

Review

The Botany, Phytochemistry and the Effects of the *Juglans regia* on Healthy and Diseased Skin

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Abstract: This review aims to provide a detailed overview of the botanical, phytochemical, and dermatological properties of *Juglans regia* (*J. regia*). The entire tree contains a wealth of chemical compounds, including phenols, tannins, alkaloids, saponins, reducing sugars, and amino acids, which contribute to its significant nutritional and pharmacological value. Extracts and oils from all parts of *J. regia* have been studied for their effects on various skin conditions, demonstrating antioxidant, antimicrobial, anti-inflammatory, UV-protective, and chemoprotective properties. Additionally, these substances have shown potential in promoting wound healing, anti-aging, skin hydration, anti-tyrosinase activity, and hair dyeing. These benefits have been evaluated in various in vitro and in vivo studies. The therapeutic potential of *J. regia* suggests that its components could be integrated into treatment protocols and skincare routines. However, to optimize effectiveness and safety, future research should focus on in vivo studies in human subjects to determine the ideal concentrations and formulations of *J. regia* active compounds for specific skin conditions.

Keywords: *Juglans regia*; active compounds; skin diseases; skincare; dermatology; cosmetics

1. Introduction

Natural products, especially plant materials have been used in the treatment of dermatological conditions from ancient times. The use of herbal preparations in the form of standardized extracts or vegetable oils and formulations in dermatology and cosmetics increased considerably, due to well-known side effects of conventional treatment options and efficacy and safety of natural products [1]. Herbal extracts, vegetable oils and isolated active compounds from various plants are increasingly used not only as food supplements, over-the-counter drugs, but also in cosmetic formulations. Recent studies have been focused on investigating the effects of various plant extracts, oils and isolated compounds on different skin conditions, such as inflammatory skin diseases, skin infections, skin

cancer, acne, UV-induced skin damage, vitiligo, alopecia and wounds. From the promising results in experimental research, the extended interest in herbal formulations effects on various skin conditions resulted in numerous studies in which researchers investigate the mechanisms of action and dermatological effects of many active compounds derived from plant materials [2].

The high incidence of skin diseases, that affect 30–70% of world population and can occur at any age, leads to an extensive need to investigate various treatment options for these patients. Certain skin conditions possess the disability weight of a mild acute infectious disease case, while squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) can lead to fatal outcomes [3].

Despite the extensive research about numerous systemic effects of the *Juglans regia* L. (*J. regia*), to our knowledge, there are no comprehensive reviews about the dermatological effects and mechanisms of action of the *J. regia* on healthy and diseased skin [4]. Therefore, the aim of this review is to present the existing data about the dermatological effects of the *J. regia* and its use in cosmetic products on healthy skin, as well as its use in various formulations for different skin conditions (Figure 1).

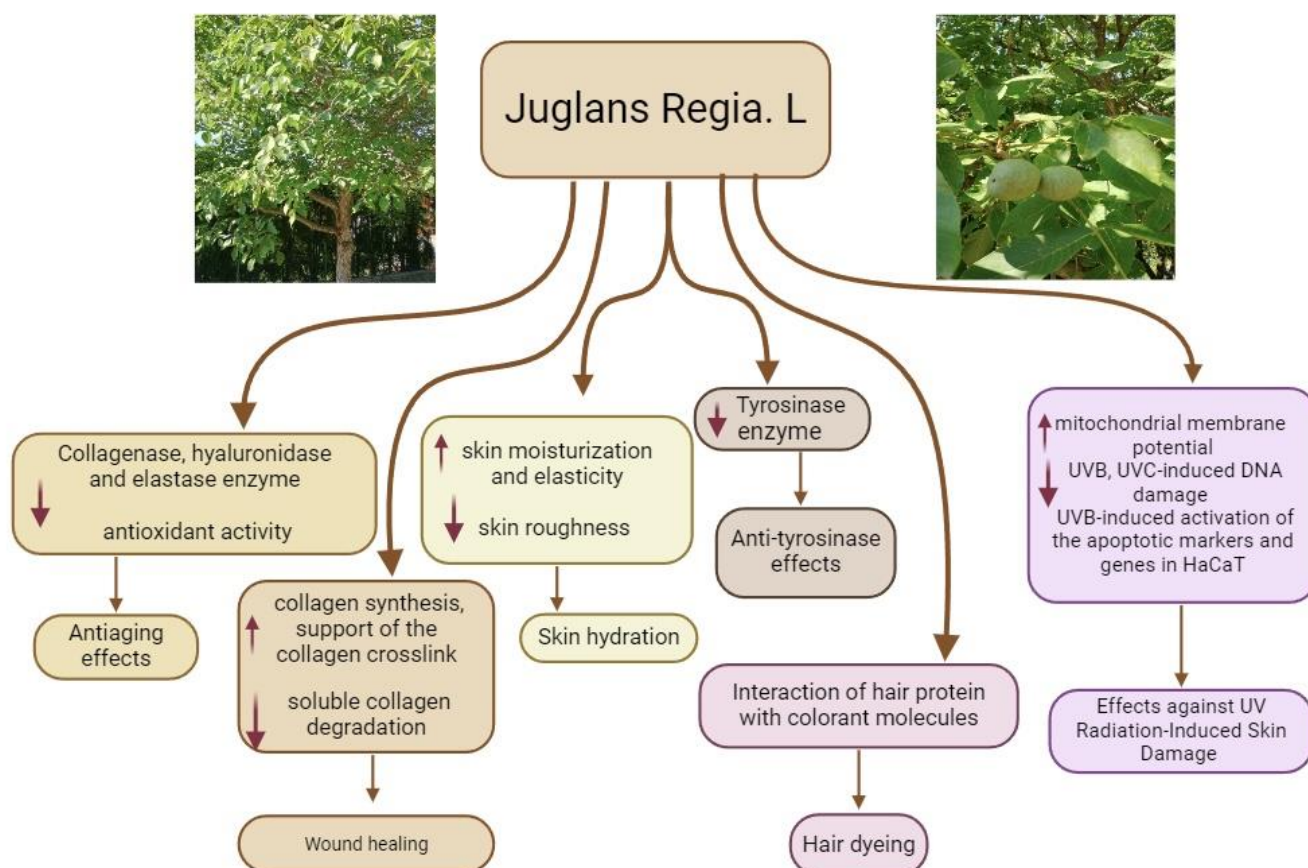


Figure 1. Skin protection induced by *J. regia*.

1.1. Taxonomy

Regarding the taxonomy classification, *J. regia* belongs to the kingdom of *Plantae*. In further classification, it is classified in the subkingdom *Tracheobionta* which represents the subkingdom of vascular plants. Moreover, this plant belongs to a superdivision *Spermatophyta* which means that it is a seed plant. Further classification places it in the division of flowering plants (*Magnoliophyta*) and in the class of dicotyledons (*Magnoliopsida*). In terms of subclass taxonomic classification, this plant belongs to a subclass of Hamamelididae, followed by the order *Juglandales*. Moving further in the hierarchy, *J. regia* belongs to the family *Juglandaceae* (the walnut family), with the more specific classification in genus *Juglans* L. Finally, with regard to the species level of taxonomic classification, it is declared as *J. regia* L. [5].

1.2. Botany

The *J. regia* is native to Eastern Europe, Central Asia and North America regions. This plant usually grows at an altitude of 1200–2000 m above sea levels and in the preferable conditions of sunny climate and moderate winters [6]. This plant, commonly known as Persian walnut, Circassian walnut and English walnut, grows in regions such as Eastern Balkan, Himalayas and Southwest China, and it is native to Kyrgyzstan. It needs warm and sheltered site and deep and rich soils with neutral pH values (6.0–7.5) for its optimal growth [7].

This deciduous tree reaches the average height of approximately 25–35 m and it is 2 m wide. The color of the smooth bark with wide fissures is silver-grey. On a cross section, there is the sap wood which is creamy white and the heart wood which has a dark chocolate color [8]. The bark is olive-brown and smooth at the beginning and, as the tree becomes older, its color turns silvery-grey and it has coarser texture. The length of the leaves is about 20–40 cm and they are grouped in leaflets that are odd-pinnate oriented and alternately arranged [9]. The color of the leaves is yellowish green, while the odor is aromatic. The leaves are ovate and lanceolate shaped [8].

The male and female reproductive organs are located at the same plant. The male flowers represent the drooping catkins which are 4–10 cm long. The female flowers are terminally located and they are often in a group of 2–5 flowers that form a green fruit. In the autumn season, the fruit with the green leathery husk turns into a brown corrugated nut [9].

This fruit is covered with the shell with two compartments and contains the brown edible fruit. The nut diameter can be 5–7.5 cm, while the fruit is 1.25–5 cm long. The ripening process of the nut leads to the softening of the husk, which turns black. The ripening of the nut happens in autumn, from September till October [6]. The seed of the *J. regia* is very big and it has a rich flavor [9]. From an anatomical perspective, fruits are structured with essential components, such as the seed and the pericarp. The seed consists of the seed coat and surrounding flesh, while the pericarp is composed of three distinct layers, including the exocarp (outermost layer), mesocarp (middle layer), and endocarp (innermost layer). In dry fruits, such as walnuts, the pericarp layers are indistinguishable, leading to the husk being interpreted as both exocarp and mesocarp, and the shell as the endocarp. Within the walnut, the seed is represented by the enclosed kernel which is enclosed with the skin [10]. The pollination of walnut seeds is followed by the growth of the rootstock. The production of fruit begins after 8 to 10 years, with the average yield of 50–70 kg per one tree [6] (Figures 2 and 3).



Figure 2. The *J. regia* tree.



Figure 3. The *J. regia* fruit.

1.3. Active Compounds

Various factors (including temperature, time, geographic location, climate conditions and other) cause the difference in chemical composition of the *J. regia*. Every part of the tree is rich in chemical compounds and can be used for different cause. The fruit is nutritionally valuable and its oil contains tocopherols, phytosterols and polyunsaturated fatty acids. Therefore, walnuts are a valuable source of tocopherol and essential fatty acids [11]. The efficiency of oil and valuable component extraction is tied to the selection of the convenient extraction methodology. The selection of an appropriate extraction method is critical for isolating specific compounds of interest. In laboratory-scale applications, chloroform/methanol and hexane are often preferred solvents due to their efficacy in extracting a wide range of edible oils. However, solvent extraction techniques can potentially alter the composition of minor constituents, which play significant roles in antioxidative, functional, and pro-oxidative properties. Cold-press (CP) extraction is a commercially available method utilized for oilseed processing. This method preserves the natural color, flavor, and overall quality attributes of the oil to a greater extent compared to solvent-based extraction methods. While minor components may undergo some modification during cold-pressing, the technique generally maintains the integrity and desirable characteristics of the oil. The Modified Bligh and Dyer (MBD) extraction method with the use of chloroform and methanol led to the highest quantitative yield of oil extraction, oil oxidative stability and antioxidant activity of the *J. regia* oil [12]. The disadvantage of the conventional solvent extraction is the lower quality oil that requires the extensive purification process. Supercritical fluid extraction (SFE) represents an alternative approach for oil extraction, which can replace the conventional industrial extraction methods, such as pressing and solvent extraction. SFE offers several advantages, notably the elimination of solvent residues and enhanced preservation of aromatic compounds [13].

There are many active compounds isolated from the *J. regia* bark, leaves, kernels and seeds, such as phenols (phenolic acids: gallic, ellagic, syringic, 5-Ocaffeoylquinic, caffeic, p-coumaric, ferulic and sinapic acid), tannins (glansrins A, B and C, casuarinin and stenophyllarin), alkaloids, saponins, reducing sugars, amino acids (alanine, valine, methionine, aspartic acid, glycine, isoleucine, leucine, threonine, serine, glutamic acid, proline, tyrosine, phenylalanine, histidine, lysine and arginine) [4]. The *J. regia* leaves are characterized by a diverse array of phytochemicals. These include phenolic acids such as 3- and 5-caffeoylquinic acid, and 3- and 5-p-coumaroylquinic acid, alongside flavonoids such as quercetin derivatives (quercetin galactoside, quercetin pantocide derivatives, quercetin arabinoside, quercetin xyloside, quercetin rhamnoside). Additionally, essential fatty acids, particularly linoleic acid, are present, along with ascorbic acid. The leaves also contain

naphthalene derivatives, notably 5-hydroxy-1,4-naphthoquinone, and juglone (5-hydroxy-1,4-naphthoquinone). Other identified compounds include tannins, alkaloids, proteins, steroids, and carbohydrates. These constituents contribute to the biological activities and potential health benefits associated with walnut leaf extracts, including antioxidant and antimicrobial properties [11].

Juglone, a naphthoquinone compound, is present in various parts of the walnut tree. Initially found as a glycoside in aerial plant parts, particularly in leaves, it undergoes hydrolysis to form the active compound, classified as an alkaloid. Juglone exhibits slight solubility in hot water and moderate solubility in alcohol. This characteristic makes it one of the most abundant compounds in walnut leaves, where other constituents are typically water-soluble or lipid-soluble [11].

The green husk of walnut fruits contains emulsions, glucose, and organic substances such as citric acid, malic acid, phosphate, and calcium oxalate. Among the compounds identified in walnut leaves and green husks, juglone and phenolic compounds stand out as the most significant, Figure 4. Notably, juglone is only present in fresh, green walnuts and is absent in dried leaves, thereby indicating a distinctive property of the fresh plant material. The walnut green husk, despite being a byproduct with limited direct utility, adds value to walnut products due to its rich phytochemical composition and, therefore, potential therapeutic effects [11].

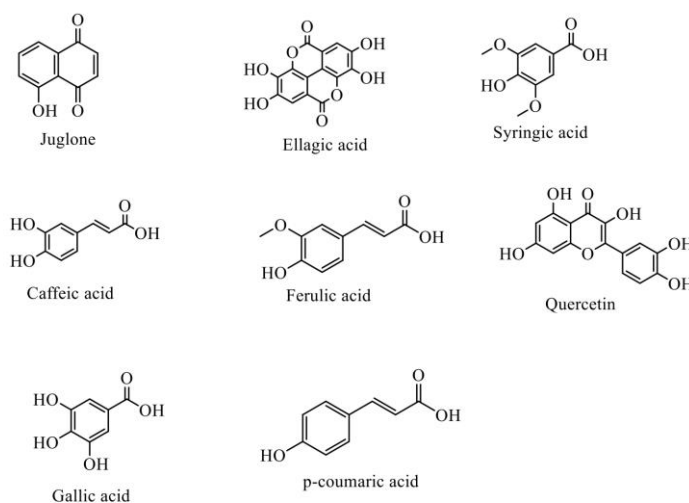


Figure 4. Chemical structures of some of the most abundant active compounds in *J. regia*.

Spectrophotometric analysis of the *J. regia* flowers pollen extracts revealed a very high concentration of total phenolic compounds (values higher than the values obtained from kernel by 2.1 times, green husk by 1.1 times, leaves by 3.0 times, shoot by 2.9 times and stem by 1.9 times) and flavonoids (values higher than the values obtained from the kernel by 9.0 times, green kernel by 8.7 times, leaves by 6.9 times, shoot by 51.8 times, and stem by 16.4 times) [14].

The *J. regia* seeds are rich sources of phenolic compounds, particularly phenolic acids such as gallic, ellagic, syringic, caffeic, p-coumaric, ferulic, and sinapic acids. Additionally, they contain various tannins including glansrins A, B, and C, casuarinin, and stenophyllarin, among others. These compounds are notable for their antioxidant properties and contribute significantly to the potential health benefits associated with the *J. regia* seed [7].

The chemical constituents in different parts of the *J. regia* are shown in Table 1. Furthermore, the values of certain nutritional constituents are shown in Table 2.

Table 1. Active compounds in different parts of the *J. regia*.

Part of the Plant	Active Compound	Reference
Leaf	Phenolic acids, tannins, essential fatty acids, ascorbic acid, flavonoids, caffeic acid, paracomaric acid, juglone, naphthaquinones	Verma et al. [8] Delaviz et al. [11]
Green husk of the fruit	Emulsion, glucose, organic materials such as citric acid, malic acid, phosphate and calcium oxalate, naphthols, tannins	Gupta et al. [7] Verma et al. [8]
Fruit and walnut oil	Fatty acids, tocopherols, phytosterols, total phenolic (tannins), monoacylglycerol, diacylglycerol, triacylglycerol, oleic and linoleic acid, poly unsaturated fatty acids	Gupta et al. [7] Verma et al. [8]
Bark	Polyphenols	Verma et al. [8]
Seed	Glutelins, globulins, albumin and prolamins	Gupta et al. [7]
Flower	Gallic acid, coumarin, quercetin, polyphenols, flavonoids, sterols, fats, proteins, vitamins, minerals	Verma et al. [8]
Stem	Juglone, sitosterol, ascorbic acid, quercetin-3-larabinoside, phenols, flavonoids, naphthquinones	Verma et al. [8]

Table 2. Nutritional content values per 100 g of different constituents [9].

Chemical Compound	Nutritional Content per 100 g	Part of the Plant
Vitamin A	20 mg	Walnuts
Vitamin C	1.3 mg	
Vitamin E	20.83 mg	
Vitamin K	207 mg	
Folates	98 mg	
Niacin	1.125 mg	
Pantothenic acid	0.570 mg	
Pyridoxine	0.537 mg	
Ribofavin	0.150 mg	
Thiamin	0.541 mg	
Palmitoleic acid	0.77 mg	
Oleic acid	25.26 mg	
Gadoleic acid	0.05 mg	
Linoleic acid	57.10 mg	
Linolenic acid	10.34 mg	
Myristic acid	0.24 mg	
Palmitic acid	4.28 mg	
Stearic acid	1.85 mg	
Arachidic acid	0.19 mg	

2. Dermatological Effects of *J. regia*

Besides numerous systemic benefits of various parts of the *J. regia*, there are many potential dermatological effects that can be valuable in the pharmaceutical and cosmetic industry. These industries are constantly searching for new active ingredients from natural sources because of their efficacy, better safety profiles and environmentally friendly connotations. Therefore, there are many studies that analyze the effects of active ingredients from

natural sources on healthy and diseased skin. The active ingredients from different extracts derived from the *J. regia* possess the positive activity on various skin conditions [15].

2.1. Antioxidant Activity

The aqueous *J. regia* bark extract was investigated for its antioxidant activity using different in vitro assays, such as 2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) radical (ABTS) assay, 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) assay, superoxide assay and hydrogen peroxide assay. The *J. regia* bark extract showed varying degrees of radical scavenging activity with the range of the IC₅₀ values from 0.582 mg/mL to 1.2 mg/mL. The extract was most effective in scavenging DPPH radicals with the IC₅₀ value of 0.582 mg/mL. The researchers indicated the presence of high concentrations of phenols and flavonoids, which are responsible for the antioxidant activity of the analyzed extract [16].

The DPPH radical scavenging assay was also used in the study that investigated the antioxidant activity of the methanol *J. regia* pericarp (green husk) extract. Various concentrations of the extract induced the scavenging effect from 25.32% to 79.35% and the IC₅₀ value was 1.223 mg/mL. The results of the antioxidant activity of the analyzed extract are attributed to different phenolic compounds that are present in the *J. regia* pericarp [17].

Furthermore, the ethanol extract of the *J. regia* leaf extract was also assessed for its antioxidant activity. The results in this in vitro study were expressed as EC₅₀ value that was 137 ± 10 µg/mL with the use of the DPPH assay. The analysis of the reducing power resulted in the EC₅₀ value of 27.6 ± 0.02 µg/mL. The reported EC₅₀ values after 60 and 120 min were 10.8 ± 0.5 µg/mL and 51 ± 1 µg/mL respectively in the analysis of oxidative hemolysis inhibition (OxHLIA) assay. Moreover, the thiobarbituric acid reactive substances (TBARS) assay was also used for the assessment of the antioxidant capacity in this study, with the result of the EC₅₀ value of 11.83 ± 1.06 µg/mL [15].

Further investigation of the antioxidant activity of this plant includes the comparison of the ethanol extracts of the *J. regia* whole shelled nut, skin and kernel. The results of this study regarding the Trolox Equivalent Antioxidant Capacity (TEAC), ABTS and DPPH indicated the high antioxidant activity of these extracts in the following order: kernel < whole nut < skin extract. Moreover, the use of the Iron Chelating Capacity, 2-thiobarbituric acid (TBA) and Bulk Stripped Corn Oil Model System method didn't show a significant difference between the antioxidant activities of these three extracts. Researchers of this study suggested the high presence of phenolic compounds which induce the antioxidant effect of these extracts, especially of the tan/brown walnut skin. [18].

Moreover, the antioxidant effects of the methanol *J. regia* green walnut skin extract were investigated in the recent in vitro study. The results of the DPPH radical scavenging method indicated a significant antioxidant activity of the analyzed extract, in which high levels of polyphenols and flavonoids were reported. Researchers highlighted that the methanol extract from green walnut skin could potentially be used as an alternative to synthetic antioxidants [19].

These findings suggest a significant antioxidant activity of different parts of the *J. regia*, as valuable sources of various active compounds known for their radical scavenging potential. Because of these important properties of different *J. regia* extracts, they should be considered for the extensive use in the pharmaceutical and cosmetic formulations [15].

Another part of the *J. regia* that showed a significant antioxidant activity was the methanol male flowers pollen extract. The results obtained from the ABTS radical and reactive oxygen species (ROS) scavenging, the copper ion reducing capacity (CUPRAC), and iron ion chelating methods indicated a significantly higher antioxidant activity in comparison to the antioxidant activity of the other parts of the plant [14].

The scientific evidence that supports the antioxidant effects of the *J. regia*, which are investigated until the present day, is presented in Table 3.

Table 3. The antioxidant activity of *J. regia*.

<i>J. regia</i> Formulation	Effect	Model	Material	Dosage/ Concentration	Mechanism	Reference
Bark extract	Antioxidant activity	Measuring of DPPH, ABTS, superoxide, hydrogen peroxide scavenging activity,	DPPH, ABTS, superoxide, hydrogen peroxide assays	0.1–1.5 mg/mL	Scavenging of different free radicals and reactive oxygen species	Bhatia et al. [16]
Pericarp extract	Antioxidant activity	Measuring of DPPH scavenging activity	DPPH assay	0.5–2.0 mg/mL	Scavenging of free radicals	Kojicic et al. [17]
Leaf extract	Antioxidant activity	Measuring of DPPH scavenging activity, reducing power, TBARS, formation inhibition and OxHLIA inhibition	DPPH, ferric reducing power, OxHLIA assays	10 mg/mL	Scavenging of free radicals, inhibition of the lipid peroxidation activity, inhibition of the oxidative hemolysis	Besrouer et al. [15]
Whole shelled nut, skin and kernel extract	Antioxidant activity	Measuring of DPPH and ABTS scavenging activity, reducing power, TBARS, TEAC method	DPPH, ABTS, TBARS, TEAC, iron reducing, Bulk Stripped Corn Oil Model System assays	0.02–0.05 mg; 0.005–0.0125 mg; 0.5–0.75 mg	Scavenging of different free radicals, ion chelating ability	Samaranayaka et al. [18]
Green walnut skin extract	Antioxidant activity	Measuring of DPPH scavenging activity	DPPH assay	0.1 –1 mg/mL	Scavenging of free radicals	Rafiei Dehkordi et al. [19]
Male flower pollen extract	Antioxidant activity	Measuring of ABTS and ROS scavenging activity, assessment of the copper and iron reducing capacity	ABTS, ROS, CUPRAC, iron reducing assays	80%, v/v	Scavenging of free radicals and ion reducing activity	Żurek et al. [14]

2.2. Antimicrobial Activity

Acne vulgaris is a prevalent dermatological condition characterized by inflammatory lesions that typically require medical intervention. The formation of acne lesions primarily results from the presence of *Propionibacterium acnes*, as well as other microorganisms like *Staphylococci*. These organisms induce the inflammation, which can be triggered by an elevated sebum production, free fatty acids derived from sebum and abnormal keratinization of the sebaceous ducts. Current acne treatments include the topical antibiotics (e.g., clindamycin), benzoyl peroxide, tea tree oil (TTO), or the systemic antibiotics (e.g., tetracycline). However, the treatments involving TTO and benzoyl peroxide are associated with the adverse effects such as skin dryness, pruritus, and sensations of stinging and burning. Given the rising prevalence of antibiotic-resistant microorganisms, the exploration of novel therapeutic alternatives, such as the formulations with active compounds from natural sources, is necessary [20]. The study which analyzed in vitro inhibitory effects of acetone leaf extracts from the *J. regia* and *Psidium guajava* on different causative agents of acne lesions included thirty-eight subjects of both genders with various forms of acne. The cultures from acne lesions revealed that *P. acnes* was present alone or together with *Staphylococci* spp. in 47% of cases. The frequencies of *Staphylococcus aureus* and *Staphylococcus epidermidis* were 13% and 24%, respectively. The antimicrobial activity of the analyzed extracts compared to TTO and the antibiotic use, was determined by the diameter of the zone inhibition of the several obtained isolates. The significant antimicrobial activity of the *J. regia* leaf extract against various microorganisms, including *Candida albicans*, was reported. The antimicrobial activity of the *J. regia* leaf extract was higher than various concentrations of TTO in most of the analyzed isolates. Along with the proven antimicrobial activity, researchers reported the anti-inflammatory and antioxidant activity, which can further contribute to the efficient acne treatment [20].

The effects of the *J. regia* leaf extract were also investigated in the study where the ethanol extract was incorporated into an oil in water (O/W) base cream. The *J. regia* extract exhibited significant antibacterial activity against *Proteus vulgaris*, with the lowest Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC), comparable to the positive control. It also demonstrated effectiveness against *Staphylococcus lugdunensis* and *Staphylococcus aureus*, with MIC values ranging between 2–4 mg/mL, while *Staphylococcus epidermidis* showed the least susceptibility. The results indicate stronger

bactericidal effects of the extract against Gram-negative bacteria compared to Gram-positive strains. The resistance observed among Gram-positive bacteria may be attributed to their peptidoglycan cell walls [15].

Further research aimed to investigate the antimicrobial activity of the methanol *J. regia* root extract. The findings of this study and the MIC values between 7.81 and 31.25 mg/mL indicate that all tested formulations exhibited strong antibacterial efficacy against both Gram-negative and Gram-positive bacteria, as well as the fungi strains, commonly implicated in skin infections. Notably, the investigated extracts demonstrated a considerable antibacterial activity compared to the established reference drugs known for their efficacy [21].

The acetone *J. regia* green husk extract incorporated in a hair dye formulation also exhibited the antimicrobial activity which was determined by the disc diffusion method. The extract demonstrated efficacy against all tested microorganisms except for *E. coli*. The antimicrobial activity was higher against Gram-positive bacteria in comparison to Gram-negative bacteria. This disparity is attributed to the lipopolysaccharide layer in the outer membrane of Gram-negative bacteria, which potentially hinders dye penetration to their target sites [22].

Moreover, the extracts derived from the *J. regia* fruits demonstrated a significant antifungal activity against two pathogenic yeasts, namely *Candida albicans* and *Cryptococcus neoformans*, both known for causing human diseases. These aqueous extracts also demonstrated the antibacterial activity against several Gram-positive and Gram-negative bacteria [23].

The methanol *J. regia* leaf and bark extracts demonstrated a significant antiviral activity against Sindbis virus, with the MIC value of 1.5 mg/mL. The reported results indicate that the *J. regia* is a plant which represents the valuable source of active compounds that possess the potential to be an efficient therapy option in viral infections [24]. The antimicrobial activity of the *J. regia* various extracts is shown in Table 4.

Table 4. The antimicrobial activity of *J. regia*.

<i>J. regia</i> Formulation	Effect	Model	Material	Dosage/ Concentration	Mechanism	Reference
Leaf extract	Antibacterial and antifungal activity, effects against acne vulgaris	Determination of the diameter of the zone inhibition of obtained isolates	Isolates of several microorganisms obtained from the human skin	10%, 15% and 20%	The antimicrobial effects of tannins, triterpenoids and flavonoid glycosides	Qadan et al. [20]
Leaf extract	Antibacterial activity	Determination of the MIC and MBC	Isolates of several microorganisms obtained from the human skin	10 mg/mL	The antimicrobial effects of present active compounds	Besrouer et al. [15]
Root extract	Antibacterial and antifungal activity	Determination of MIC	Disc diffusion assays	12.5, 25, 50 mg	Not entirely determined antimicrobial mechanism, formation of a barrier against microbial contamination	Huo et al. [21]
Green husk extract	Antibacterial activity	Determination of the inhibition diameter	Disc diffusion assays	6% (w/v), 12% (w/v)	Penetration into the hair interior and antimicrobial activity	Beiki et al. [22]
Fruit extract	Antibacterial and antifungal activity	Determination of MIC	Microorganism assays	100 mg/mL	The antimicrobial effects of present active compounds	Pereira et al. [23]
Leaf and bark extract	Antiviral activity	Determination of MIC	Vero cell cultures	200 µg/mL	Direct antiviral effects	Mouhajir et al. [24]

2.3. Anti-Inflammatory Activity

The anti-inflammatory potential of the ethanol *J. regia* leaf extract was assessed using RAW 264.7 macrophages cells. Researchers reported the EC₅₀ value of 109 ± 5 µg/mL, referring to the concentration that inhibits half of nitrogen-monoxide (NO) produced by the macrophage cells. According to the previous research, the anti-inflammatory mechanism was associated with the notable reductions in mRNA expression levels of tumor necrosis factor (TNF-α), interleukins (IL-1 and IL-6), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and cyclooxygenase enzyme (COX-2) [15].

The methanol *J. regia* root extract, incorporated into an ointment in different concentrations, also demonstrated the in vivo anti-inflammatory activity with the use of the carrageenan-induced rat paw edema model. The reported results suggested the significant anti-inflammatory effects in the experimental group in comparison to the control group, especially 4 h after the treatment [21].

Further research revealed the in vitro anti-inflammatory activity of the methanol *J. regia* fruit extract and its isolated active compound gallic acid. The results obtained from the cell-enzyme linked immunosorbent assay, as well as the endothelial cells and KS483 osteoblastic cell cultures, suggested the inhibitory effect on the TNF-α-induced endothelial activation and expression of intracellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1) adhesion molecules, at the *J. regia* fruit extract concentration range of 10–200 mg/mL. Furthermore, researchers suggested that various compounds present in walnuts, including vitamins (α-tocopherol), certain phenolics, and polyunsaturated fatty acids (PUFA), possess the capability to hinder the endothelial activation and expression of adhesion molecules. Therefore, while ellagic acid is quantitatively predominant polyphenol compound in the extract, it may not necessarily be the principal factor determining the anti-inflammatory properties of walnut extract [25].

The anti-inflammatory effects of the methanol *J. regia* leaf extract and *Olea europaea* L. leaf extract were compared in an in vitro study with the use of stabilization of human red blood cell culture. The anti-inflammatory activity, alongside the antioxidant activity, was determined with the IC₅₀ values. The *J. regia* extract demonstrated the highest anti-inflammatory and antioxidant effects, suggesting its superiority against the other compared extracts [26].

Moreover, the anti-inflammatory effects of different extracts of the *J. regia* bark were compared. Methanol, ethanol, aqueous and hydro-ethanol extracts were analyzed using the human red blood cell membrane stabilization (HRBC) method. The reported results indicated a significant anti-inflammatory activity of various *J. regia* bark extracts (including the fact that the aqueous extract demonstrated the highest activity) and their potential as an effective therapeutic agent in the treatment of acute inflammations [27].

Nanotechnology finds numerous applications in medicine and pharmacy. Green synthesis of iron nanoparticles is considered environmentally friendly compared to the chemical methods. These green-synthesized iron nanoparticles are employed in the degradation of organic materials. Therefore, the aqueous *J. regia* peel fruit extract, incorporated into Iron-Oxide Nanoparticles, was analyzed for its anti-inflammatory effects. The iron nanoparticles were reported to demonstrate a significant anti-inflammatory activity and effectively stabilized erythrocyte membranes compared to standard drugs. This discovery proposes a novel source of membrane stabilizers that could serve as an alternative treatment for managing the inflammatory-related disorders and diseases [28].

The scientifically supported data about the anti-inflammatory activity of the *J. regia* are summarized in Table 5.

Table 5. Anti-inflammatory effects of *J. regia*.

<i>J. regia</i> Formulation	Effect	Model	Material	Dosage/ Concentration	Mechanism	Reference
Leaf extract	Anti-inflammatory activity	in vitro determination of the EC ₅₀ value	RAW 264.7 macrophages cells	10 mg/mL	Reduction in mRNA expression levels of TNF- α , IL-1, IL-6, NF- κ B and COX-2	Besrouer et al. [15]
Root extract incorporated into an ointment	Anti-inflammatory activity	Carrageenan-induced rat paw edema model	Wistar albino rats	1% w/w, 2.5% w/w, 5% w/w, 10% w/w,	Effects attributed to antioxidant activity	Huo et al. [21]
Fruit extract	Anti-inflammatory activity	in vitro determination of the ICAM-1 and VCAM-1 expression	Cell-enzyme linked immunosorbent assay, endothelial and KS483 osteoblastic cell cultures	10–200 mg/mL	Inhibition of the TNF- α -induced endothelial activation and inhibition of the expression of ICAM-1 and VCAM-1	Papoutsi et al. [25]
Leaf extract	Anti-inflammatory activity	Stabilization of human red blood cell membrane by heat induced membrane lysis model	Human red blood cell culture	7.69% (w/w)	Membrane stabilization effect by inhibiting heat induced lysis of human red blood cell membrane as an indicator of anti-inflammatory function	Polat et al. [26]
Bark extract	Anti-inflammatory activity	Stabilization of human red blood cell membrane by heat induced membrane lysis model	Human red blood cell culture	100, 200 mg/mL	Stabilization of lysosomal membranes, limiting the inflammatory response by preventing the release of lysosomal constituents of activated neutrophils (bactericidal enzymes and proteases)	Kumar et al. [27]
Fruit peel extract	Anti-inflammatory activity	Determination of the albumin denaturation inhibition and heat induced hemolysis inhibition	Human albumin and human red blood cell cultures	2 mg/mL	Inhibiting protein denaturation and preventing the inflammation, protection against damaging effect of heat solution	Abdulalsalam et al. [28]

3. Use of *J. regia* in Different Skin Conditions

3.1. Effects against UV Radiation-Induced Skin Damage and Chemoprotective Effects

Sunlight is the primary source of ultraviolet radiation, which encompasses three principal components: UVA (400–320 nm), UVB (320–280 nm), and UVC (280–100 nm). Among these, UVB radiation is the most impactful type that penetrates the Earth's surface. Moreover, it is the most damaging and it predominantly affects to the epidermal layer of the skin [29]. Ultraviolet B (UVB) radiation represents a potent inducer of apoptosis across various cellular types, including both tumor and normal cells. Numerous studies have established that UVB-mediated cell death predominantly occurs through the generation of ROS. This oxidative stress triggers the depletion of cellular antioxidants, provokes DNA damage, and culminates in apoptotic pathways activation [30].

The methanol *J. regia* male flower extract protective effects against UVB radiation were evaluated in an in vitro study carried out in human epidermal keratinocytes (HaCaT) and alkaline single cell gel electrophoresis. The reported results indicated that the pretreatment with the *J. regia* extract for 30 min prior to UVB-irradiation of the HaCaT cell line significantly increased the mitochondrial membrane potential, prevented UVB-induced loss of the mitochondrial membrane potential, reduced the UVB-induced DNA damage and UVB-induced activation of the apoptotic markers and genes in HaCaT [31].

The chronic exposure to UV radiation results in the macroscopic and microscopic cutaneous changes, which leads to the photoaging of the skin [32]. Another in vitro study analyzed the protective effects of the ethanol *J. regia* kernel extract on the UVC induced oxidative DNA damage. This research was carried out on acellular and cellular models. The results indicate the protective effect of the *J. regia* extract against the single and double DNA strand breaks, suggesting its antigenotoxic activity. After exposure to UVC radiation, the plasmid DNA strand breaks result in the formation of the linear or double helix forms of the strand. The reported results showed the increase of the supercoiled form (from 35% up to 64%) with absence of the linear or double helix forms of the DNA strand. The results of the fast Halo assay indicated a significant protective effect of the *J. regia* extract on the extent of DNA breakage. These results suggest the potential of the *J. regia* kernel extract as a genotoxic agent, as an adjuvant in the chemotherapies and radiotherapies [33].

The UV-radiation destructive effects on the skin result in premature aging, thinning of the skin, formation of wrinkles and spider vein formation. Therefore, use of the adequate sun protective formulation with the determined Sun Protective Factor (SPF) is necessary for prevention of the aforementioned negative effects. The in vitro calculation of the SPF value of the aqueous *J. regia* seed extract indicated its lower UV protective potential in comparison to the *Calendula Officinalis* extract and higher UV protective potential in comparison to the *Ficus Bengalensis* extract. The reported SPF value of the *J. regia* seed extract suggests its insufficient protective effects against UV radiation when it is used alone. On the other hand, the analyzed extract possesses a significant potential to be used as an adjuvant compound incorporated into sunscreens and other sun-protective formulations [34].

Furthermore, the measurement of inhibition of human renal epithelial cancer cells A-498, 769-P and colon cancer Caco-2 cell line proliferation by the methanol and petroleum ether *J. regia* seed, green husk and leaf extracts was carried out. The inhibition of the proliferation of the A-498 cell line was reported to be similar with the use of the analyzed extracts. On the other hand, the *J. regia* leaf extract exhibited higher antiproliferative efficiency in the 769-P and colon cancer Caco-2 cell models, in comparison with the *J. regia* seed and green husk extracts. The reported significant antiproliferative activity of different *J. regia* extracts suggests that multiple parts of the *J. regia* represent a valuable source of effective natural chemo-preventive agents [35].

Moreover, the study which analyzed the antitumor effects of the *J. regia* isolated active compound, juglone, used the ovarian cancer SKOV3 cell line and 3-(2,5-dimethyldiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The reported results indicate the significant juglone dose dependent induced inhibition of the SKOV3 cell survival and its potential as the anti-proliferation agent for some cancer types [36].

The scientific evidence that supports the effects against UV radiation-induced skin damage and chemoprotective effects of the *J. regia* are presented in Table 6.

Table 6. The UV-protective and chemoprotective effects of *J. regia*.

<i>J. regia</i> Formulation	Effect	Model	Material	Dosage/ Concentration	Mechanism	Reference
Flower extract	UVB protection	in vitro determination of the effects against UVB irradiation effects	HaCaT cell line	80 µg/mL	Increase in the mitochondrial membrane potential, prevention of the UVB-induced loss of the mitochondrial membrane potential, reduction of the UVB-induced DNA damage and UVB-induced activation of the apoptotic markers and genes in HaCaT	Muzaffer et al. [31]
Kernel extract	UVC protection	in vitro determination of the UVC protection using the acellular and cellular models	HaCaT cell line, Plasmid DNA cleavage, Halo assay,	7.5 mg/µL	Prevention of the UVC induced oxidative DNA damage by the reduction of the linear or double helix forms of the strand	Calcabrini et al. [33]

Table 6. Cont.

<i>J. regia</i> Formulation	Effect	Model	Material	Dosage/ Concentration	Mechanism	Reference
Seed extract	UV protection	in vitro determination of the SPF	in vitro SPF calculation	200 µg/mL	Prevention of the UV induced skin damage	Shah et al. [34]
Seed, green husk and leaf extracts	Anticancer activity	evaluation of the cancer cell proliferation inhibition potential	Human renal epithelial cancer cells A-498, 769-P and colon cancer Caco-2 cell line	31.25, 62.5, 125, 250 and 500 mg/mL	Prevention of the initiation of the carcinogenic process and inhibition of the cancer promotion and progression	Carvalho et al. [35]
Juglone	Anticancer activity	evaluation of the cancer cell proliferation inhibition potential	Ovarian cancer SKOV3 cell line and MTT assay	6.25, 12.5, 25, 50 or 100 µM	Induction of the cell G0/G1 phase arrest and cell apoptosis, and the inhibition of the cell invasion in SKOV3 cells	Fang et al. [36]

3.2. Effects on Wound Healing

The wound healing process represents complex, dynamic and well-organized mechanisms that result in repaired connective tissues, re-epithelization, regeneration and return of the normal anatomical and functional characteristics [37]. It includes three different phases: inflammatory reaction, proliferation, and remodeling. Other than synthetic components, the wound healing process can also be induced by the effects of various natural products [38].

In an in vivo study using the *Wistar albino* rats, the methanol *J. regia* root extract was analyzed for its wound healing properties. The extract was incorporated into an ointment and different experimental groups of animals were treated with 1%, 2.5%, 5%, and 10% *w/w* preparations, after the incision wound creation. After 6 and 12 days of treatment, there was a significant increase in the percentage of wound healing contraction in the experimental groups in comparison to the control group and the increase in protein content and collagen synthesis. The reported results indicate the significant effects on the acceleration of the wound healing process [21].

The wound incision methodology in the *Wistar albino* rats was further used in the assessment of the ethanol *J. regia* green husk extract wound healing effects. The experimental models were treated with an extract incorporated into an ointment. After 10 days, the use of this preparation led to a significant increase in the wound re-epithelization, neovascularization and polymorphonuclear cell count [39].

Moreover, the methanol *J. regia* leaf extract was also analyzed with the use of the *Wistar albino* rats as an animal model. After the wound initiation, the experimental animals were treated with the ointment containing the extract. After 7, 14 and 21 days of treatment, there was a significantly higher wound closure rate, volume of the newly formed epidermis and dermis, density of fibroblasts, collagen density and cell proliferation in a dose-dependent manner in the experimental groups in comparison to the control group. The reported results demonstrated that topical administration of the *J. regia* extract significantly accelerates the wound healing process [40].

Contemporary technology using nanoparticles contributes to several benefits, such as efficiency, simplicity, use of waste products (peel and fruit), cost efficiency and an environmentally friendly nature. Silver nanoparticles are characterized by a high surface-to-volume ratio, strong surface interaction, active multi-central surface, enhancing antibacterial, antioxidant, catalytic, electrical, and anticancer properties [41]. The acetonitrile *J. regia* pellicle and leaf extracts incorporated into silver nanoparticles were investigated for their wound healing properties on the incision wound model performed in the *Wistar albino* rats. The reported results didn't suggest a significant difference of the wound healing properties when compared to Solcoseryl® gel. On the other hand, the researchers reported an acceptable scheme of wound healing effects of the silver nanoparticles formulation, suggesting its potential for the incorporation of plant extracts with the aim of wound treatment [42].

The wound healing properties of different *J. regia* extracts incorporated into various formulations are presented in Table 7.

Table 7. Wound healing effects of *J. regia*.

<i>J. regia</i> Formulation	Effect	Model	Material	Dosage/ Concentration	Mechanism	Reference
Root extract incorporated into an ointment	Wound healing process	Incision wound methodology	Wistar albino rats	1%, 2.5%, 5%, 10% w/w	Increase in collagen synthesis, support of the collagen crosslink and decrease of the soluble collagen degradation	Huo et al. [21]
Green husk extract incorporated into an ointment	Wound healing process	Incision wound methodology	Wistar albino rats	20% w/w	Increase in re-epithelization, neovascularization and polymorphonuclear cell count	Taheri et al. [39]
Leaf extract incorporated into an ointment	Wound healing process	Wound initiation methodology	Wistar albino rats	2%, 5%	Increase in density of fibroblasts, collagen density and cell proliferation	Nasiry et al. [40]
Pellicle and leaf extracts incorporated into silver nanoparticles	Wound healing process	Incision wound methodology	Wistar albino rats	2%	Increase in the tensile strength of a wound, collagen synthesis and angiogenesis	Al-Nadaf et al. [42]

3.3. Anti-Aging Effects

The clinical manifestations of aged skin include xerosis (dryness), laxity (looseness), wrinkles, slackness, as well as the presence of benign neoplasms, such as seborrheic keratoses and cherry angiomas. These changes are accompanied by specific histological features. The decrease in the number of melanocytes and Langerhans cells is observed in the epidermis. The most noticeable changes occur at the epidermal-dermal junction, characterized by flattened rete ridges leading to a reduced contact between the epidermis and dermis. This results in a diminished exchange of nutrients and metabolites between these layers. In the dermis, several fibroblasts may be present, alongside with the loss of the dermal volume [43].

The aqueous *J. regia* seed extract alongside with the *Moringa oleifera* Lam., *Vitis vinifera* L., *Camellia sinensis* L. and *Punica granatum* L. extracts were incorporated into an anti-aging cream, which was analyzed for its in vitro anti-aging activity. The reported results indicated the significant anti-aging and anti-wrinkle effects in comparison to the standard gallic acid. These findings suggest the collagenase and elastase enzyme inhibition potential of the incorporated extracts, which can be used in further anti-aging formulations [44].

Further investigation of potential of various plant extracts for enhancing the skin quality and appearance led to the analysis of different plant extracts, such as the ethanol *J. regia* leaf extract, alongside the *Rosmarinus officinalis* L., *Salvia officinalis* L., *Hypericum perforatum* L., *Sedum telephium* L., *Balsamita major* L., *Calluna vulgaris* (L.) Hull., *Cistus criticus* L. and *Castanea sativa* Mill. extracts. The reported results exhibited a good effect on the hyaluronidase activity, and a fair efficacy on the elastase and collagenase inhibition activity of the *J. regia* extract, which indicates its potential anti-aging effects that need further investigation [45].

The effects of the *J. regia* extracts on the skin aging process are exhibited in Table 8.

Table 8. The anti-aging effects of *J. regia*.

<i>J. regia</i> Formulation	Effect	Model	Material	Dosage/ Concentration	Mechanism	Reference
Seed extract	Anti-aging effects	in vitro determination of the anti-aging effects	Anticollagenase and antielastase assay	1% w/w	Collagenase enzyme inhibition, elastase enzyme inhibition, antioxidant activity	Somavanshi et al. [44]
Leaf extract	Anti-aging effects	Hyperosmotic Aging Model, Immunosuppressive Skin Aging Model	NaCl-stimulated keratinocytes, enzymatic assays	1 mg/mL	Collagenase, elastase and hyaluronidase inhibition, antioxidant activity, UV-protective effects	Baini [45]

3.4. Skin Hydration

Maintaining of the stratum corneum water content is crucial not only for preserving its mechanical properties but also for facilitating normal and orderly desquamation of the tissue [46,47].

Positive effects of the *J. regia* leaf extract on dry skin were investigated in the study in which it was incorporated into the nutrient face cream in the concentration of 1–5%. The skin tolerability and efficacy assessment of the formulation were performed in 7 healthy volunteers. The reported results indicated the safe application of the *J. regia* leaf extract incorporated into a face cream, as well as the positive effects on the increase of skin moisturization of 11% and skin elasticity of 9% and the reduction of skin roughness of 3%, after twice-a-day application for 21 consecutive days. Additional observations of this study included the absence of the pH, sebum and skin temperature values variations. These findings indicate the *J. regia* leaf extracts potential as a natural active compound in dermatological and cosmetic formulations for the use on dry skin [45].

The recent evidence of the *J. regia* extract on skin dryness is presented in Table 9.

Table 9. The effects of *J. regia* on skin hydration, the tyrosinase-inhibitory effects and the hair dyeing properties of *J. regia*.

<i>J. regia</i> Formulation	Effect	Model	Material	Dosage/ Concentration	Mechanism	Reference
Leaf extract	Hydrating effects	in vivo determination of safety and hydrating effects	Human volunteers	3%	Increase of skin moisturization and skin elasticity and the reduction of skin roughness	Baini [45]
Leaf, green husk and seed extracts	Anti-tyrosinase activity	modified dopachrome method with L-DOPA	Tyrosinase inhibitory assay (mushroom tyrosinase)	1.33, 6.66, 13.33 mg/mL	Tyrosinase inhibition of flavonoids and phenolic acid	Akin et al. [48]
Green husk extract	Hair dyeing properties	in vitro determination of hair color with the Kubelka–Munk equation	Hair samples	0.3 g	Interaction of hair protein with colorant molecules	Beiki et al. [22]

3.5. Anti-Tyrosinase Effects

Certain dermatological conditions, such as freckles, chloasma, senile plaques, and even malignant melanoma occur due to the overactivation and overexpression of tyrosinase. Therefore, the tyrosinase inhibitors can be used in the treatment of these aesthetic problems [47].

The methanol *J. regia* leaf, green husk and seed extracts inhibitory activity on tyrosinase enzyme was investigated. The reported results indicated the anti-tyrosinase activity of all three extracts. The IC₅₀ value of the leaf extract was 3.99, followed by the IC₅₀ value of the seed extract (8.837) and finally, the green husk extract (IC₅₀ = 10.154). Therefore, the inhibitory efficiency of leaf extract was determined to be much stronger than the seed and husk extracts. These findings suggest three different parts of the *J. regia*, especially the *J. regia* leaf extract, possess a high potential as an inexpensive and easily accessible source of effective tyrosinase inhibitors [48].

The tyrosinase-inhibitory potential of the *J. regia* extracts is presented in Table 9.

3.6. Hair Dyeing

Synthetic hair dyes can cause various adverse effects, such as allergic reactions, toxicity, mutagenicity, cancer. Therefore, there is an increasing interest in natural dyes which are less allergic, non-toxic for humans, biodegradable and eco-friendly [49].

In an in vitro study, the acetone *J. regia* green husk extract was analyzed for its hair dyeing properties, which are determined with the Kubelka–Munk equation and the dyed hair morphology was determined with the scanning electron microscope. Researchers

reported a significant contribution of the extract to hair lightness and color strength and good morphology and uniform surface of dyed hair [22].

The acetone *J. regia* green husk extract is analyzed for its hair dyeing properties, which are presented in Table 9.

4. Discussion

Numerous active compounds are present in different parts of the *J. regia*. Many pharmacological effects can be induced after the oral administration of the *J. regia* parts that are rich in active chemicals, such as phenols, tannins, alkaloids, etc. Therefore, the *J. regia* can be utilized as an adjunctive therapy in various conditions. This constation can be confirmed with the fact that the *J. regia* has been used in traditional medicine as anti-inflammatory, antimicrobial and antihelminthic agent, as well as the antipyretic, antidiarrhoeal, hypoglycaemic, carminative, and for the treatment of asthma, sinusitis, cold, stomach ache, skeleton disorders and different types of cancer. Further clinical research is necessary for the precise determination of the mechanism of action in these medical conditions [50]. In addition to eliciting beneficial effects following oral administration, various components of the *J. regia* are utilized for diverse dermatological applications, encompassing both pathological and physiological states of the skin. Past studies indicate the dermatologic utility of distinct plant parts, demonstrating efficacious treatment outcomes across a spectrum of skin disorders. This review consolidates findings from studies until the present day that contribute to valuable information about the activity of the *J. regia* in diverse dermatological conditions, while also examining the impacts of different plant-derived materials obtained from the *J. regia*.

Numerous phenolic compounds have been identified in *J. regia*, including pyrogallol, *p*-hydroxybenzoic acid, vanillic acid, ethyl gallate, protocatechuic acid, gallic acid, 3,4,8,9,10-pentahydroxydibenzo pyran-6-one, tannins, adenosine, adenine, and others [51]. The high antioxidant activity of the *J. regia* is reported in the aforementioned studies. These studies suggest the potential of the active compounds obtained from the *J. regia* represent the valuable antioxidant agents with the potential for the incorporation in various pharmaceutical and cosmetical formulations.

The antimicrobial activity of the *J. regia* active compounds against Gram-positive and Gram-negative bacteria, as well as different types of viruses, fungi and helminths, can be utilized in natural dermal preparations in the treatment of different skin infections.

The anti-inflammatory activity through complex mechanisms is significantly observed in aforementioned studies. These findings are also consistent with research where the aqueous and ethanol *J. regia* leaf extracts demonstrated the high level of the anti-inflammatory action [52]. This pharmacological property can lead to the utilization of the *J. regia* as a natural anti-inflammatory agent in the treatment of various inflammatory diseases, as well as disorders involving skin inflammation.

Numerous in vitro studies indicated the strong UV-protective and chemoprotective activity. Various mechanisms and strong potential of many active compounds of the *J. regia* result in the prevention of skin damage induced by the UV radiation. Therefore, the different kinds of the *J. regia* extracts should be incorporated into UV-protective formulations which are very important in cosmetic and pharmaceutical industries. Furthermore, the active compounds obtained from various parts of the *J. regia* possess the potential as a natural cancer adjunctive therapy. The methanol *J. regia* flower extract has been reported to be protective against photodamaging effects, such as photoaging, skin cancer, oxidative damage and inflammation. The SPF value of the aforementioned extract is comparable to some of the commercial sunscreens [31].

Different parts of the *J. regia* possess wound healing properties through complex mechanisms, which are important in the treatment of different skin conditions and dermatological consequences of systemic diseases, such as diabetes mellitus. Presented in vivo studies in animal models indicated the significant wound healing activity of the *J. regia* root, green husk, pellicle and leaf extracts. The results of the presented studies are consistent with the results of the recent research in which the ethanol *J. regia* fruit extract

exhibited the lowest wound healing properties, while the ethyl acetate *J. regia* fruit extract was comparable to the reference treatment (Baneocin) [53]. Therefore, there is a great potential for the utilization of the *J. regia* extracts in various wound healing ointments and other formulations.

The protective activity against xerosis and laxity, as well as wrinkles, slackness and benign neoplasms contribute to the anti-aging effects of the *J. regia*. The collagenase and elastase enzyme inhibition, as well as the antioxidant activity were reported for the *J. regia* seed and leaf extract, leading to a conclusion that these parts of the plant possess the anti-aging activity. These extracts can be incorporated into various anti-aging formulations, alongside other plant extracts known for their anti-aging effects. Further investigation of the effectiveness of these anti-aging formulations should be performed in vivo on human volunteers with the aim of more precise determination of their effects.

In the context of human skin physiology, cutaneous water content is recognized as a critical factor influencing various skin functions, including the barrier function and the envelope function. Insufficient water levels are linked to several dermatological dysfunctions [54]. Therefore, the skin hydration effect of various active compounds incorporated into different cosmetic products is of paramount importance. The *J. regia* leaf extract enabled the increase of skin moisturization and skin elasticity and the reduction of skin roughness. These attributes position it as a promising candidate for future skin hydrating formulations, such as night creams.

Hyperpigmentation is a prevalent skin condition with diverse etiology and it represents the consequence of various skin diseases, injuries, photodamage and genetic mutations. The conventional therapy approach to hyperpigmentation includes the oral administration of tranexamic acid or isotretinoin, alongside the topical administration of corticosteroids, silver compounds, hydroquinone and keratolytics. However, due to the side effects associated with the conventional therapy, there is an increasing interest in natural derived formulations for the hyperpigmentation treatments. These formulations utilize natural active compounds known for their tyrosinase-inhibiting properties [55]. To our findings, the *J. regia* leaf, green husk and seed extracts exhibited the significant anti-tyrosinase activity, which indicates the potential utilization of the aforementioned extracts in natural derived formulations that are equally effective and safer option in the hyperpigmentation treatment.

The well-known adverse effects of synthetic hair dyes lead to an increasing interest in natural products that possess certain hair pigmentation activity. One of the natural hair-coloring effective options is the *J. regia* green husk extract, which enables the uniform surface and good morphology of the dyed hair. Therefore, the further assessment of the efficacy and safety of the *J. regia* green husk extract incorporated into the hair-coloring products should be performed on human volunteers.

Regardless of the better safety profile of the natural derived products in comparison with the conventional therapy options, there are still possible adverse reactions encompassing the use of natural products. One of the most abundant active compounds of the *J. regia*, juglone, can cause skin irritation and hyperpigmentation, although these adverse reactions associated with the use of juglone are very rare in human population [51]. However, there is a case report of the skin hyperpigmentation and large tense blisters involving the palms and fingers in 65-year-old female patient associated with the acute extensive consumption of the *J. regia* [56]. Toxicity studies represent the efficient method to evaluate and confirm the safety of different medication and plant products. The investigation of the acute toxicity represents the first step in the toxicological analysis and its objective is to understand the biological activity of a certain chemical compound, as well as its mechanism of action and possible adverse effects. In the toxicity study performed on the *Wistar albino* rats, there were no mortality or acute toxicity in rats treated with the methanol *J. regia* septum extract in the dose of 5000 mg/kg body weight. These findings suggest that the analyzed extract which possess the LD₅₀ values above 5000 mg/kg body weight, can be considered as non-toxic [56].

5. Conclusions

This review provides a comprehensive summary of the current knowledge regarding the effects of different *J. regia* extracts on both healthy and diseased skin. Although the scientific evidence of the impacts of the *J. regia* on skin health is still constrained, the represented studies suggest the great potential in the management of diverse skin conditions. Numerous positive effects of the *J. regia* on general health as well as the few promising data regarding the effects of different parts of the *J. regia* on healthy and diseased skin indicate its high level of the therapeutic potential and positive cosmetic properties. In order to fully understand the benefits of the *J. regia* in skin care and treatment of dermatological conditions, further research is necessary to determine the precise mechanisms of action of various *J. regia* active compounds. These findings will contribute to the complete knowledge about the diverse potential of the *J. regia* in medicine, pharmacology and cosmetics, as well as the full potential of this plant in dermatology and skincare. Furthermore, the analysis of the interaction of the *J. regia* with other compounds incorporated into skincare products, and their compatibility is desirable in order to define its role in cosmetic products. Alongside the long-term studies which would contribute to the analysis of the prolonged activity of this plant, further focus on the optimal concentrations of certain active compounds, as well as formulations, will allow the evaluation of the *J. regia* efficacy and safety in specific dermatological conditions.

6. Future Directions

The present review offers a comprehensive overview of the botany, phytochemistry, and dermatological impacts of the *J. regia*, with the specific emphasis on the dermatological activity and its therapeutic mechanisms in different skin conditions. All parts of the *J. regia* are notably rich in polyphenols and many other active compounds, which confer substantial therapeutic properties, thereby positioning it as a promising candidate for enhancing skin health. Both in vivo and in vitro studies have demonstrated encouraging potential regarding the beneficial effects of the *J. regia* on skin health, although there is an expressed minority of the in vivo research. Therefore, future perspectives should refer to more extensive in vivo studies involving human volunteers, which are crucial for the validation of the findings obtained from the laboratory experimental research, as well as for the definition of optimal concentrations and formulations in specific skin conditions.

Investigation focused on elucidating the precise mode of action of the *J. regia* can provide significant insights in its effectiveness and safety profile, which enables its integration into clinical skincare protocols. Therefore, there is a compelling need for more extensive investigation of precise mechanisms of many significant effects of this plant in the future. Long-term studies evaluating the prolonged effects of the *J. regia* are necessary for the evaluation of its sustainability and lasting benefits. Such investigations would provide insights into its viability as a long-term intervention in skincare, as well as its role in preventive dermatological measures. The research regarding interactions between the *J. regia* and other natural or synthetic active ingredients in various formulations will allow the insight in the potential synergism or potential incompatibilities. Therefore, the definition of these factors is also necessary in order to determine the formulation strategy for a specific dermatological condition. Future research efforts should prioritize the identification of optimal formulations and concentrations of the *J. regia* in certain skin conditions in order to reach the maximum efficacy and safety of dermatological and skincare preparations and integration in evidence-based treatment options.

These future directions could highlight the maximum potential of the *J. regia* as a natural source of compounds valuable for numerous benefits for skin health and alleviation of certain skin conditions, which significantly improve the overall quality of life in this population of patients.

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