIONAL APPLICATION OF *ARGANIA SPINOSA*

The various parts and organs of the Argan tree have long been used by the local population of southern Morocco in traditional medicine for the treatment of many illnesses as well as in cosmetics for skin care and aesthetics. In fact, argan almonds are used as a powder form by external application for the treatment

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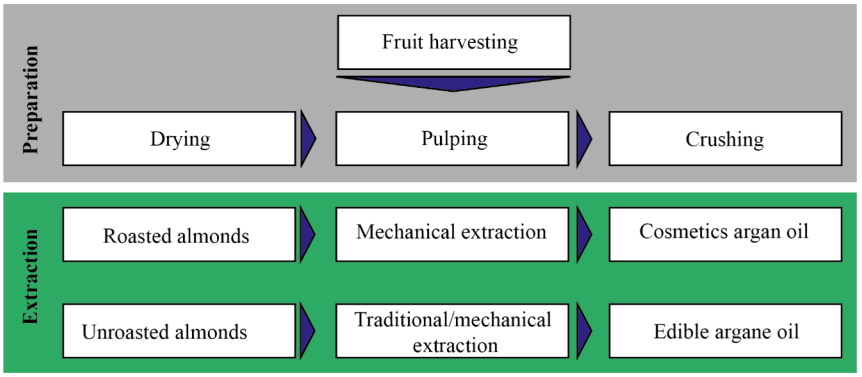

Figure 4. Extraction steps of *Argania spinosa* oil.

of eczema, burns, and hair revitalization, and by oral administration for the treatment of diabetes and general nutrition.[34,35] While, the fixed oil is still currently used alone or often flavored with essential oils (rosemary, black cumin, etc.) by oral administration for the treatment of rheumatism, hypercholesterolemia, lung infections, gastrointestinal problems and the prevention of cardiovascular disease, and as an antioxidant and hepatoprotective agent.[36] Moreover, Argan oil is renowned for its cosmetic properties. In fact, it is used to moisturize and nourish skin and hair, to increase hair strength, and to treat scarring, brittle nails and hair loss.[37] Regarding Argan leaves, they are used after a decoction process to treat diabetes, gastritis and ulcers, fever and headaches.[38,39] Similarly, Argan pulp is often used orally after a decoction process to treat diabetes, gastritis, and ulcers, as an antimicrobial agent (antibacterial, antifungal) and is sometimes combined with other plants (juniper leaves, thyme, ...). It can also be used as an infusion to treat dysentery, migraine and fever.[40,41] On the other hand, flowers are used as cosmetics, thanks to their rich antioxidant compounds. After drying, the flowers are macerated, and the extract obtained is applied as dermal product for the face.[41] Finally, Argan roots are used by decoction alone or in combination with Juniper leaves and Oregano for the treatment of diabetes and colopathy.[34] Finally, Argan tree trunk bark is used as a decoction in combination with Juniper leaves to treat gastritis, ulcers and colopathy[41] Figure 3 and Table 2.

■ *ARGANIA SPINOSA* PHYTOCHEMISTRY

Fixed Oil Chemical Composition. Argan oil is the main product of the Argan tree and has taken a huge share of studies carried out on the Argan tree in terms of composition, quality, and biological activity.

Extraction Methods. Argan oil could be extracted based on two methods: the first is the traditional method mainly used by the local population in the south of Morocco (Figure 4), while the second is the mechanical extraction method. In traditional method, the initial steps consist of carefully removing the pulp, then crushing the kernel with stones to remove the shell and obtain the almonds, which are then air-dried in clay containers and lightly roasted. After cooling, the almonds are ground into a brownish paste, which is mixed with soft water and kneaded for several hours. Afterward, the mixture is then left to settle to obtain a hazelnut-flavored oil. The residue obtained after extraction contains around 10% residual oil. Among the disadvantages of this method are the extraction time, which exceeds 1 h to obtain one liter of oil, and the oil yield, which does not exceed 30%. The oil obtained by this method also has a poor shelf life, due to the water added during the extraction procedure.[42]

However, the mechanical method, recently introduced as part of the industrialization of argan oil extraction, enables the kernels to be pressed mechanically, without the need to mix the paste with water, and gives a higher yield (around 45%). On the other hand, the extraction process is rapid, taking around 30 min to extract 1 L of oil. Finally, the quality of the oil obtained is slightly higher, with a lower acidity index than that of traditionally extracted argan oil.[43]

Saponifiable Fraction. The saponifiable fraction of argan oil shows a characteristic fatty acid and triglyceride profile.

Fatty Acids. The fatty acid's profile of argan oil is tabulated in Table 3; it was indicated the presence of four main fatty acids

Table 3. Argan Oil's Fatty Acid Composition

Fatty acid[a]	Min	Max	Average	Reference
C18:0	4.30%	9.0%	6.65%	44, 46−48, 51, 52
C18:1	34.6%	59.0%	46.8%	
C18:2	29.3%	44.2%	36.75%	
C16:0	5.0%	16.3%	10.65%	
C20:0	0.0%	0.8%	0.4%	
C14:0	0.13%	0.17%	0.15%	
C20:1	0.07%	0.47%	0.27%	
C18:3	0.1%	0.35%	0.22%	
C16:1	0.08%	0.18%	0.13%	

[a]Stearic acid: C18:0; Oleic acid: C18:1; Linoleic acid: C18:2; Palmitic acid: C16:0; Arachidonic acid: C20:0; Myristic acid: C14:0; cis-11-Eicosenoic acid: C20:1; Linolenic acid: C18:3; palmitoleic acid: C16:1.

including oleic acid (34.6−57.%), linoleic acid (29.3−44.2%), palmitic acid (5−16.2%), and stearic acid (4.3−12%).[44−48] Also, the presence of other fatty acids with a small percentage was noted as mentioned by Ait. aabd et al. (2013) and Kharbach et al. (2018), such as arachidic acid (0.3−0.8%), myristic acid (0.13−0.17), eicosenoic acid (0.07−0.47), linoleic acid, and palmitoleic acid.[44,49]

The various studies carried out on the argan fatty acid profile have agreed that oleic acid is the major fatty acid, followed by linoleic acid (Figure 5). However, the study by El adib et al. (2015) on Argan oil produced by varieties introduced in Tunisia reported that the most abundant fatty acid is linoleic acid, followed by oleic acid. In addition, the same authors suggested that this difference might be due to the effect of climatic conditions, as well as the introduction of this species into an environment different from its original one. Cosmetic argan oil

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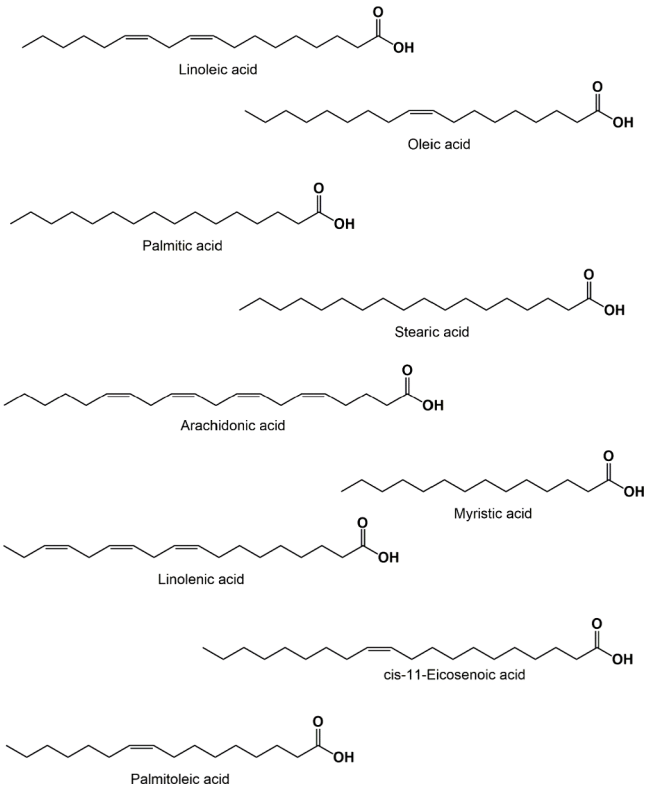

Figure 5. Main fatty acids found in *Argania spinosa* oil.

(unroasted kernels) showed the highest oleic acid content (57%); this difference might be due to the fact that the almonds used to extract cosmetic argan oils are not roasted.[50] In fact, the roasting stage that precedes the extraction of edible argan oil could highly influence the oil by degrading the chemical composition of argan oil.[46]

Triglycerides. Triacylglycerols (TAGs) are the major and most typical constituents of argan oil.[53] They consist of a glycerol linked to three fatty acid molecules. The TAGs of argan oils are dominated by palmitoyl-oleoyl-oleoylglycerol (POO), with percentages ranging from 15.17 to 16.32%, followed by linoleoyl-oleoyl-oleoylglycerol (LOO) at 16.27% followed by linoleoyl-oleoyl-palmitoylglycerol (LOP) with a percentage ranging from 13.22 to 14.57% while linoleoyl-palmitoyl-stearoylglycerol (LPS) represents the lowest percentage with a value ranging from 0.11 to 0.66% (Table 4).[54]

Unsaponifiable Fraction. The unsaponifiable fraction consists mainly of tocopherols, sterols, polyphenols, and minerals.

Tocopherols. The numerous studies carried out on the tocopherol composition of Argan oil have shown that argan oil is characterized by the presence of four types of tocopherols (Table 5): α-tocopherols, β-tocopherols, γ-tocopherols, and δ-tocopherols. γ-tocopherols represent the highest content, ranging from 283 to 701.1 mg/kg, followed by δ-tocopherols (21−84 mg/kg), α-tocopherols (13−74 mg/kg), and β-tocopherols (0−7 mg/kg). Total tocopherols content ranges from 317 to 775.5 mg/kg, with an average of 546.2 mg/kg, making argan oil an important source of tocopherols (provitamin E) (Figure 6).[48,54−57]

Table 5. Tocopherols Found in Argan Oil

Compounds	Min	Max	Average	References
α-Tocopherols (mg/kg)	13.0	74.0	43.5	48, 54−57
β-Tocopherols (mg/kg)	0.0	7.0	3.5	
γ-Tocopherols (mg/kg)	283.0	701.1	492.0	
δ-Tocopherols (mg/kg)	21.0	84.0	52.5	
Total tocopherols content (mg/kg)	317.0	775.5	546.25	

Sterols. The argon oil sterol fraction is mainly composed of Schotenol and Spinasterol. Their contents vary between 43.39 and 48.47 mg/100 g for Schotenol and between 34.9 and 43.2 mg/100 g for Spinasterol (Table 6 and Figure 7). These two compounds distinguish argan oil from other vegetable oils.[10] On the other hand, other sterols, such as δ-7-avenasterol, Stigma 8,22 and Stigma 7,24 are present at moderate levels, with mean values of 5.1, 4.6, and 4.25 mg/100 g, while Campesterol and Cholesterol are present in trace amounts, with values of 0.205 and 0.15 mg/100 g respectively.[54,55,57]

Polyphenols. Argan oil is characterized by a very low total polyphenol content, ranging from 0.3 to 14.18 mg/kg. Ferulic acid is the major component with a content that varies between 4.02 and 4.45 mg/kg followed by syringic acid, vanillic acid, p-hydroxybenzoic acid, and caffeic acid (Table 7 and Figure 8).[58] Catechin, tyrosol, and catechol were also detected, but only in trace form and at levels of 0.1 mg/kg or less. However, the presence or absence of any of these compounds depends on a number of factors, such as the pretreatment of the kernels, the extraction method, the origin of the mother plant, and climatic conditions.[59]

Mineral Composition. Minerals constitute the main group of micronutrients essential for normal body growth. Plant foods are an important source of essential minerals, nutrients and bioactive compounds.[60] Furthermore, Argan oil was characterized by the presence of 12 elements, dominated by calcium (Ca) as the major compound, followed by phosphorus (P) and magnesium (Mg), (Table 8). Other minerals were detected in smaller proportions, such as potassium (K), iron (Fe), and copper (Cu).[61] On the other hand, the study performed by Kamal et al. (2017) has demonstrated that the major element in argan oil is iron (Fe), followed by copper (Cu), while calcium (Ca) was absent. The same author reported that the extraction method influences the chemical composition. Indeed, these results showed that the concentration of metals in oil obtained by traditional extraction was higher than that obtained by

Table 4. Composition of Triacylglycerols[a] in Argan Oil[54]

LLL	LLO	LLP	LOO	LOP	PPL	OOO	POO	OPP	LPS	SOO	SOP
6.84−7.69%	12.20−13.80%	5.77−6.55%	13.93−16.27%	13.22−14.57%	1.86−2.14%	11.32−14.03%	15.17−16.32%	3.76−4.39%	0.11−0.66%	4.10−6.04%	1.77−4.00%

[a]LLL: trilinoleoylglycerol, LLO: linoleoyl-linoleoyl-oleoylglycerol, LLP: linoleoyl-linoleoyl-palmitoylglycerol, LOO: linoleoyl-oleoyl-oleoylglycerol, LOP: linoleoyl-oleoyl-palmitoylglycerol, PPL: palmitoyl-plamitoyl-linoleoylglycerol, OOO: trioleoylglycerol, POO: palmitoyl-oleoyl-oleoylglycerol, OPP: oleoyl-palmitoyl-palmitoylglycerol, LPS: linoleoyl-palmitoyl-stearoylglycerol, SOO: stearoyl-oleoyl-oleoylglycerol, and SOP: stearoyl-oleoyl-palmitoylglycerol.

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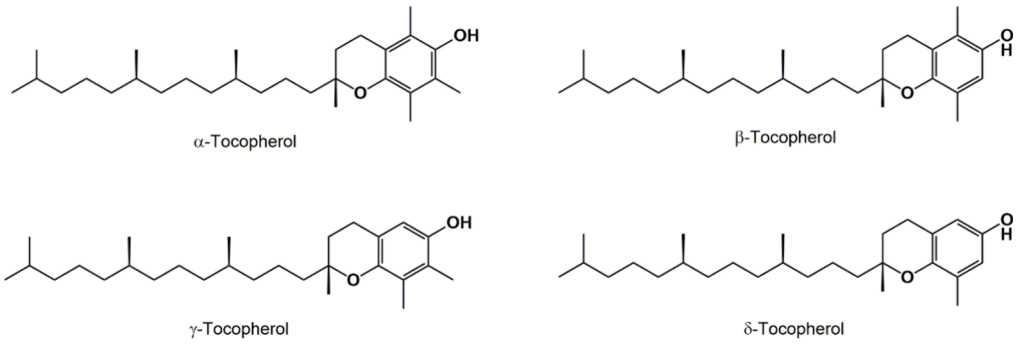

Figure 6. Main tocopherols found in *Argania spinosa* oil.

Table 6. Main Sterols Found in Argan Oil

Sterols (mg/100 g)	Min	Max	Average	References
Schotenol	43.39	48.47	45.93	54, 55, 57
Spinasterol	34.9	43.2	39.05	
δ-7-avenastérol	4.2	6	5.1	
Stigmasta 8,22E-diene-3*β*-ol	3.8	5.40	4.6	
Stigmasta-7,24-dien-3-ol	2.57	5.94	4.255	
Campesterol	0.11	0.3	0.205	
Cholesterol	0.1	0.2	0.15	

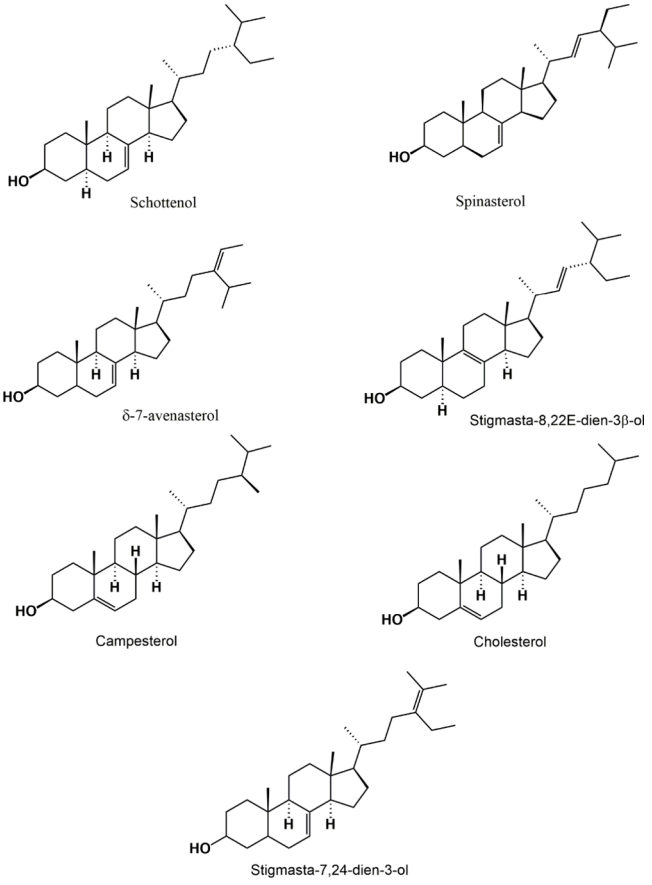

Figure 7. Main sterols present in *Argania spinosa* oil.

Table 7. Polyphenols Present in Argan Oil

Compounds	Content (mg/kg)	References
Gallic acid	0.22−0.24	58
p-Hydroxybenzoid acid	1.43−1.98	
Vanillic acid	1.63−1.59	
Caffeic acid	1.28−1.10	
Syringic acid	3.60−3.72	
p-Coumaric acid	0.47−0.52	
Ferulic acid	4.02−4.45	
Sinapic acid	0.23−0.25	
Epicatechine	0.12−0.14	
Quercandin	0.12−0.19	
Catechine	0.1	
Tyrosol	0.1	
Catechol	0.1−0.3	
Total	13−14.18	

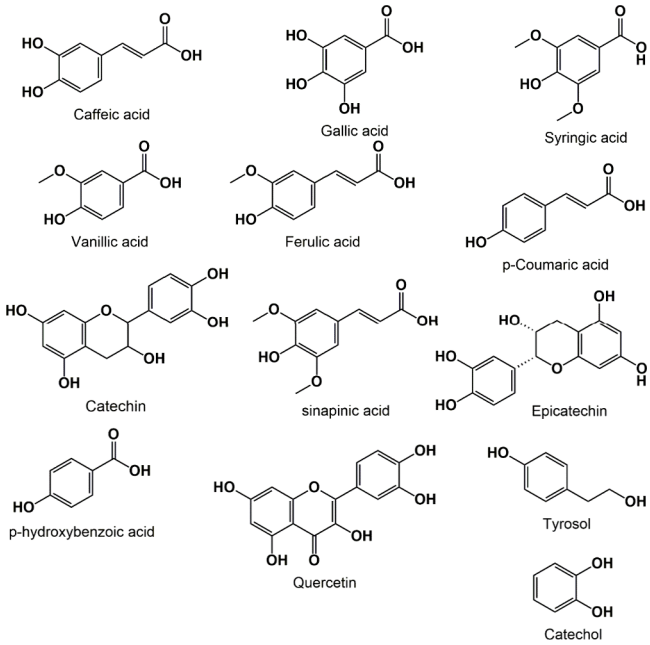

Figure 8. Main phenolic acids found in *Argania spinosa* oil.

mechanical extraction. The author explains this by contamination during the extraction process, especially for iron (Fe) and copper (Cu).[62]

Variation of Chemical Composition. The composition might vary slightly or greatly, depending on numerous factors, including the extraction process. According to Ouchbani et al. (2021), high temperature affects the physicochemical quality parameters of the oil obtained, such as free acidity, peroxide value, and specific extinction at 232 and 270 nm, but these values remain below the limits set by the Moroccan extra-virgin oil standard.[63] Ait aabd et al. (2013) have reported that the effect of the year was significant on the chemical composition of argan oil,

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Table 8. Mineral Composition of Argan Oil

	Edible oil (mg/L)	Cosmetic oil (mg/L)	Traditional extraction (mg-μg*/kg)	Mechanical extraction (mg-μg*/kg)	References
Calcium (Ca)	6.7−8.45	6.72−10.58	-	-	61, 62
Cadmium (Cd)	0.1	0.01	-	-	
Chrome (Cr)	-	-	10.8−55.3*	10.0−48.1*	
Copper (Cu)	0.01−0.03	0.02−0.03	160.4- 695.7*	158.4−385.0*	
Iron (Fe)	0.35−0.64	0.01−0.93	0.8−3.1	0.8−1.7	
Potassium (K)	0.91−1.78	0.62−3.56	-	-	
Magnesium (Mg)	1.92−2.63	1.74−3.17			
Manganese (Mn)	0.01	0.01−0.02	18.1−70.8*	15.5−68.5*	
Phosphore (P)	2.07−2.68	1.87−2.51	-	-	
Tin (Sn)	0.11−0.62	0.09−1.30	-	-	
Zinc (Zn)	0.02−0.04	0.01−0.06	-	-	
Lead (Pb)	-	-	28.5−450.0*	− 100.0*	

Table 9. Phenolic Compounds Detected in *Argania spinosa*

Compounds	Leaves (mg/kg)	Pulp (mg/100 g)	Almonds (mg/100 g)	Oil cake (mg/100 g)	References
Procyanidin B1	-	-	0.1−0.6	-	69, 70, 72, 73
Catechin	-	-	0.4−0.45	-	
Procyanidin B	-	-	0.2−0.25	-	
Gallocatechin Gallate	-	-	0.2−0.3	-	
Epicatechin	-	-	0.6−0.7	0.2−0.3	
Myricetin-3-O-hexose	6.5	-	-	-	
Rutin	-	9.8	0.02−0.03	-	
Isoquercetin	-	28.4−30.6	0.2−0.3	-	
Myricetin-O-pentose	1.5	-	-	-	
Myricitrin	12.9−16.8	-	-	-	
Hyperoside	2.5−10.9	21.1−24.4	-	-	
Quercetin-O-pentose	3.6	-	-	-	
Quercetin	5.7−6.3	0.2−0.3	-	-	
Myricetin-3-0-galactoside	3.3−3.6	-	-	-	
TPC (FC mg GAE/g)	29.91−77.28	75.8−76	8.2−8.9	4.8−5	
TPC (HPLC)	36−45.3	59.5−66.7	1.79−2.45	0.2−0.3	

in particular on the fatty acid profile and especially the oleic acid content. At the same time, geographical origin had a significant influence on all fatty acids profile.[44] On the other hand, the study by Nerd et al. (1994) concerning the effect of introducing the Argan tree into two desert regions of Israel, noted that the chemical composition of the oils obtained was satisfactory and that the influence of the region did not affect its fatty acid composition.[64] In contrast, Aithammou et al. (2019) have reported that the Age of Argan trees does not influence the quality of argan oil or its chemical fatty acid composition, while a significant difference was noted between clones, harvest date and geographical origin regarding fatty acid and tocopherol content.[56]

Regarding the oxidative stability of argan oil, a study by Matthäus et al. (2010) has indicated that the adoption of mechanical extraction using roasted almonds provides better protection of the oil against oxidation.[57] Similarly, Gharby et al. (2021) have studied the stability of argan oil composition (mechanical extraction, unroasted) in the face of accelerated oxidation at 60 °C for 12 weeks. They showed that fatty acids composition and levels remained unchanged for 12 weeks, while tocopherols level decreased significantly.[48] While, Hilali et al. (2005) have demonstrated that mechanical press extraction does not alter the chemical composition of argan oil, and produces oils with a chemical composition similar to that of oils obtained by traditional extraction (total tocopherols content, fatty acids, and physicochemical quality).[65] However, in the study made by Hilali et al. (2020), it was indicated that the variability of argan oil chemical composition is highly influenced by extraction method, origin, and altitude. The results showed that almond roasting increases the peroxide value and decreases the percentage of α-tocopherols and the unsaponifiable fraction, while no statistical differences were found between origins in physicochemical quality, fatty acids, and tocopherols composition, but triglycerides composition was affected by origin. Argan oils from northeastern Morocco gave the highest values. Finally, mechanical extraction gave the best results in terms of chemical composition.[54] Kharbach et al. (2022) have recently studied the polyphenol composition of argan oil from five different origins. The results enabled the oils to be classified according to geographical origin. In addition, they pointed out that the quality and quantity of flavonoids and phenolic acids depend on the origin.[66]

As noted by Hilali et. al. (2020) and Gharby et. al. (2011), numerous factors could have a high a significant effect on tocopherols content including methods, origin, and pretreatment (roasting or not of the kernels).[54,55] In fact, mechanical extraction using roasted almonds gave the best tocopherol levels, while the use of goat-digested kernels and roasted almonds extracted by the traditional method gave the lowest results, while sterol content was unaffected.[57] Meanwhile, it was indicated by Gharby et. al. (2011) that cosmetic argan oil contained the highest level of γ-tocopherols, while the lowest level was recorded by edible argan oil that had undergone roasting prior to

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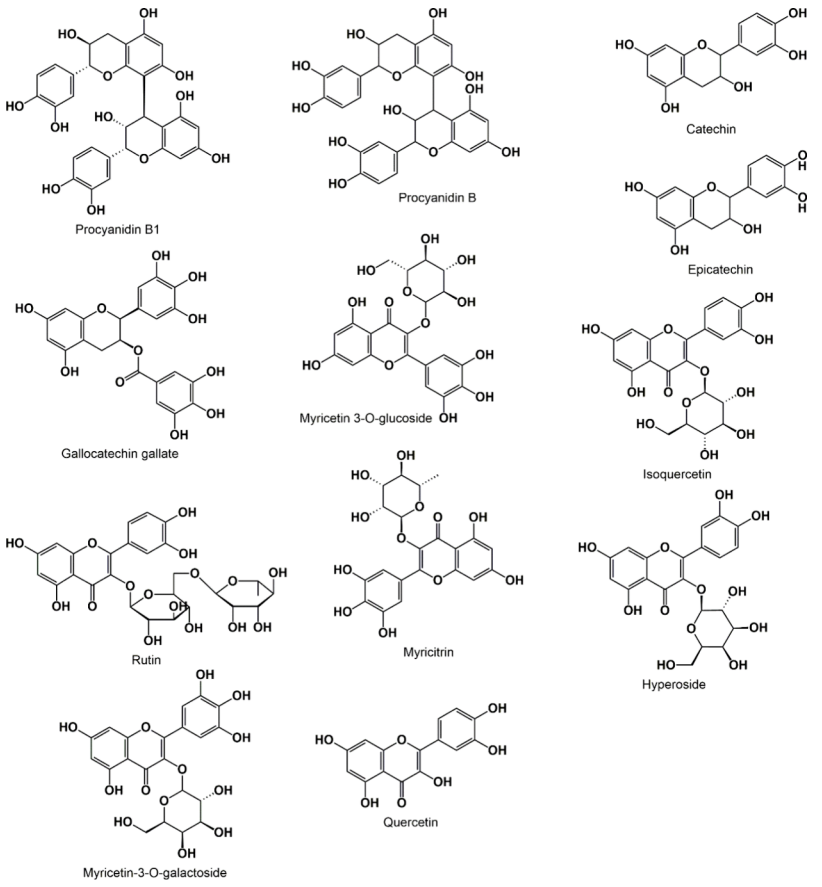

Figure 9. Phenolic compounds found in *Argania spinosa* leaves and pulp.

oil extraction.[55] Furthermore, climatic conditions are known to have a significant impact on the composition and on tocopherols content. According to. Elgadi et al. (2021), tocopherols content is influenced by origin, continentality, and altitude.[67] Studies by Kharbach et al. (2018) and (2019) have produced a geographical classification of argan oils based on tocopherol content.[49,68]

For analyzing the chemical composition of argan oil, future research should take into consideration the genotype or the mother tree and track how the chemical composition evolves over several years. This involves introducing different genotypes into various regions of the country to conserve genetic resources and study how the selected trees perform in different locations. Research on the chemical composition of phytosterols, triglycerides, and minerals in argan oil is still in its early stages. Thus, it needs to be conducted across multiple regions in which the argan tree grows naturally or has been introduced.

CHEMICAL COMPOSITION OF DIFFERENT *ARGANIA SPINOSA* PARTS

Phenolic Compounds. *Argania spinosa* tree leaves were the most studied parts after argan oil. In fact, the study conducted by Tahrouch et al. (2000) was the first to reveal leaves chemical composition and reported that Argan leaves are characterized by the presence of Myricitrin and Hyperoside as major compounds (Table 9 and Figure 9). While, other molecules were found to be in trace including Myricetin-3-0-galactoside, Quercitrin, and Myricetin-O-pentose.[69] However, in the study assessed by Kechebar et al. (2017), it was reported the presence of three phenolic compounds, such as naringenin, rutin, and epicatechin.[70] In recent studies, Bourhim et al. (2021) have evaluated the chemical composition of argan leaves methanolic extract and have indicated the presence of gallic acid and quercetin.[71] Total polyphenols content ranges from 36 to 45.3 mg/kg by the HPLC method,[69,72] while by the Folin Ciocalteu method gave values that oscillate between 29.9 and 77.2 mg equivalent GA/g dry weight.[70] On the other hand, Argan pulp is found to be characterized by the presence of numerous phenolic compounds, such as isoquercetin and hyperoside (Table 9), which are the major compounds with a portion of 30.6 and 24.5 mg/100 g, respectively. However, rutin was present in small quantities (9.8 mg/100 g), and quercetin was detected in trace (0.3 mg/100 g). The total polyphenol content assay indicated that polyphenols content found was around 66.7 mg/100 g using the HPLC method, while it was 76 mg GA equivalent/g using the Folin Ciocalteu method.[70]

Argan kernels are characterized by a phenolic compound composition that is slightly different from other parts, with epicatechin and catechin as the main compounds, at 0.6 and 0.45 mg/100 g, respectively. Total polyphenols content is generally low, with values of 8.2 to 8.9 mg equivalent GA/g using the Ciocalteu folin method and 1.79 to 2.45 mg/100 g using the HPLC method.[70] Only one phenolic compound was detected in an argan oil cake, epicatechin, with a value of 0.2 to 0.3 mg/100 g. The total polyphenols content was 0.2 to 0.3 mg/100 g using the HPLC method, while the Folin Ciocalteu colorimetric method produced a slightly higher value of 4.8 to 5 mg equivalent GA/g.[70]

Saponins. Saponins are also detected in Argan cake oil and almonds (Table 10 and Figure 10). Charrouf et al. (1992) have

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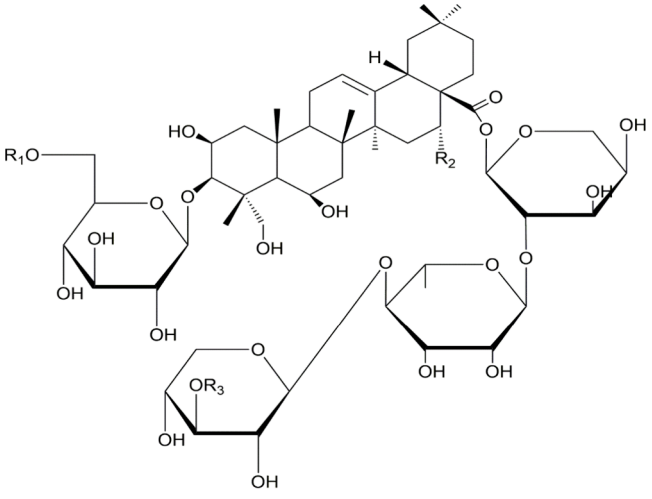
Table 10. Saponins Detected in *Argania spinosa* (%)

Compounds	Cake oil	Pulp	Wood	Bark	References
Arganine A	39.0	-	-	-	74, 75
Arganine B	8.0	-	-	-	
Arganine C	3.2	-	-	-	
Arganine D	4.2	-	-	-	
Arganine E	3.4	-	-	-	
Arganine F	3.2	-	-	-	
Arganine G	-	-	0.012	-	
Arganine H	-	-	0.004	-	
Arganine J	-	-	0.010	-	
Arganine K	-	0.02	-	-	
Arganine L	-	-	-	[a]	
Arganine O	-	-	-	[a]	
Arganine P	-	-	-	[a]	
Arganine Q	-	-	-	[a]	
Arganine R	-	-	-	[a]	

[a]Detected without quantitative data.



Compound	Name	R1	R2	R3
1	Arganine A	Glucose	OH	Rhamnopyranose
2	Arganine B	Glucose	OH	Apiofuranose
3	Arganine C	H	OH	Rhamnopyranose
4	Arganine D	Glucose	H	Rhamnopyranose
5	Arganine E	Glucose	H	Apiofuranose
6	Arganine F	H	H	Apiofuranose
7	Arganine A	H	H	Apiofuranose

Figure 10. *Argania spinosa L. Skeels* saponin.

isolated six saponins that were named Arganine A to F.[74] While, Oulad-Ali et al. (1996) have reported tree saponins in the trunk of the Argan tree, namely, Arganine G, H, and J at a concentration of 6%.[75] However, Alaoui et al., (2001) have reported the presence of Arganine K in argan pulp.[76] On the other hand, El Fakhar et al., (2007) have noticed the presence of five new saponins in the bark of the Argan tree (Arganine L, O, P, Q, and R).[77] Generally, saponins are characterized by antifungal and antibiotic activity, suggesting the possible involvement of saponins in the exceptional longevity of the Argan tree and its high resistance to various aggressions.[78]

Polysaccharides. Numerous studies investigated the complex sugar structures found in different parts of the argan tree. Researchers first isolated specific polymers from the cell wall of *Argania spinosa* leaves using an alkaline extraction method focusing primarily on two main polymers: xylan and xyloglucan. These were analyzed by using various techniques, including enzyme degradation and advanced forms of chromatography and mass spectrometry. The findings revealed that the xylan in *Argania spinosa* has a backbone made of β-(1 → 4)-linked D-xylopyranose units, with 4-O-methyl-D-glucuronic acid substitutions. The xyloglucan oligosaccharides, produced with an enzyme (endo-(1 → 4)-β-D-glucanase), indicated an XXXG-type xyloglucan structure, which included a unique XUFG fragment with a complex side chain.[79]

The second study focused on the *Argania spinosa* fruit pulp cell wall, where the cell wall was separated into different polysaccharide components and analyzed their monosaccharide composition and chemical structure. The principal findings showed the presence of three main types of pectic polysaccharides: homogalacturonan, rhamnogalacturonan-I (RG-I), and rhamnogalacturonan-II (RG-II). RG-I was particularly abundant and had high levels of arabinose and galactose, suggesting it has significant branching.[80] Finally, a third study examined the xylan-type polysaccharides from *Argania spinosa* leaves collected in Tindouf, Algeria. These polysaccharides were isolated by using sequential alkaline extractions and were further purified. The analysis, which included enzymatic hydrolysis, chromatography, sugar analysis, and mass spectrometry, revealed that the xylan from *A. spinosa* leaves has a β-(1 → 4)-D-xylopyranose backbone, which also includes 4-O-methyl-D-glucuronic acid and L-arabinose residues.[81]

Volatile Compounds. Argan tree leaves are characterized by the presence of volatile compounds with a low content varying between 0.03 and 0.05%.[82] Despite this low content, numerous studies have evaluated the essential oil composition obtained by hydrodistillation of Argan leaves and identified over 30 compounds (Table 11, Figure 11). Cubenol was the major compound, ranging from 31.02 to 35.7%, followed by 1,10-diepi-cubenol (22.50%), camphor (8.6 and 2.6%) and eucalyptol (5.40 to 8.49%).[82−84] In contrast Nafis et al (2021) have reported different findings from those found in the

Table 11. *Argania spinosa* Leaves Volatile Compounds[82−85]

Compounds	%
Cubenol	31.02
1,10-Di-*epi*-cubenol	22.50−35.7
Camphre	2.6−8.6
Viridiflorol	7.1
Linalool	5.6
Eucalyptol	5.40−8.49
α-Pinene	3.2−1.16
Camphene	2.1−0.2
β-Pinene	2.8−1.36
Myrcene	5.8−3.3
Bornylacetate	9.3
β-Eudesmol	0.7−8.3
Gerany acetate	19.18
Methyleugenol	10.98
Linalylacetate	10.59
Bornyl acetate	1.8
Germacrene D	14.3−0.2
β-Selinene	1
Epi-cubelol	0.5
α-Muurolene	0.3
γ-Cadinene	2.3
cis-Calamene	1.1
Selina-3,7(11)-diene	5.1
α-Calacorene	0.6

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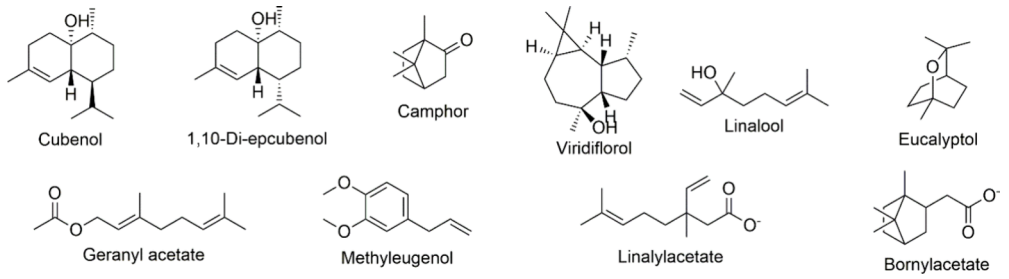

Figure 11. Major volatile compounds identified in *Argania spinosa L. Skeels* leaves.

bibliography, with geranyl acetate as the major compound, followed by methyl eugenol and linalyl acetate with values of 19.18 and 10.98%, respectively.[85]

The EO composition from Argan fruit pulp was investigated by Harhar et al. (2010), with yields varying between 0.06 and 0.08%. Oxygenated terpene derivatives were the main constituents of argan pulp essential oils, accounting for 79.5% of (Table 12, Figure 12). Camphor was the main compound present in pulp essential oil with a value of 35.5%, followed by 1,8-cineole with a level of 16.0%.[86]

Table 12. Volatile Compounds Present in Argan Pulp[86]

Compounds	%
Furan-2-carbaldehyde	2.2
2-Methylbutanoic acid	4.9
1,8-Cineole	16
Linalol	1.6
Camphor	35.5
Endoborneol	11.8
Cyclohex-3-en-ol	11.1

Variation of the Chemical Composition. Studies targeting variation in secondary metabolite content have mainly focused on Argan leaves. Variation in total polyphenols content was often significant between regions, ranging from 80 to 85 mg equivalent GA/g DW. On the other hand, water stress was reported to be an important factor influencing the biochemical composition of Argan leaves. Total polyphenols content after exposure to severe water stress reached a value of 100 mg equivalent GA/g DW.[87] On the other hand, the study by Djied et al (2016) showed that polyphenols content in Argan leaves was highly influenced by climate. In fact, Argan trees originating from a climate characterized by high aridity showed a high level of compounds belonging to the flavonoid family, with a value of 20% compared with 8.7% recorded in trees originating from areas with a semiarid climate. A study of the histolocalization of these compounds in parts of the plant led to the conclusion that this increase protects the plant against irradiation and the various abiotic stresses it faces.[88] Current research has mainly focused on leaves and fruit pulp, neglecting the flowers and branches of the Argan tree, which have been documented in the literature as products previously used in traditional medicine. Therefore, their chemical composition needs investigated for better elucidation of the biocompounds (primary and secondary metabolites),[89] present in these unexplored parts of Argan.[90]

EXTRACTION AND CHARACTERIZATION OF *ARGANIA SPINOSA L. SKEELS* BIOACTIVE COMPOUNDS

Several techniques have been used to study the composition of the different parts and products of this plant (Table 13), targeting several families of bioactive compounds. Argan oil has been extensively studied due to its widespread use worldwide. It has undergone a comprehensive range of phytochemical analyses to detail its composition, particularly because it is used both as a food product and in cosmetics. To characterize the fatty acids in argan oil, gas chromatography−mass spectrometry (GC-MS) is used, which follows a process of esterification. Tocopherols are analyzed using High-Performance Liquid Chromatography (HPLC) through various protocols, and sterols are also analyzed using GC-MS.[3,67,68] Regarding polyphenols profile of argan oil, argan oil is often fractionated using a hydroalcoholic solvent with varying proportions of methanol/water (50/50) (v/v) or (80/20) (v/v) and analyzed using HPLC or by total polyphenols content measurement using the Folin-Ciocalteu method.[91] Studies on the chemical investigations of Argan leaves have focused on polyphenols, flavonoids, and tannins, using a variety of methods ranging from simple quantification assays to liquid chromatography coupled to detectors such as UV or mass spectroscopy. The extraction methods used are mainly based on maceration using hydroalcoholic solvents (ethanol 70%, ethanol 80%, methanol 80%)[32,71,92]

Saponins are often extracted either from the leaves or from the oil cake (press cake) using 70% ethanol, followed by degreasing with *n*-hexane or ethyl acetate, then extraction with n-butanol, and the final product analyzed by thin layer chromatography (TLC) for the visual verification of the presence of saponins in

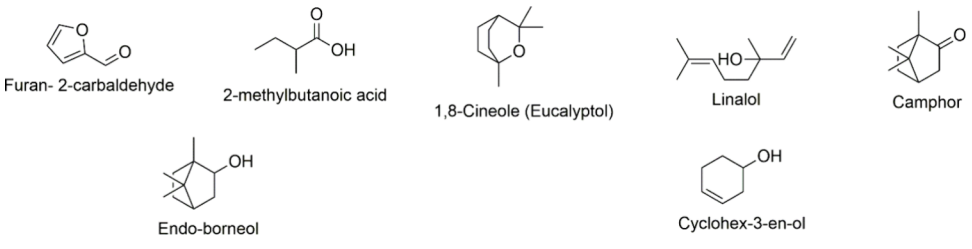

Figure 12. Major volatile compounds identified in *Argania spinosa* pulp.

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Table 13. Extraction and Characterization of *Argania spinosa L. Skeels* Bioactive Compounds from Different Plant Parts

Plant parts	Bioactive compounds family	Extraction techniques	Solvents	Method used	References
Leaves	Polyphenols	Maceration	Ethanol 70%	Folin−Ciocalteu	92
		Maceration	Distilled water, methanol, and ethyl acetate	Folin−Ciocalteu	96
		Ultrasonic bath	Defatted using petroleum ether (60−80 °C) → extracted with methanol/water (70/30, v/v)	Folin−Ciocalteu UPLC-ESI-QTOF-MS	97
		Radleys Fermenter RR98072	70% Aqueous ethanol	LC/MS	98
		Maceration	Methanol−water solution (85:15 v/v) → then defatted with hexane	Folin−Ciocalteu	99
		Maceration and Ultrasonic bath	Methanol 80%	HPLC and LC-MS	100
	Essential oil	Hydrodistilation−clevenger	Distilled water	GC-MS	101
		Steam distillation	Distilled water	GC-MS	102
		Hydrodistilation−clevenger	Distilled water	GC-MS	103
	Saponins	Maceration	70% Ethanol → defatted with *n*-hexane and ethyl acetate, then aqueous layer extracted with n-butanol	Thin layer chromatography (TLC)	93
	Polysaccharide	Continuous stirring/centrifugation	Ethanol 80% (water/ethanol, v/v) ethanol 95% (ethanol/acetone, v/v) succeeded by sequential extraction with 1 and 4 M KOH then acidified with AcOH to pH 6	High performance anion exchange (HPAE)	94
Seeds/oil	Fatty acids	Cold-pressed	_	GC-MS	104
		Cold-pressed	_	GC-MS	105
		Soxhlet	Hexane	GC-MS	3
	Tocopherols	Cold-pressed	_	HPLC	105
		Soxhlet	Hexane	HPLC-DAD	3
		Cold-pressed,	Then diluted with 2,2,4-trimethyl pentane	HPLC	106
	Phytosterols	Oil Boiling	30 mL Ethanolic KOH (2 M) distilled water (25 mL) and petroleum ether (75 mL)	Gas chromatography	105
	Polyphenols	Cold-pressed then fractionating	methanol/water (2 mL) (80:20 v/v)	Folin−Ciocalteu	91
		Cold-pressed then fractionating	Water/methanol (50 v/v)	HPLC-DAD-TOF/MS	107
	Essential oil	Supercritical CO_2	_	GC-MS	108
Fruit press cake	Saponins	Maceration	70% Ethanol→ defatted with *n*-hexane and ethyl acetate, then aqueous layer extracted with n-butanol	Thin layer chromatography (TLC)	93
		Maceration and centrifugation	Distilled water and ethanol (0−100%, (v/v))	Spectrophotometer	109
Pulp	Polyphenols	Soxhlet/Maceration	Defatted for 6H with *n*-hexane then shaker with acetone/water/formic acid (70:29.5:0.5 v/v/v)	LC-MS and Folin−Ciocalteu	110
	Essential oil	Microwave-assisted extraction, Hydro-distilation (4 h) and steam-distillation (3 h)	Distilled water	GC-MS	111
	Saponins	Maceration	70% Ethanol → defatted with *n*-hexane and ethyl acetate, then aqueous layer extracted with n-butanol	Thin layer chromatography (TLC)	93
Flowers	Polyphenols	Maceration	Ethanol 70%	Folin−Ciocalteu	92
Branches	Polyphenols	Maceration	Ethanol 70%	Folin−Ciocalteu	92

the final extract.[93] The study of argan tree polysaccharides has been of great interest to researchers, with a view to obtaining new polymers from the fruit pulp, which is considered a byproduct consumed by livestock.[33] The polysaccharide extraction process consists of maceration using 80% ethanol (water/ethanol, v/v) followed by 95% ethanol (ethanol/acetone, v/v) extraction. Then a sequential double extraction using 1 and 4 M potassium hydroxide (KOH). The obtained product was acidified with acetic acid (AcOH) to pH = 6. Finally, the resulting product was analyzed by high-performance anion exchange chromatography which is an analytical method for sorting and analyzing anions, which include organic acids, carbohydrates, and other negatively charged ions. Utilizing a specific column, it divides ions according to how they interact with a stationary phase and a mobile phase, which frequently contains a basic solution.[94] Investigation of the chemical composition of twigs and flowers is limited to simple dosage and their detailed chemical composition has not been studied in depth.[92] Although analyzing the chemical composition of the different parts of this plant provides essential information, standardizing separation protocols—especially for polyphenols—and establishing HPLC conditions for complete separation of various argan products would improve the consistency of research results.[95]

ARGANIA SPINOSA PHARMACOLOGICAL PROPERTIES

Pharmacological Properties. Argan oil, the main product of the Argan tree, has been the focus of most scientific research on the pharmacological aspects of the Argan tree. This is due to the multitude of uses for this oil and the various virtues associated with it. Indeed, it is traditionally reputed to have important medicinal effects, notably antidiabetic, antirheumatic, hypercholesterolemic, pulmonary infection, ...).[36]

Antioxidant Activity. The antioxidant activity of argan oil has been evaluated by several research teams (Table 14). Indeed, Marfil et al. (2011) have evaluated the antioxidant capacity of the MeOH fraction of argan oil using tree methods. It was shown that argan oil has a free radical scavenging capacity in the range of 0.19−0.87 mmol trolox/kg and a ferric to ferrous iron reduction capacity of 0.62−2.32 mmoltrolox/kg.[12] While, the evaluation of antioxidant capacity by the ABTS method showed higher values in the range of 14.16−28.02 mmol trolox/kg. On the other hand, the methanolic fraction of argan oil

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Table 14. Pharmacological Properties of Argania spinosa oil

Pharmacological assay	Extracts	Methods	Results	References
Antioxidant	*n*-Hexane extract (Soxhlet)	ABTS•	14.16−28.02 mmol trolox/kg	118
	MeOH fraction from Argan oil	DPPH•	0.19−0.87 mmol trolox/kg	
		FRAP	0.62−2.32 mmol trolox/kg	
		ABTS•	14.1−2.31 mmol trolox/kg	
	Cold press extraction	TAC	100 mg/mL (OD_{50})	119
		DPPH•	>100 mg/mL (IC_{50})	
	MeOH fraction	DPPH•	IC_{50}: > 1500 μg/mL	45
		β-carotene	IC_{50}: > 1500ug/mL	
		Iron chelating power	1.8−2.6 mg EDTAE/g DW	
	Cold press of roasted almonds	β-carotene	IC_{50} = 0.028 ± 0.0008 mg/mL	120
	Cold press of unroasted almonds	β-carotene	IC_{50} = 0.026 ± 0.002 mg/mL	
	Cold press of roasted almonds	DPPH•	IC_{50} = 157 ± 0.016 μg/mL	
	Cold press of unroasted almonds	DPPH•	IC_{50} = 97 ± 0.002 μg/mL	
	Cold press of roasted almonds	Metal chelating activity	255.94 ± 10.77 μg/mL	
	Cold press of unroasted almonds	Metal chelating activity	173.37 ± 28.37 μg/mL	
Antidiabetic	MeOH fraction	α-amylase	2.7−1.4 mg AE/g DW	51
	Cold press of roasted almonds	α-Amylase	In *vitro* IC_{50}: 2.17 mg/mL	113
		α-Glucosidase	In *vitro* IC_{50}: 0.11 mg/mL	
	Cold press of unroasted almonds	α-Amylase	In *vitro* IC_{50}: 0.78 mg/mL	
		α-Glucosidase	In *vitro* IC_{50}: 0.081 mg/mL	
	Cold press of roasted almonds	Hemoglobin Antiglycation	In *vitro* IC_{50} = 1.09 ± 0.31 mg/mL	
	Cold press of unroasted almonds	Hemoglobin Antiglycation	In *vitro* IC_{50} = 0.16 ± 0.031 mg/mL	
	Cold press of unroasted almonds	*Glycemic level variations* of STZ-diabetic rats	Blood glucose UnRoil: At 2 mg/kg: 1.2 ± 0.13 g/L	121
	Cold press of roasted almonds	*Glycemic level variations* of STZ-diabetic rats	Blood glucose at 2 mL/kg: 1.07 ± 0.04 g/L	
	Cold press of roasted and unroasted almonds	*body weight variations* STZ-diabetic rats	Results: 2 mL/kg of Roil and UnRoil in STZ-diabetic rats significantly prevented the reduction in body weight compared to the STZ-diabetic group	
Antibacterial	*n*-Hexane extract (Soxhlet)	Agar diffusion technique	*S. aureus*: 8 mm	115
			S. epidermis: 10 mm	
			E. coli: Not active	
			P. aeruginosa: Not active	
			A. baumannii: Not active	
	Cold press extraction	Agar diffusion technique (against *P. aeruginosa*)	Argan oil + H_2O_2 (1/1):23.8 mm	116
			AO + H_2O_2 (2/1):. 24.6 mm	
			AO + H_2O_2 (1/2): 23.1 mm	
			AO: NA	
			H_2O_2: NA	

showed a protective capacity of β-carotene against bleaching with an IC_{50} of 1500 μg/mL while the iron chelating capacity is in the range of 1.8 to 2.6 mg EDTAE/g DW.[45] In addition, Brahmi et al. (2020) have evaluated the total antioxidant activity (TAC) of argan oil obtained by mechanical cold extraction, the results obtained showed an OD_{50} of 100 mg/mL[112] (Table 14).

Antidiabetic Activity. The antidiabetic activity of argan was evaluated in the study performed by El Adib et al. (2015) which has indicated the inhibition percentage of α-amylase by the methanolic fraction of argan oil. The results reported showed an inhibition capacity of 2.7 to 1.4 mg acarbose/g DW.[45] Similarly, Daoudi et al. (2020) have compared the α-amylase and α-glucosidase inhibitory activity of argan oil between roasted and unroasted almonds. The α-amylase inhibition results showed that roasted argan oil showed the highest activity, with IC_{50} values of 2.17 mg/mL (roasted almond oil) and 0.78 mg/mL (unroasted almonds oil), and an IC_{50} of 0.11 mg/mL (roasted oil) and 0.081 mg/mL (unroasted almonds) for the α-glucosidase inhibition test[113] (Table 14).

Anticancer Activity. Argan oil polyphenols have demonstrated an inhibitory effect on the proliferation of prostatic cell lines named DU145, LNCaP, and PC3. The IC_{50} values calculated at 24 h for DU145, LNCaP, and PC3 cell lines were 75, 100, and 50 mg/mL respectively. PC3 was more sensitive than the other two cell lines. Sterols and 2-methoxyestradiol showed antiproliferative activity against prostate cancer[114] (Table 14).

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Table 15. Pharmacological Properties of *Argania spinosa* Plant Parts

Pharmacological assay	Part used	Extracts	Methods	Results[a]	References
Antioxidant	Leaves	Soaking in MeOH	DPPH•	IC_{50} = 3.9−5 μg/mL	50
			β-carotene	IC_{50} = 45.2−46 μg/mL	
			Iron chelation power	24−21 mg EDTAE/g DW	
		Soaking in 85% of MeOH	DPPH•	IC_{50} = 20 μg/mL	122
			HRSA	IC_{50} = 18 μg/mL	
			FRAP	OD_{50} = 15 μg/mL	
		Soaking in 70% EtOH	DPPH	IC_{50} = 7.52 ± 0.17 μg/mL	126
		Aqueous	DPPH	IC_{50}= 8.51 ± 0.065 μg/mL	
		Soaking in 70% EtOH	ABTS	IC_{50} = 33.85 ± 0.28 μg/mL	
		Aqueous	ABTS	IC_{50} = 41.01 ± 0.06 μg/mL	
	Pulp	Soaking in MeOH	DPPH•	IC_{50} = 5.6−17.1 μg/mL	45
			β-carotene	IC_{50} = 126−360 μg/mL	
			Iron chelation power	15.5−11.6 mg EDTAE/g DW	
		Soaking in 70% EtOH	DPPH	IC_{50} = 164.27 ± 0.8 μg/mL	126
		Aqueous	DPPH	IC_{50} = 177.34 ± 0.85 μg/mL	
		Soaking in 70% EtOH	ABTS	IC_{50} = 210.64 ± 1.55 μg/mL	
		Aqueous	ABTS	IC_{50} = 255.34 ± 1.26 μg/mL	
	Branches	Soaking in MeOH	DPPH•	IC_{50} = 8.11 μg/mL	127
			ABTS•	IC_{50} = 50.20 μg/mL	
		Soaking in 70% EtOH	DPPH	IC_{50} = 15.77 ± 0.11 μg/mL	126
		Aqueous	DPPH	IC_{50} = 17.03 ± 0.03 μg/mL	
		Soaking in 70% EtOH	ABTS	IC_{50} = 61.25 ± 0.49 μg/mL	
		Aqueous	ABTS	IC_{50} = 68.68 ± 0.39 μg/mL	
	Shell	Soaking in MeOH	DPPH•	NA	127
			ABTS•	NA	
	Seed	Soaking in 70% EtOH	DPPH	IC_{50} = 5.85 ± 0.16 μg/mL	126
		Aqueous	DPPH	IC_{50} = 6.48 ± 0.085 μg/mL	
		Soaking in 70% EtOH	ABTS	Not active	
		Aqueous	ABTS	Not active	
Antidiabetic	Leaves	Soaking in MeOH	α-amylase Inhibition	8.4−4.5 mg AE/g DW	45
	pulp	Soaking in MeOH	α-amylase Inhibition	92.1−113.8 mg AE/g DW	
Antibacterial	Leaves	Soaking in MeOH	Agar diffusion technique	*S. aureus*: 12 mm	123
				B. cerus 15.6 mm	
				B.subtilis 16.6 mm	
				E.coli 10.3 mm	
				P. aeruginosa 11.6 mm	
		Soaking in 70% EtOH	Agar diffusion technique	*E. coli*: *NA*	126
				M. resistans: NA	
				R. ornithinolytica: NA	
				S. saprophyticus: 13 ± 0.05 mm	
		Aqueous		*E. coli*: NA	
				M. Resistans: 15 ± 0.02 mm	
				R. ornithinolytica: NA	
				S. saprophyticus: 13 ± 0.07 mm	
		Essential oil	Agar diffusion technique	*S. aureus*: 28 ± 1.5 mm	
				P. aeruginosa: 24 ± 0.9 mm	
			MIC: Micro dilution	*S. aureus*: 0.5 ± 0.1(mg/mL)	128

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Table 15. continued

Pharmacological assay	Part used	Extracts	Methods	Results[a]	References
				P. aeruginosa: 0.3 ± 0.02 (mg/mL)	
			MBC	*S. aureus*: 0.7 ± 0.03(mg/mL)	
				P. aeruginosa: 0.4 ± 0.03 (mg/mL)	
	Pulp	Soaking in 70% EtOH	Agar diffusion technique	*E. coli*: NA	126
				M. resistans: NA	
				R. ornithinolytica: NA	
				S. saprophyticus: NA	
		Aqueous		*E. coli*: NA	
				M. resistans: NA	
				R. ornithinolytica: NA	
				S. saprophyticus: NA	
	Branch	Soaking in 70% EtOH	Agar diffusion technique	*E. coli*: NA	
				M. resistans: NA	
				R. ornithinolytica: NA	
				S. saprophyticus: NA	
		Aqueous		*E. coli*: NA	
				M. resistans: NA	
				R. ornithinolytica: NA	
				S. saprophyticus: NA	
	Seed	Soaking in 70% EtOH	Agar diffusion technique	*E. coli*: NA	
				M. resistans: NA	
				R. ornithinolytica: NA	
				S. saprophyticus: NA	
		Aqueous		*E. coli*: NA	
				M. resistans: NA	
				R. ornithinolytica: NA	
				S. saprophyticus: NA	
Antifungal	Leaves	Soaking in 70% EtOH	disc diffusion method	Botrytis cinereal: NA	126
				Fusarium oxysporum: 1.92 ± 0.02 mm	
		Aqueous		*Botrytis cinereal*: NA	
				Fusarium oxysporum: NA	
	Pulp	Soaking in 70% EtOH		*Botrytis cinereal*: NA	
				Fusarium oxysporum: 13.46 ± 0.08 mm	
		Aqueous		*Botrytis cinereal*: NA	
				Fusarium oxysporum: 32.69 ± 0.08 mm	
	Branch	Soaking in 70% EtOH		*Botrytis cinereal*: NA	
				Fusarium oxysporum: 0 mm	
		Aqueous		*Botrytis cinereal*: NA	
				Fusarium oxysporum: 1.92 ± 0.06 mm	
Anticancer	Pulp	24-h Soaking (ethyl acetate, petroleum ether), decoction	cytotoxic activity (cancer cells (MCF7) responsible for breast cancer)	Ethyl acetate IC_{50}: 42 μg/mL	125
				Petroleum ether IC_{50}: >100 μg/mL	
				Decoction IC_{50}: >100 μg/mL	
Antimalarial	Pulp	24-h Soaking (ethyl acetate, petroleum ether), decoction	Antimalarial activity against chloroquine-resistant strains of P. falciparum	Ethyl acetate IC_{50} = 35 μg/mL	
				Petroleum ether IC_{50} >100 μg/mL	
				Decoction IC_{50} = 52 μg/mL	

[a]NA: Not active

Antibacterial Activity. Argan oil appears to have a significant antibacterial activity. Indeed, the study carried out by Lotfi et al (2015) on Gram-positive and Gram-negative bacteria and targeting the effect of the oil on these bacteria showed that the antibacterial activity of argan oil is significant against *Staphylococcus aureus* (8 mm) and *Staphylococcus*

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epidermis (10 mm), while *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* strains were resistant. This observed antimicrobial activity is mainly due to the oil's richness in sterols, triterpenes, and tocopherols.[115] On the other hand, Naher et al (2014) evaluated the effect of combining argan oil with hydrogen peroxide H_2O_2 (1.5%) at different ratios (1/1, 2/1, 1/2) on antibacterial activity against the *Pseudomonas aeruginosa* strain. The results showed that the use of argan oil alone or hydrogen peroxide alone gave no antibacterial activity, whereas when the two were combined, a considerable destructive effect was recorded and the diameter of the zones of inhibition reached 23.8 mm, 24.6 mm, and 23.1 mm for mixtures of argan oil and H_2O_2 in the proportions of 1:1, 2:1, and 1:2, respectively[116] (Table 14).

Anti-obesity and Dyslipidemic Activity. A clinical study conducted by Drissi et al. (2004) demonstrated the lipid-lowering effect of argan oil by comparing the lipid profile (particularly c-LDL and Lp(a)) of argan oil consumers (62 subjects) and nonconsumers (34 subjects). Indeed, it was found that argan oil consumers had lower levels of plasma LDL cholesterol (12.7%, $P < 0.05$) and Lp(a) (25.3%, $P < 0.05$) than nonconsumers. In argan oil consumers, plasma lipoperoxides were lower (58.3%, $P < 0.01$), and the molar ratio of α-tocopherol/total cholesterol (21.6%, $P < 0.05$) and α-tocopherol concentration (13.4%, $P < 0.05$) were higher compared to the nonconsumers group. Despite higher levels of plasma antioxidants and lower levels of lipoperoxides in argan oil consumers, susceptibility to LDL oxidation remained fairly similar.[117] A strong positive correlation was observed between increased concentrations of phenolic extracts, sterols, tocopherols, and the LDL-Lag phase ($P < 0.05$)[117] (Table 14).

PHARMACOLOGICAL PROPERTIES OF ARGAN LEAVES

Antioxidant Properties. The leaves of the Argan tree have often been of major interest in pharmacological research, due to their increased use in traditional medicine by the local population in the treatment of several diseases, on one hand, and their availability, on the other hand. Their antioxidant activity has been assessed by several authors using different methods. El Adib et al (2015) evaluated the antioxidant activity of the methanolic extract of Argan tree leaves using three methods including DPPH●, B-carotene, and iron chelating power. The results showed that the methanolic extract has a very high free radical scavenging capacity compared with the other methods. Indeed, the IC_{50} values obtained ranged from 3.9 to 5 μg/mL for the DPPH test and from 45.2 to 46 μg/mL for the β-carotene bleaching test. The iron chelating capacity test yielded a value of 24 to 21 mg EDTAE/g DM.[45] Djidel et al. (2014) evaluated the antioxidant activity of the hydroalcoholic extract (85% methanol) of Argan tree leaves using three methods: DPPH●, HRSA, and FRAP (Table 15). The results showed that Argan leaves are characterized by a very high antioxidant activity, which is thought to be due to their high phenolic compounds content.[92,122]

Antidiabetic Properties. El Adib et al. (2015) have shown that the leaves of the Argan tree possess significant antidiabetic activity. This was assessed by the capacity of methanolic leaves extract to inhibit α-amylase. They recorded a value of 4.5 to 8.4 mg AE/g DW[45] (Table 15).

Antibacterial Properties. The leaves of the Argan tree are characterized by significant antibacterial power, thanks to their richness in polyphenols (Table 15). Dakiche et al (2017) demonstrated this activity on five different bacterial strains using the agar diffusion technique. The results obtained showed that the highest inhibition diameter was obtained against the *Bacillus subtilis* strain with a value of 16.6 mm, while the *E. coli* strain was the most resistant, with an inhibition diameter of 10 mm.[123] On the other hand, Bonvicini et al (2017) evaluated the antibacterial activity of argan leaves extracts (aqueous and lipophilic extracts) against several methicillin-resistant strains. Results showed that the lowest MIC_{50} was recorded against *S. aureus* (250 μg/mL) by both extracts while a MIC_{50} of 2000 μg/mL was observed for *K. pneumoniae*. Finally, *E. coli* was the most resistant strain, with a MIC_{50} of over 2000 μg/mL.[124] Argan leaf essential oils showed interesting antibacterial properties. Indeed, the highest antibacterial activity was recorded against Gram-positive bacteria, with MICs ranging from 7.81 mg/mL to 15.62 mg/mL. Gram-negative bacteria, with the exception of *Pasteurella multocida* and *K. pneumoniae* (7.81 mg/mL), were the most resistant, with MICs of 31.24 mg/mL[83] (Table 15).

Pharmacological Properties of Argan Pulp. Recently, studies have focused on other parts of the plant with the aim of maximizing its value. Pulps have been included in this research, as they constitute an unused part of the Argan fruit after extraction of the kernels and are often used as cattle feed.

Antioxidant Properties. The evaluation of the antioxidant activity of the methanolic extract of Argan fruit pulp by several methods showed very satisfactory results, particularly with regard to DPPH● antiradical activity, with an IC_{50} of 5.6 to 17.1 μg/mL. In contrast, the results of the β-carotene bleaching test gave a higher IC_{50} in the range 126 to 360 μg/mL. Finally, evaluation of the iron chelating power of methanolic extracts resulted in a value of 15.5−11.6 mg EDTAE/g DW[45] (Table 15).

Antidiabetic Properties. The study by. El Adib et al. (2015) showed that the methanolic extract of Argan pulp harvested in several ripening stage (January, February, March, and April) is characterized by an interesting antidiabetic activity (*in vivo*) this was evaluated by the α-amylase inhibition test (*in vitro*) with values ranging between 92.1 and 164.2 mg acarbose/g DW in function of the month and the variety. In addition, El Adib et al. (2015) showed that the ripening process of Argan pulp increase the inhibition of pancreatic α-amylase[45] (Table 15).

Anticancer Properties. El Babili et al. in 2010 have demonstrated the cytotoxic activity of cold ethyl acetate extract (maceration) of Argan fruit pulp against cancer cells (MCF7) (responsible for breast cancer in women) with IC_{50} of 42 μg/mL and >100 μg/mL for the petroleum ether extract and decoction, the standard used (doxorubicin) showed a IC_{50} of 0.218 μg/mL[125] (Table 15).

Antimalarial Properties. El Babili et al. (2010) found that the ethyl acetate extract of Argan fruit pulp showed interesting antimalarial activity against chloroquine-resistant strains of *Plasmodium falciparum*. This extract showed the highest antimalarial activity with an IC_{50} of 35 mg/mL. This could indicate a significant potential for isolating pure compounds with much higher antimalarial activity from this fraction. The extract obtained using decoction was also of interest, as it exhibited antimalarial activity with an IC_{50} equal to 52 mg/mL[125] (Table 15).

The conclusions drawn suggest that the biological activity of the extracts varies according to several factors, such as genotype, harvesting year, region, etc. However, other factors must be considered, such as the harvesting season of the plant material,

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which could possibly have a significant impact on the chemical composition as well as the biological activities, in order to obtain a plant material that is reliable and standardized over the harvesting period. Other research must be performed for better understanding of the pharmacological effects obtained.[129]

Clinical Studies. Regarding the clinicals studies, the work conducted by Drissi et al. (2004) assessed the impact of regular virgin Argan oil consumption on lipid profiles and antioxidant status among Moroccan subjects. Involving 96 healthy individuals (20 men, 76 women), 62 regular argan oil consumers, and 34 nonconsumers were analyzed for fasting plasma lipids, antioxidant vitamins, and LDL oxidation susceptibility. The results indicated that argan oil consumers had significantly higher polyunsaturated fatty acids intake, lower plasma LDL cholesterol, along with reduced plasma lipoperoxides and increased α-tocopherol concentrations.[117] However, it is important to note that the study had a relatively small sample size and lacked long-term follow-up, which may limit the generalizability and reliability of the findings. The second study, that was conducted by Jirabundansuk et al. (2014) compared the efficacy of a moisturizer containing spent grain wax, *Butyrospermum parkii* extract, and *Argania spinosa* kernel oil (S) with 1% hydrocortisone cream (HC) in treating mild to moderate atopic dermatitis. Twenty-nine patients aged from 2 to 15 years applied (S) cream to one side of their body and (HC) cream to the other side twice daily for 4 weeks. Both treatments significantly improved SCORAD scores after 2 weeks which is a tool used to assess the severity of atopic dermatitis ($p < 0.001$). At 4 weeks, improvements in SCORAD scores continued for both treatments without a statistically significant difference ($p > 0.05$). Although the (S) cream side showed a higher remission rate, while the difference was not statistically significant ($p > 0.05$). The study concluded that (S) cream was as effective as (H)C cream in treating and maintaining mild to moderate childhood atopic dermatitis.[130] Nonetheless, the study's small sample size and short duration may limit its ability to fully capture the long-term efficacy and safety of the treatments, necessitating further research to confirm these results. More clinical studies need to be carried out, especially on other argan parts, in order to accelerate the integration of these argan-based products into the phytotherapy market.

MECHANISM OF ACTION OF KEY BIOMOLECULES FROM THE ARGAN TREE

Argan oil, which is the principal product derived from the argan tree, is highly reputed for its health benefits due to its richness in various bioactive compounds, such as unsaturated fatty acids and tocopherols, which have provitamin E activity. Regarding unsaturated fatty acids, argan oil is highly rich in oleic and linoleic acids. Numerous mechanisms of action have been suggested for the antiproliferative effects of these unsaturated fatty acids. The first mechanism involves a reduction in the synthesis of eicosanoids derived from arachidonic acid, which may contribute to the inhibition of cancer cell growth. Additionally, unsaturated fatty acids have been shown to induce specific changes in the gene expressions. For example, oleic acid (OA) is able to suppress the overexpression of HER2 (erbB-2), a well-known oncogene that plays a critical role in the development, aggressive progression, and metastasis of various human cancers. Moreover, other research indicates that unsaturated fatty acids could influence the activity of intracellular signaling components. Notably, calcium ions (Ca^{2+}) are key intracellular factors involved in signal transduction pathways that drive cell growth and proliferation, as well as other essential processes such as gene expression.[131] Furthermore, unsaturated fatty acids are well-documented for their ability to induce apoptosis in various cell lines. A key event in this apoptotic pathway is the collapse of the mitochondrial membrane potential, leading to mitochondrial dysfunction and the generation of reactive oxygen species (ROS). Elevated ROS production is, in fact, linked to the initiation of apoptotic cell death in different types of cancer cells.[131]

Regarding the antidiabetic potential of argan oil has been well documented in several studies. This could be due to the anti-inflammatory properties of these unsaturated fatty acids. One of the most important cytokines typically involved in metabolic inflammatory processes is TNF-α. *In vitro* studies using a rat pancreatic cell line (INS-1 cells), which exhibits glucose-dependent insulin secretion, have demonstrated the potential of oleic acid (OA) to exert pleiotropic effects, such as inducing insulin production and inhibiting TNF-α action, in response to a high-glucose culture medium. The molecular mechanisms by which OA counteracts TNF-α action are varied and may involve the PPAR-γ receptor, as it is known that fatty acids and their metabolites activate PPAR-γ, which can mitigate the inflammatory effects of TNF-α. Furthermore, the translocation of PPAR-γ to the nucleus is thought to mediate the anti-inflammatory properties of fatty acids. In this context, TNF-α leads to increased peripheral insulin resistance, inhibition of its secretion, and the promotion of inflammation.[132]

In addition to its antidiabetic and anticancer activities, Argan oil exhibits therapeutic effects on blood pressure and cardiovascular diseases. In fact, the protective effect of regular unsaturated fatty acids such as oleic acid intake on health risk parameters, particularly in cardiovascular diseases, is primarily reported in the Mediterranean region, where diets are associated with high monounsaturated fatty acids intake due to greater consumption of olive oil.[133] The potential of OA to reduce cardiovascular risks may be linked to an improvement in the serum lipoprotein profile (HDL-to-LDL ratio) in patients with hypercholesterolemia as reported by clinical trials mentioned earlier.[132] Vitamin E (tocopherols) collectively refers to 8 different structurally related tocopherols and tocotrienols that all possess antioxidant activity. In recent years it has become evident that the different forms of vitamin E also exhibit biological activity unrelated to their antioxidant activity by modulating cell signaling processes.[134] Argan oil is highly rich in tocopherols, especially γ-tocopherol (γT). Tocopherols have the ability to act as anti-inflammatory either by affecting transcription of inflammatory genes by modulating the signaling pathways involved in upregulation of these genes or by inhibiting the activity of enzymes involved in eicosanoid biosynthesis. αT acts primarily through inhibition of cell signaling, while γT potently inhibits the COX-2-mediated biosynthesis of prostaglandine E2. Akt, protein kinase B; p38MAPK, p38 mitogen-activated protein kinase; PDK, phosphoinositide-dependent kinase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLC, phospholipase C; PP2A, protein phosphatase 2A.[135] At the same time, tocopherols act as a powerful antioxidant; *in vitro* evidence of the function of vitamin E as a peroxyl radical-scavenging antioxidant and inhibitor of lipid peroxidation is well documented. Protection by vitamin E against oxidative damage would be expected in humans to result in a reduction of DNA oxidation.[135]

Regarding the phenolic compounds, one of the major phenolic acids found in argan oil is ferulic acid, this compound

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is endowed with hepatoprotective activity, and could effectively act against acetaminophen-induced liver injury by down-regulating the expression of CYP 2E1 and the inhibition of Toll-like receptor (TLR) 4-mediated inflammatory responses.[136] In parallel, ferulic acid protects against the initiation of apoptotic signaling in the spleen by obstructing of the free radical chain reaction and by scavenging ROS.[137] Meanwhile, ferulic acid has a potential therapeutic response exhibiting antioxidant and hypoglycemic effects, which might help in circumventing stress-mediated diabetic cardiomyopathy in rats.[138] Also, quercetin is one of the major components of Argan leaves, which was found to have a large spectrum of biological activity, such as antiobesity in which quercetin acts as an inhibitors of fat accumulation in maturing human fat cells by blocking the uptake of glucose from the blood. Moreover, quercetin is also found to exert antiadipogenesis activity by activating the adenosine monophosphate-activated protein kinase signal pathway in 3T3-L1 preadipocytes. Parallelly, quercetin was found to protect against coronary heart diseases. The exhibited research shows that intake of antioxidant quercetin protects against coronary heart diseases caused by oxidized low density lipoprotein. It has also shown an antiplatelet aggregating effect via inhibition of thromboxane. Finally, this flavonoid and its derivates (mainly found in different Argan parts) was found to have an antidiabetic activity, and has been found to be an inhibitor of the enzyme aldose reductase, which plays a role in converting glucose (sugar) to sorbitol (a sugar alcohol) in the body.[139]

Biotechnology and Nanotechnology. Nanotechnology is a preferred approach for improving the delivery and activity of bioactive substances. Some studies were interested in the microfibrillated cellulose (MFC) derived from the *Argania spinosa* shell in the creation of nanoemulgels. The MFC nanoemugel produced showed many application possibilities including healthcare and cosmetics due to their high skin permeability and effective encapsulation of bioactive compounds.[140]

Regarding the genetic aspect of the plant, a study conducted by Rup et al. in (2024) aimed to study the genomics of the argan tree and identify the genes responsible for the biosynthesis pathways of fatty acids and tocopherols characterizing the plant. The results of the genome annotation using AUGUSTUS were improved by RNA sequencing, identifying a total of 62,590 gene loci, 82,286 isoforms, and a BUSCO completeness of 91.7%. The results of this analysis represent an initial step to provide breeders, Geneticists and industries with adequate genomic information that can facilitate the improvement of economically important traits, and selectively adapt the tree to the increasing impacts of climate change.[141]

Toxicological Studies. Studies on the toxicity of argan products are rare, and only two studies have been found, the first focusing on the toxicity of saponins and the second on the ethanolic extract from argan kernels. This could be explained by the reputed use of argan oil as a food product as well as the use of other products (flowers, leaves, and twigs) in traditional medicine. The acute toxicity of the extracted saponins using *per os* administration showed a toxicity effect with a LD_{50} of 1.3 g/kg. Concerning the chronic toxicity, the administration of (Saponins) at a dose of 100 and 200 mg/kg caused a decrease of the glycemia as well as a possible renal toxicity three months after *per os* administration.[142] A study conducted by Makbal *et* al. 2021, performed two toxicity tests, an acute oral toxicity and 28-day subacute oral toxicity. The acute oral toxicity was tested against male mice using Argan fruit shell ethanol extract (AFSEE) at 2 and 5 g/kg doses. Mice were monitored for toxicity signs, behavior changes, and deaths over 14 days. Body weight, dietary intake, and organ weight were recorded. The study concluded that no significant adverse effects was observed. A 28 day subacute oral toxicity study was conducted according to OECD guidelines. Mice were divided into five groups, with four groups receiving AFSEE at 250, 500, 1000, and 2000 mg/kg daily and one control group receiving water. Observations for toxic signs, body weight, and food intake were recorded daily. The results showed that the oral administration of single doses (2 and 5 mg/kg body weight) of Argan fruit shell ethanol extract did not induce any mortality among treated animals during the 14 days of the assay.[143] Nonetheless, further research is needed to fully confirm the safety profile of argan saponins for human consumption and use.

CONCLUSION

The present review represents an insight into phytochemistry and pharmacological properties of *Argania spinosa* and its derivates. Meanwhile, this comprehensive review has reported the history of argan and argan oil and its traditional uses by Moroccan population. These uses have been supported by numerous studies demonstrating its pharmacological effectiveness. Furthermore, *Argania spinosa* has revealed a unique composition endowed with high levels of fatty acids, phenolic compounds, and volatile compounds. Also, argan has revealed great pharmacological potential which was not only linked to the fixed oil but it is worth noting that other parts of argan tree such as leaves, branches, and pulp have showed their richness with several bioactive composition and promising biological properties. This highlights the beneficial health benefits of argan tree and encourages further research in order to unveil other compounds and their pharmacological prospects which will open new paths for harnessing *Argania spinosa* benefits. More extensive clinical trials to validate these findings in diverse populations and under varied conditions. Investigating the long-term effects and safety of argan-derived products, especially in human subjects, is crucial to establishing comprehensive health guidelines. Exploring the sustainable harvesting and cultivation practices of the argan tree will also be essential to ensure the increasing demand does not negatively impact local ecosystems or communities. Moreover, interdisciplinary studies involving modern biotechnology and traditional knowledge could lead to the development of novel argan-based therapeutic and cosmetic products. Finally, understanding the socioeconomic impact of argan production on the local communities, particularly in Morocco, could provide insights into how this industry could significantly supports sustainable development and improve livelihoods.

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■ REFERENCES

(1) Rammal, H.; Bouayed, J.; Younos, C.; Soulimani, R. Notes ethnobotanique et phytopharmacologique d'Argania spinosa L. *Phytothérapie* **2009**, *7* (3), 157−60. Jun

(2) Chaussod, R.; Adlouni, A.; Christon, R. L'arganier et l'huile d'argane au Maroc : vers la mutation d'un système agroforestier traditionnel ? *Cahiers Agricultures* **2005**, *14* (4), 351−356.

(3) Azizi, S.-e.; Dalli, M.; Mzabri, I.; Berrichi, A.; Gseyra, N. Chemical characterization of oils produced by some native and introduced genotypes of argan tree in eastern Morocco using HPLC-DAD/GC-MS, and the evaluation of their physicochemical parameters. *OCL* **2022**, *29*, 14.

(4) Bellefontaine, R.; Ferradous, A.; Alifriqui, M.; Monteuuis, O. Multiplication végétative de l'arganier, Argania spinosa, au Maroc : le projet John Goelet. *BOIS FORETS Trop* **2010**, *304* (304), 47.

(5) Azizi, S.-e.; Mzabri, I.; Mohammed, D.; Noureddine, K.; Abdelbasset, B.; Nadia, G. Eastern Morocco Argania spinosa propagation and growth: A follow-up study. *Aust J. Crop Sci.* **2022**, *16* (5), 612−619.

(6) Emberger, L. Le domaine naturel de l'Arganier. *Bull. Société Bot Fr.* **1925**, *72* (4), 770−4.

(7) Moukrim, S.; Lahssini, S.; Mharzi Alaoui, H.; Rifai, N.; Arahou, M.; Rhazi, L. Modelisation De La Distribution Spatiale Des Especes Endemiques Pour Leur Conservation: Cas de l'Argania spinosa (L.) Skeels. *Revec* **2018**, *73* (2), 153−166.

(8) Tazi, M. R.; Berrichi, A.; Haloui, B. Esquisse cartographique de l'aire de l'arganier Argania spinosa (L.) Skeels au Maroc nord-oriental. *Bulletin de l'Institut Scientifique* **2003**, *25*, 53−55.

(9) Nerd, A.; Irijimovich, V.; Mizrahi, Y. Phenology, breeding system and Fruit development of Argan [Argania spinosa, Sapotaceae] cultivated in Israel. *Econ Bot.* **1998**, *52* (2), 161−167.

(10) Mechqoq, H.; El Yaagoubi, M.; El Hamdaoui, A.; Momchilova, S.; Guedes da Silva Almeida, J. R.; Msanda, F.; El Aouad, N. Ethnobotany, phytochemistry and biological properties of Argan tree (Argania spinosa (L.) Skeels) (Sapotaceae) - A review. *J. Ethnopharmacol* **2021**, *281*, No. 114528.

(11) Boukhobza, M.; Pichon-Prun, N. L'arganier ressource économique et médicinale pour le Maroc. *Phytothérapie* **1988**, *27*, 21−26.

(12) Marfil, R.; Gimenez, R.; Martinez, O.; Bouzas, P. R.; Rufian-Henares, J. A.; Mesias, M.; Cabrera-Vique, C. Determination of polyphenols, tocopherols, and antioxidant capacity in virgin argan oil (Argania spinosa, Skeels). *Eur. J. Lipid Sci. Technol.* **2011**, *113* (7), 886−893.

(13) Joguet, N.; Maugard, T. Characterization and quantification of phenolic compounds of Argania spinosa leaves by HPLC-PDA-ESI-MS analyses and their antioxidant activity. *Chem. Nat. Compd.* **2013**, *48*, 1069.

(14) Kamal, R.; Kharbach, M.; Vander Heyden, Y.; Doukkali, Z.; Ghchime, R.; Bouklouze, A.; et al. In vivo anti-inflammatory response and bioactive compounds' profile of polyphenolic extracts from edible Argan oil (*Argania spinosa* L.), obtained by two extraction methods. *J. Food Biochem [Internet]* **2019**, *43* (12), 13066.

(15) Charrouf, Z.; Guillaume, D. Should the Amazigh Diet (Regular and Moderate Argan-Oil Consumption) have a Beneficial Impact on Human Health? *Crit Rev. Food Sci. Nutr.* **2010**, *50* (5), 473−477.

(16) WFO. *World Flora Online*, 2022. http://www.worldfloraonline.org (accessed on 12 May 2022).

(17) Perrot, E. *Le Karité, l'argan et quelques autres Sapotacées à graines grasses de l'Afrique*; Challamel, A., Ed.; 1907.

(18) Zahidi, A.; Bani-Aameur, F.; El Mousadik, A. Variability in leaf size and shape in three natural populations of Argania spinosa (L.) Skeels. *Int. J. Curr. Res. Acad. Rev.* **2013**, *1* (3), 13−25.

(19) Ait Aabd, N.; El Ayadidi, F.; Msanda, F.; El Mousadik, A. Genetic variability of argan tree and preselection of the candidate plus trees. *Not Bot Horti Agrobot Cluj-Napoca.* **2010**, *38* (3), 293−301.

(20) Benabid, A. *Flore et écosystèmes du Maroc: Evaluation et préservation de la biodiversité*; 2000.

(21) M'hirit, O. et al. L'arganier est une espèce fruitière forestière à usages multiples. *Forestière. Formation forestière continue, Thème ≪l'arganier≫ Station de Recherche*; 1989.

(22) Bani-Aameur, F. Morphological Diversity of Argan (Arganza Spznosa (L.) Skeels) Populations in Morocco. *Forest Genetics* **2004**, *11* (3−4), 311−316.

(23) Bani-Aameur, F.; Alouani, M. Viabilité et dormance des semences d'arganier (Argania spinosa (L.) Skeels). *Ecol Mediterr* **1999**, *25* (1), 75−86.

(24) Bani-Aameur, F. Floraison et production de fruits de l'arganier. *Des modèles biologiques à l'amélioration des plantes*; 2001; pp 173−179.

(25) Bani-Aameur, F.; Louali, L.; Dupuis, P. Maturation et chute des fruits de l'arganier. *Actes Jnst. Agron. Veto (Maroc)* **1998**, *18* (3), 151−158.

(26) Sahki, A.; Sahki, R. *Le Hoggar-Promenade botanique*; Atelier Esope: Lyon, 2004; 311 p.
(27) Emberger, L. À propos de la distribution géographique de l'arganier. *Bull. Soc. Sc. Nat. Maroc* **1924**, *4* (7), 151−153.
(28) Faouzi, K.; Rharrabti, Y.; Boukroute, A.; Mahyou, H.; Berrichi, A. Cartographie de l'aire de répartition de l'arganier (Argania spinosa L. Skeels) dans la région orientale du Maroc par le GPS combiné au SIG. *Nat. Technol.* **2015**, *12*, 16−24.
(29) Réda, K.; Benamar, B. Évidence Cartographique De La Dissemination Recente De L'Arganier Au Nord Du Maroc. *Algerian J. Arid Environ.* **2020**, *10* (2), 70−77.
(30) Moukrim, S.; Lahssini, S.; Rhazi, M.; Alaoui, H. M.; Benabou, A.; Wahby, I.; et al. Climate change impacts on potential distribution of multipurpose agro-forestry species: Argania spinosa (L.) Skeels as case study. *Agrofor Syst.* **2019**, *93* (4), 1209−1219.
(31) Charrouf, Z.; Guillaume, D. Sustainable development in Northern Africa: the argan forest case. *Sustainability* **2009**, *1* (4), 1012−22.
(32) Chebouti-Meziou, N.; Aoudia, Y.; Khelkhal, C. Phytochemical Screening and Insecticidal Effect of Aqueous Extracts of Argan Leaves (*Argania spinosa*) on Peach Aphid (*Myzus persicae*). *Int. Multidiscip Sci. GeoConference SGEM* **2017**, *17*, 887−894.
(33) Zeghlouli, J.; Schiavone, N.; Askanian, H.; Guendouz, A.; El Modafar, C.; Michaud, P.; et al. Thermal, Morphological and Mechanical Properties of a BioPE Matrix Composite: Case of Shell, Pulp, and Argan Cake as Biofillers. *Materials* **2023**, *16* (6), 2241.
(34) Abouri, M.; El Mousadik, A.; Msanda, F.; Boubaker, H.; Saadi, B.; Cherifi, K. An ethnobotanical survey of medicinal plants used in the Tata Province, Morocco. *Int. J. Med. Plants Res.* **2012**, *1* (7), 99−123.
(35) Ouhaddou, H.; Boubaker, H.; Msanda, F.; El Mousadik, A. An ethnobotanical study of medicinal plants of the Agadir Ida Ou Tanane province (southwest Morocco). *J. Appl. Biosci.* **2015**, *84*, 7707−22.
(36) Barkaoui, M.; Katiri, A.; Boubaker, H.; Msanda, F. Ethnobotanical survey of medicinal plants used in the traditional treatment of diabetes in Chtouka Ait Baha and Tiznit (Western Anti-Atlas), Morocco. *J. Ethnopharmacol.* **2017**, *198*, 338−50.
(37) Boukhobza, M.; Pichon-Prun, N. L'arganier ressource économique et médicinale pour le Maroc. *Phytothérapie* **1988**, *27*, 21−26.
(38) Katiri, A.; Barkaoui, M.; Msanda, F.; Boubaker, H. Ethnobotanical survey of medicinal plants used for the treatment of diabetes in the Tizi n'Test region (Taroudant Province, Morocco). *J Pharmacogn Nat Prod.* **2017**, *3* (1), 1000130.
(39) Khallouki, F.; Eddouks, M.; Mourad, A.; Breuer, A.; Owen, R. W. Ethnobotanic, ethnopharmacologic aspects and new phytochemical insights into moroccan argan fruits. *Int. J. Mol. Sci.* **2017**, *18* (11), 2277.
(40) El Hafian, M.; Benlandini, N.; Elyacoubi, H.; Zidane, L.; Rochdi, A. Étude floristique et ethnobotanique des plantes médicinales utilisées au niveau de la préfecture d'Agadir-Ida-Outanane (Maroc). *J. Appl. Biosci.* **2014**, *81*, 7198−213.
(41) Moukal, A. L'arganier, Argania spinosa L. (skeels), usage thérapeutique, cosmétique et alimentaire. *Phytotherapie* **2004**, *2* (5), 135−141.
(42) Charrouf, Z.; Guillaume, D. Ethnoeconomical, ethnomedical, and phytochemical study of Argania spinosa (L.) Skeels. *J. Ethnopharmacol* **1999**, *67* (1), 7−14. Oct
(43) Charrouf, Z.; El Kabouss, A.; Nouaim, R.; Bensouda, Y.; Yameogo, R. Etude de la composition chimique de l'huile d'argan en fonction de son mode d'extraction. *Al-Biruniya* **1997**, *13* (1), 35−39.
(44) Ait Aabd, N.; El Asbahani, A.; El Alem, Y.; El Finti, A.; Msanda, F.; El Mousadik, A. Variation in oil content and fatty acid composition in preselected argan trees with morphological characters and geographical localization. *Mediterr J. Nutr Metab.* **2013**, *6* (3), 217−25.
(45) El Adib, S.; Aissi, O.; Charrouf, Z.; Ben Jeddi, F.; Messaoud, C. Argania spinosa var. mutica and var. apiculata: Variation of Fatty-Acid Composition, Phenolic Content, and Antioxidant and a-Amylase-Inhibitory Activities among Varieties, Organs, and Development Stages. *Chem. Biodivers.* **2015**, *12* (9), 1322−38.
(46) Zaaboul, F.; Raza, H.; Lazraq, A.; Deng, B.; Cao, C.; Liu, Y. F. Chemical Composition, Physical Properties, and the Oxidative Stability of Oil Bodies Extracted From *Argania spinosa*. *J. Am. Oil Chem. Soc.* **2018**, *95* (4), 485−495.
(47) Chergui, A.; Hafid, L. E.; Ajal, E. A.; Zakariya, I.; Nejjari, R.; Reda Tazi, M. Evolution of Biometric Parameters and Oil Fatty Acid Composition of Argan "Argania spinosa L. Skeels" Fruits from Beni-Snassen (Eastern Region of Morocco) During Ripening. *Pharmacogn J.* **2020**, *13* (2), 296−308.
(48) Gharby, S.; Guillaume, D.; Nounah, I.; Harhar, H.; Hajib, A.; Matthäus, B.; et al. Shelf-life of Moroccan prickly pear (Opuntia ficus-indica) and argan (Argania spinosa) oils: a comparative study. *Grasas Aceites.* **2021**, *72* (1), No. e397.
(49) Kharbach, M.; Kamal, R.; Mansouri, M. A.; Marmouzi, I.; Viaene, J.; Cherrah, Y.; et al. Selected-ion flow-tube mass-spectrometry (SIFT-MS) fingerprinting versus chemical profiling for geographic traceability of Moroccan Argan oils. *Food Chem.* **2018**, *263*, 8−17.
(50) El Adib, S.; Aissi, O.; Charrouf, Z.; Ben Jeddi, F.; Messaoud, C. Argania spinosa var. mutica and var. apiculata: Variation of Fatty-Acid Composition, Phenolic Content, and Antioxidant and a-Amylase-Inhibitory Activities among Varieties, Organs, and Development Stages. *Chem. Biodivers.* **2015**, *12* (9), 1322−38.
(51) El Adib, S.; Aissi, O.; Charrouf, Z.; Ben Jeddi, F.; Messaoud, C. Argania spinosa var. mutica and var. apiculata: Variation of fatty-acid composition, phenolic content, and antioxidant and α-amylase-inhibitory activities among varieties, organs, and development stages. *Chem. Biodivers.* **2015**, *12* (9), 1322−38.
(52) Charrouf, Z.; Guillaume, D. Argan oil: Occurrence, composition and impact on human health. *Eur. J. Lipid Sci. Technol.* **2008**, *110* (7), 632−6.
(53) Maurin, R.; Fellat-Zarrouck, K.; Ksir, M. Positional analysis and determination of triacylglycerol structure ofArgania spinosa seed oil. *J. Am. Oil Chem. Soc.* **1992**, *69* (2), 141−5.
(54) Hilali, M.; El Monfalouti, H.; Kartah, B. E. Evaluation of the chemical composition of Argan (Argania spinosa L.) oil according to its extraction method, origin of production and altitude. *J. Worlds Poult Res.* **2020**, *10* (3), 111−8.
(55) Gharby, S.; Harhar, H.; Kartah, B.; Monfalouti, H. E. Analyse chimique et sensorielle de l'huile d'argane. *Les Technologies de Laboratoire* **2011**, *6* (22), 13−23.
(56) Aithammou, R.; Harrouni, C.; Aboudlou, L.; Hallouti, A.; Mlouk, M.; Elasbahani, A.; et al. Effect of clones, year of harvest and geographical origin of fruits on quality and chemical composition of Argan oil. *Food Chem.* **2019**, *297*, No. 124749.
(57) Matthäus, B.; Guillaume, D.; Gharby, S.; Haddad, A.; Harhar, H.; Charrouf, Z. Effect of processing on the quality of edible argan oil. *Food Chem.* **2010**, *120* (2), 426−32.
(58) Kamal, R.; Kharbach, M.; Imig, J. D.; Eljmeli, M.; Doukkali, Z.; Mrabti, H. N.; et al. Antioxidant activities, total polyphenolic compounds and HPLC/DAD/MS phenolic profile of argan oil derived from two different methods of extractions. *J. Mater. Environ. Sci.* **2017**, *8* (4), 1320−1327.
(59) Rojas, L. B.; Quideau, S.; Pardon, P.; Charrouf, Z. Colorimetric Evaluation of Phenolic Content and GC-MS Characterization of Phenolic Composition of Alimentary and Cosmetic Argan Oil and Press Cake. *J. Agric. Food Chem.* **2005**, *53* (23), 9122−7. Nov 1
(60) Gharby, S.; Oubannin, S.; Bijla, L.; Gagour, J.; Hajir, J.; Aabd, N. A.; et al. Evaluation of Proximate Composition, Elemental Profiling, Physicochemical Characterization and Stability Oxidative Under Accelerated Aging Conditions of Black Cumin (Nigella Sativa L.) and Argan (Argania Spinosa L. Skeels). *Elem Profiling Physicochem Charact Stab Oxidative Accel Aging Cond Black Cumin Nigella Sativa Argan Argania Spinosa Skeels*, 2022. https://ssrn.com/abstract=4081140.
(61) Ennoukh, F. E.; Bchitou, R.; Mohammed, F.; Guillaume, D.; Harhar, H.; Bouhaouss, A. Study of the effects of extraction methods on Argan oil quality through its metal content. *Ind. Crops Prod* **2017**, *109*, 182−4.
(62) Marfil, R.; Cabrera-Vique, C.; Giménez, R.; Bouzas, P. R.; Martínez, O.; Sánchez, J. A. Metal Content and Physicochemical

https://doi.org/10.1021/acsomega.4c05618
ACS Omega 2024, 9, 36043−36065

Parameters Used as Quality Criteria in Virgin Argan Oil: Influence of the Extraction Method. *J. Agric. Food Chem.* **2008**, *56* (16), 7279−84.
(63) Ouchbani, T.; Bennis, M.; Khaili, A.; Zahar, M.; Nakajima, M. Effects of the heating temperature during the press extraction process on the yield and quality of cosmetic argan oil. *Euro-Mediterr J. Environ. Integr.* **2021**, *6* (1), 11.
(64) Nerd, A.; Eteshola, E.; Borowy, N.; Mizrahi, Y. Growth and oil production of argan in the Negev Desert of Israel. *Ind. Crops Prod.* **1994**, *2* (2), 89−95.
(65) Hilali, M.; Charrouf, Z.; Aziz Soulhi, A. E.; Hachimi, L.; Guillaume, D. Influence of Origin and Extraction Method on Argan Oil Physico-Chemical Characteristics and Composition. *J. Agric. Food Chem.* **2005**, *53* (6), 2081−7.
(66) Kharbach, M.; Viaene, J.; Yu, H.; Kamal, R.; Marmouzi, I.; Bouklouze, A.; et al. Secondary-metabolites fingerprinting of Argania spinosa kernels using liquid chromatography−mass spectrometry and chemometrics, for metabolite identification and quantification as well as for geographic classification. *J. Chromatogr A* **2022**, *1670*, No. 462972.
(67) Elgadi, S.; Ouhammou, A.; Zine, H.; Maata, N.; Aitlhaj, A.; El Allali, H.; et al. Discrimination of Geographical Origin of Unroasted Kernels Argan Oil (Argania spinosa (L.) Skeels) Using Tocopherols and Chemometrics. *Durazzo A, editor.J. Food Qual.* **2021**, *2021*, 1−9.
(68) Kharbach, M.; Kamal, R.; Marmouzi, I.; Barra, I.; Cherrah, Y.; Alaoui, K.; et al. Fatty-acid profiling vs UV-Visible fingerprints for geographical classification of Moroccan Argan oils. *Food Control.* **2019**, *95*, 95−105.
(69) Tahrouch, S.; Andary, C.; Rapior, S.; Mondolot, L.; Gargadennec, A.; Fruchier, A. Polyphenol investigation of Argania spinosa (Sapotaceae) endemic tree from Morocco. *Acta Bot Gallica* **2000**, *147* (3), 225−32.
(70) Kechebar, M.; Karoune, S.; Falleh, H.; Belhamra, M.; Rahmoune, C.; Ksouri, R. LC-MS phenolic composition changes and antioxidant capacities of the Saharan tree Argania spinosa leaves under salinity. *Courr Savoir* **2017**, *23*, 29−38.
(71) Bourhim, T.; Villareal, M. O.; Couderc, F.; Hafidi, A.; Isoda, H.; Gadhi, C. Melanogenesis Promoting Effect, Antioxidant Activity, and UPLC-ESI-HRMS Characterization of Phenolic Compounds of Argan Leaves Extract. *Molecules* **2021**, *26* (2), 371.
(72) Fahmi, F.; Tahrouch, S.; Hatimi, A. Geoclimatic influences on flavonoids contents of the leaves of the argan tree Influences géoclimatiques sur la composition en flavonoides des feuilles de l'arganier Argania spinosa. *J. Mater. Environ. Sci.* **2013**, *4* (6), 881−886.
(73) El Monfalouti, H.; Charrouf, Z.; Belviso, S.; Ghirardello, D.; Scursatone, B.; Guillaume, D.; et al. Analysis and antioxidant capacity of the phenolic compounds from argan fruit (Argania spinosa (L.) Skeels). *Eur. J. Lipid Sci. Technol.* **2012**, *114* (4), 446−52.
(74) Charrouf, Z.; Wieruszeski, J.; Fkih-Tetouani, S.; Leroy, Y.; Charrouf, M.; Fournet, B. Triterpenoid saponins from Argania spinosa. *Phytochemistry* **1992**, *31* (6), 2079−2086.
(75) Oulad-Ali, A.; Kirchner, V.; Lobstein, A.; Weniger, B.; Anton, R.; Guillaume, D.; et al. Structure elucidation of three triterpene glycosides from the trunk of Argania spinosa. *J. Nat. Prod.* **1996**, *59* (2), 193−5.
(76) Alaoui, A.; Charrouf, Z.; Dubreucq, G.; Maes, E.; Michalski, J.; Soufiaoui, M. Saponins from the pulp of the fruit of Argania spinosa (L.) Skeels (Sapotaceae). *International Symposium of the Phytochemical Society: Lead Compounds from Higher Plants* **2001**, 137−141.
(77) El Fakhar, N.; Charrouf, Z.; Coddeville, B.; Leroy, Y.; Michalski, J. C.; Guillaume, D. New triterpenoid saponins from Argania spinosa. *J. Nat. Med.* **2007**, *61* (4), 375−80.
(78) Guillaume, D.; Charrouf, Z. Saponines et métabolites secondaires de l'arganier (*Argania spinosa*). *Cahiers Agricultures* **2005**, *14* (6), 509−516.
(79) Ray, B.; Loutelier-Bourhis, C.; Lange, C.; Condamine, E.; Driouich, A.; Lerouge, P. Structural investigation of hemicellulosic polysaccharides from Argania spinosa: characterisation of a novel xyloglucan motif. *Carbohydr. Res.* **2004**, *339* (2), 201−8.
(80) Aboughe-Angone, S.; Nguema-Ona, E.; Ghosh, P.; Lerouge, P.; Ishii, T.; Ray, B.; et al. Cell wall carbohydrates from fruit pulp of Argania spinosa: structural analysis of pectin and xyloglucan polysaccharides. *Carbohydr. Res.* **2008**, *343* (1), 67−72.
(81) Hachem, K.; Faugeron, C.; Kaid-Harche, M.; Gloaguen, V. Structural investigation of cell wall xylan polysaccharides from the leaves of Algerian Argania spinosa. *Molecules* **2016**, *21* (11), 1587.
(82) Kabouss, A. E.; Charrouf, Z.; Faid, M.; Garneau, F. X.; Collin, G. Chemical composition and antimicrobial activity of the leaf essential oil of Argania spinosa L. Skeels. *J. Essent Oil Res.* **2002**, *14* (2), 147−9.
(83) Benabdesslem, Y.; Ghomari, S.; Adli, D. E. H.; Mébarki, M.; Hachem, K. Chemical Composition and Antibacterial Activity of Essential Oil Derived from the Leaves of Argania spinosa (L.) Grown in Northwestern Algeria. *J. Essent Oil Bear Plants* **2022**, *25* (1), 103−10.
(84) El Amrani, A.; Sánchez, J. A. C.; Eddine, J. J. Chemical composition of Moroccan Argania spinosa leaf essential oils isolated by supercritical CO2, microwave and hydrodistillation. *J. Essent Oil Bear Plants.* **2015**, *18* (5), 1138−47.
(85) Nafis, A.; Hassani, L.; Marraiki, N.; Al-Rashed, S.; Elgorban, A. M.; Syed, A.; et al. Antimicrobial and synergistic effect of Moroccan native Argania spinosa essential oil for modulating of antibiotics resistance. *Nat. Prod Res.* **2021**, *35* (24), 6078−6082.
(86) Harhar, H.; Gharby, S.; Ghanmi, M.; Monfalouti, H. E.; Guillaume, D.; Charrouf, Z. Composition of the essential oil of Argania spinosa (Sapotaceae) fruit pulp. *Nat. Prod Commun.* **2010**, *5* (6), No. 1934578X1000500626.
(87) Chakhchar, A.; Wahbi, S.; Lamaoui, M.; Ferradous, A.; El Mousadik, A.; Ibnsouda-Koraichi, S.; et al. Physiological and biochemical traits of drought tolerance in Argania spinosa. *J. Plant Interact.* **2015**, *10* (1), 252−61.
(88) Souad, D.; Saida, D.; Jacqueline, G.-P.; Amina, B.; Meriem, K.-H. Investigation of Argania spinosa L.(Skeels) polyphenols growing in arid and semi-arid conditions. *Afr J. Biotechnol.* **2016**, *15* (49), 2753−2758.
(89) Butnariu, M.; Sarac, I.; Pentea, M.; Samfira, I.; Negrea, A.; Motoc, M.; et al. Approach for analyse stability of lutein from Tropaeolum majus. *Rev. Chim.* **2016**, *67* (3), 503−506.
(90) Butnariu, M.; Rodino, S.; Petrache, P.; Negoescu, C.; Butu, M. Determination and quantification of maize zeaxanthin stability. *Dig J. Nanomater Biostructures* **2014**, *9* (2), 745−755.
(91) Marfil, R.; Giménez, R.; Martínez, O.; Bouzas, P. R.; Rufián-Henares, J. A.; Mesías, M.; et al. Determination of polyphenols, tocopherols, and antioxidant capacity in virgin argan oil (Argania spinosa, Skeels). *Eur. J. Lipid Sci. Technol.* **2011**, *113* (7), 886−93.
(92) Azizi, S.; Dalli, M.; Berrichi, A.; Gseyra, N. Quantification of secondary metabolites and the evaluation of the in vitro antioxidant activity of the Argan tree of eastern Morocco. *Mater. Today Proc.* **2021**, *45*, 7314−20.
(93) Villareal, M. O.; Chaochaiphat, T.; Makbal, R.; Gadhi, C.; Isoda, H. Molecular analysis of the melanogenesis inhibitory effect of saponins-rich fraction of Argania spinosa leaves extract. *Molecules* **2022**, *27* (19), 6762.
(94) Ray, B.; Loutelier-Bourhis, C.; Lange, C.; Condamine, E.; Driouich, A.; Lerouge, P. Structural investigation of hemicellulosic polysaccharides from Argania spinosa: characterisation of a novel xyloglucan motif. *Carbohydr. Res.* **2004**, *339* (2), 201−8.
(95) Butnariu, M.; Caunii, A.; Putnoky, S. Reverse phase chromatographic behaviour of major components in Capsicum Annuum extract. *Chem. Cent J.* **2012**, *6*, 146.
(96) Lfitat, A.; Zejli, H.; Bousraf, F. Z.; Bousselham, A.; El Atki, Y.; Gourch, A.; et al. Comparative assessment of total phenolics content and in vitro antioxidant capacity variations of macerated leaf extracts of Olea europaea L. and Argania spinosa (L.) Skeels. *Mater. Today Proc.* **2021**, *45*, 7271−7.
(97) Dakiche, H.; Khali, M.; Abu-el-Haija, A. K.; Al-Maaytah, A.; Al-Balas, Q. A. Biological activities and phenolic contents of Argania spinosa L (Sapotaceae) leaf extract. *Trop J. Pharm. Res.* **2017**, *15* (12), 2563−70.
(98) Joguet, N.; Maugard, T. Characterization and quantification of phenolic compounds of Argania spinosa leaves by HPLC-PDA-ESI-MS analyses and their antioxidant activity. *Chem. Nat. Compd.* **2013**, *48*, 1069−71.

https://doi.org/10.1021/acsomega.4c05618
ACS Omega 2024, 9, 36043−36065

(99) Djidel, S.; Chater, C. F.; Khennouf, S.; Baghiani, A.; Harzallah, D. Evaluation of phenolic compounds, flavonoids and antioxidant properties of *Argania spinosa* (L.) Skeels leaf extracts. *Glob J. Res. Med. Plants Indig Med.* **2014**, *3* (11), 416.
(100) Souad, D.; Saida, D.; Jacqueline, G.-P.; Amina, B.; Meriem, K.-H. Investigation of Argania spinosa L.(Skeels) polyphenols growing in arid and semi-arid conditions. *Afr J. Biotechnol.* **2016**, *15* (49), 2753−2758.
(101) Benabdesslem, Y.; Ghomari, S.; Adli, D. E. H.; Mébarki, M.; Hachem, K. Chemical composition and antibacterial activity of essential oil derived from the leaves of Argania spinosa (L.) grown in Northwestern Algeria. *J. Essent Oil Bear Plants.* **2022**, *25* (1), 103−10.
(102) Kabouss, A. E.; Charrouf, Z.; Faid, M.; Garneau, F. X.; Collin, G. Chemical composition and antimicrobial activity of the leaf essential oil of Argania spinosa L. Skeels. *J. Essent Oil Res.* **2002**, *14* (2), 147−9.
(103) Nafis, A.; Hassani, L.; Marraiki, N.; Al-Rashed, S.; Elgorban, A. M.; Syed, A.; et al. Antimicrobial and synergistic effect of Moroccan native Argania spinosa essential oil for modulating of antibiotics resistance. *Nat. Prod Res.* **2021**, *35* (24), 6078−82.
(104) Almuhayawi, M. S.; Alruhaili, M. H.; Gattan, H. S.; Alharbi, M. T.; Nagshabandi, M. K.; Hagagy, N. Argania spinosa (L.) essential oil: Phytochemical Characterization, Molecular Docking, Anti-staphylococcal, and Anti-pseudomonal Activity. *Research Square Preprint* **2023**, DOI: 10.21203/rs.3.rs-3072825/v1.
(105) El Kharrassi, Y.; Maata, N.; Mazri, M. A.; El Kamouni, S.; Talbi, M.; El Kebbaj, R.; et al. Chemical and phytochemical characterizations of argan oil (Argania spinosa L. skeels), olive oil (Olea europaea L. cv. Moroccan picholine), cactus pear (Opuntia megacantha salm-dyck) seed oil and cactus cladode essential oil. *J. Food Meas Charact.* **2018**, *12*, 747−54.
(106) Hilali, M.; Monfalouti, H. E.; Kartah, B. E. Evaluation of the chemical composition of Argan (Argania spinosa L.) oil according to its extraction method, origin of production and altitude. *Online J. Anim Feed Res.* **2020**, *10* (3), 111−118.
(107) Kamal, R.; Kharbach, M.; Vander Heyden, Y.; Doukkali, Z.; Ghchime, R.; Bouklouze, A.; et al. In vivo anti-inflammatory response and bioactive compounds' profile of polyphenolic extracts from edible Argan oil (Argania spinosa L.), obtained by two extraction methods. *J. Food Biochem.* **2019**, *43* (12), No. e13066.
(108) Haloui, I.; Meniai, A. H. Supercritical CO2 extraction of essential oil from Algerian Argan (Argania spinosa L.) seeds and yield optimization. *Int. J. Hydrog Energy.* **2017**, *42* (17), 12912−9.
(109) Taarji, N.; Rabelo da Silva, C. A.; Khalid, N.; Gadhi, C.; Hafidi, A.; Kobayashi, I.; Neves, M. A.; Isoda, H.; Nakajima, M. Formulation and stabilization of oil-in-water nanoemulsions using a saponins-rich extract from argan oil press-cake. *Food Chem.* **2018**, *246*, 457−463.
(110) El Monfalouti, H.; Charrouf, Z.; Belviso, S.; Ghirardello, D.; Scursatone, B.; Guillaume, D.; et al. Analysis and antioxidant capacity of the phenolic compounds from argan fruit (Argania spinosa (L.) Skeels). *Eur. J. Lipid Sci. Technol.* **2012**, *114* (4), 446−52.
(111) Harhar, H.; Gharby, S.; Ghanmi, M.; Monfalouti, H. E.; Guillaume, D.; Charrouf, Z. Composition of the essential oil of Argania spinosa (Sapotaceae) fruit pulp. *Nat. Prod Commun.* **2010**, *5* (6), No. 1934578X1000500626.
(112) Brahmi, F.; Haddad, S.; Bouamara, K.; Yalaoui-Guellal, D.; Prost-Camus, E.; De Barros, J. P. P.; et al. Comparison of chemical composition and biological activities of Algerian seed oils of Pistacia lentiscus L., Opuntia ficus indica (L.) mill. and Argania spinosa L. Skeels. *Ind. Crops Prod.* **2020**, *151*, No. 112456.
(113) Daoudi, N. E.; Bouhrim, M.; Ouassou, H.; Legssyer, A.; Mekhfi, H.; Ziyyat, A.; et al. Inhibitory effect of roasted/ unroasted Argania spinosa seeds oil on α- glucosidase, α-amylase and intestinal glucose absorption activities. *South Afr J. Bot.* **2020**, *135*, 413−20.
(114) Bennani, H.; Drissi, A.; Giton, F.; Kheuang, L.; Fiet, J.; Adlouni, A. Antiproliferative effect of polyphenols and sterols of virgin argan oil on human prostate cancer cell lines. *Cancer Detect Prev.* **2007**, *31* (1), 64−9.
(115) Lotfi, N.; Chahboun, N.; El Hartiti, H.; Kabouche, Z.; El M'Rabet, M.; Berrabeh, M.; et al. Study of the antibacterial effect of Argan oil from Bechar region of Algeria on hospital resistant strains. *J. Mater. Env Sci.* **2015**, *6* (9), 2476−2482.
(116) Naher, H. S.; Al-Dahmoshi, H.; Al-Khafaji, N.; Al-Saffar, A.; Al-Saffar, H. Anti-Pseudomonal Effect of Argan Oil on Pseudomonas aeruginosa Recovered from Burn Patients in Hilla City, Iraq. *J. Infect Dis Photon.* **2014**, *113*, 270−276.
(117) Drissi, A.; Girona, J.; Cherki, M.; Godàs, G.; Derouiche, A.; El Messal, M.; et al. Evidence of hypolipemiant and antioxidant properties of argan oil derived from the argan tree (Argania spinosa). *Clin Nutr.* **2004**, *23* (5), 1159−66.
(118) Marfil, R.; Giménez, R.; Martínez, O.; Bouzas, P. R.; Rufián-Henares, J. A.; Mesías, M.; et al. Determination of polyphenols, tocopherols, and antioxidant capacity in virgin argan oil (Argania spinosa, Skeels). *Eur. J. Lipid Sci. Technol.* **2011**, *113* (7), 886−93.
(119) Brahmi, F.; Haddad, S.; Bouamara, K.; Yalaoui-Guellal, D.; Prost-Camus, E.; De Barros, J. P. P.; et al. Comparison of chemical composition and biological activities of Algerian seed oils of Pistacia lentiscus L., Opuntia ficus indica (L.) mill. and Argania spinosa L. Skeels. *Ind. Crops Prod.* **2020**, *151*, No. 112456.
(120) Daoudi, N. E.; Abdnim, R.; Elkhadraoui, G.; Mekhfi, H.; Legssyer, A.; Ziyyat, A.; et al. Investigation of In Vitro Antioxidant and Hemoglobin Antiglycation Effect of Roasted and Unroasted Argania spinosa L. Seed Oil from Morocco. *Curr. Chem. Biol.* **2023**, *17* (3), 182−90.
(121) Daoudi, N. E.; El Assri, S.; Aziz, M.; Choukri, M.; Mekhfi, H.; Legssyer, A.; et al. The effect of Argania spinosa seed oil on diabetic nephropathy in streptozotocin-induced diabetes in Wistar rats. *J. Ethnopharmacol.* **2024**, *328*, No. 118083.
(122) Djidel, S.; Chater, C. F.; Khennouf, S.; Baghiani, A.; Harzallah, D. Evaluation of phenolic compounds, flavonoids and antioxidant properties of *Argania spinosa* (L.) Skeels leaf extracts. *Glob J. Res. Med. Plants Indig Med.* **2014**, *3* (11), 416.
(123) Dakiche, H.; Khali, M.; Abu-el-Haija, A. K.; Al-Maaytah, A.; Al-Balas, Q. A. Biological activities and phenolic contents of Argania spinosa L (Sapotaceae) leaf extract. *Trop J. Pharm. Res.* **2017**, *15* (12), 2563.
(124) Bonvicini, F.; Antognoni, F.; Mandrone, M.; Protti, M.; Mercolini, L.; Lianza, M.; et al. Phytochemical analysis and antibacterial activity towards methicillin-resistant *Staphylococcus aureus* of leaf extracts from *Argania spinosa* (L.) Skeels. *Plant Biosyst - Int. J. Deal Asp Plant Biol.* **2017**, *151* (4), 649−56.
(125) El Babili, F.; Bouajila, J.; Fouraste, I.; Valentin, A.; Mauret, S.; Moulis, C. Chemical study, antimalarial and antioxidant activities, and cytotoxicity to human breast cancer cells (MCF7) of Argania spinosa. *Phytomedicine* **2010**, *17* (2), 157−60.
(126) El Idrissi, Y.; Elouafy, Y.; El Moudden, H.; Mghazli, N.; El Guezzane, C.; El Yadini, A. Evaluation of Antioxidant and Antimicrobial Activity of Saponin Extracts from Different Parts of *Argania spinosa* L. Skeels. *Prog. Microbes Mol. Biol.* **2023**, DOI: 10.36877/pmmb.a0000338.
(127) El Idrissi, Y.; El Moudden, H.; Harhar, H.; Zarrouk, A.; Tabyaoui, M. Comparison and correlation of phytochemical content with antioxidant potential of different parts of Argan tree, Argania spinosa L. *Casp. J. Environ. Sci.* **2021**, *19* (2), 261−266.
(128) Almuhayawi, M. S.; Alruhaili, M. H.; Gattan, H. S.; Alharbi, M. T.; Nagshabandi, M. K.; Hagagy, N.; et al. In vitro and in silico biopotentials of phytochemical compositions and antistaphylococcal and antipseudomonal activities of volatile compounds of Argania spinosa (L.) seed oil. *Front Bioeng Biotechnol.* **2024**, *12*, No. 1348344.
(129) Putnoky, S.; Caunii, A.; Butnariu, M. Study on the stability and antioxidant effect of the Allium ursinum watery extract. *Chem. Cent J.* **2013**, *7*, 21.
(130) Jirabundansuk, P.; Ophaswongse, S.; Udompataikul, M. Comparative trial of moisturizer containing spent grain wax, *Butyrospermum parkii* extract, *Argania spinosa* kernel oil vs. 1% hydrocortisone cream in the treatment of childhood atopic dermatitis. *J. Med. Assoc Thai.* **2014**, *97* (8), 820−826.

(131) Carrillo, C.; Cavia, M. d. M.; Alonso-Torre, S. R. Antitumor effect of oleic acid; mechanisms of action. A review. *Nutr Hosp* **2012**, *2012*, 1860−1865.
(132) Sales-Campos, H.; Reis de Souza, P.; Crema Peghini, B.; Santana da Silva, J.; Ribeiro Cardoso, C. An overview of the modulatory effects of oleic acid in health and disease. *Mini Rev. Med. Chem.* **2013**, *13* (2), 201−210.
(133) Karacor, K.; Cam, M. Effects of oleic acid. *Med. Sci. Discovery* **2015**, *2* (1), 125−132.
(134) Azzi, A. Many tocopherols, one vitamin E. *Mol. Aspects Med.* **2018**, *61*, 92−103.
(135) Reiter, E.; Jiang, Q.; Christen, S. Anti-inflammatory properties of α-and γ-tocopherol. *Mol. Aspects Med.* **2007**, *28* (5−6), 668−91.
(136) Yuan, J.; Ge, K.; Mu, J.; Rong, J.; Zhang, L.; Wang, B.; et al. Ferulic acid attenuated acetaminophen-induced hepatotoxicity though down-regulating the cytochrome P 2E1 and inhibiting toll-like receptor 4 signaling-mediated inflammation in mice. *Am. J. Transl Res.* **2016**, *8* (10), 4205.
(137) Das, U.; Biswas, S.; Sengupta, A.; Manna, K.; Chakraborty, A.; Dey, S. Ferulic acid (FA) abrogates ionizing radiation-induced oxidative damage in murine spleen. *Int. J. Radiat. Biol.* **2016**, *92* (12), 806−18.
(138) Chowdhury, S.; Ghosh, S.; Rashid, K.; Sil, P. C. Deciphering the role of ferulic acid against streptozotocin-induced cellular stress in the cardiac tissue of diabetic rats. *Food Chem. Toxicol.* **2016**, *97*, 187−98.
(139) Gupta, A.; Birhman, K.; Raheja, I.; Sharma, S. K.; Kar, H. K. Quercetin: A wonder bioflavonoid with therapeutic potential in disease management. *Asian Pac J. Trop Dis.* **2016**, *6* (3), 248−52.
(140) Bouhoute, M.; Nakajima, M.; Isoda, H. Design of nanoemulgel using Argania spinosa microfibrillated cellulose and natural emulsifiers foreseeing melanogenesis enhancement. *Carbohydr. Polym.* **2021**, *274*, No. 118632.
(141) Rupp, O.; Roessner, C.; Lederer-Ponzer, N.; Wollenweber, T. E.; Becker, A.; Lamaoui, M. Genome of Argania spinosa L.: insights into oil production and the tocopherol biosynthesis pathway. *Genet Resour Crop Evol.* **2024**, DOI: 10.1007/s10722-024-01931-6.
(142) Alaoui, K.; Belabbes, M.; Cherrah, Y.; Hassar, M.; Charrouf, Z.; Amarouch, H.; et al. Acute and chronic toxicity of saponins from *Argania spinosa*. *Ann. Pharm. Fr.* **1998**, *56* (5), 213−219.
(143) Makbal, R.; Idrissi, F. E. J.; Ouchbani, T.; Tastift, M. A.; Kiai, H.; Hafidi, A.; et al. Anti-Inflammatory, Antioxidant, Chemical Characterization, and Safety Assessment of Argania spinosa Fruit Shell Extract from South-Western Morocco. *BioMed. Res. Int.* **2021**, No. 1, No. 5536030.

https://doi.org/10.1021/acsomega.4c05618
ACS Omega 2024, 9, 36043−36065