cosmetics

MDPI

Review

Biological Activities of Paper Mulberry (*Broussonetia papyrifera*): More than a Skin-Lightening Agent

Ly Thi Huong Nguyen

Department of Physiology, College of Korean Medicine, Dongguk University, Gyeongju 38066, Korea; nguyenthihuongly_t58@hus.edu.vn

Abstract: Background: Paper mulberry is one of the most common skin-lightening agents in the beauty industry due to its strong anti-tyrosinase activity. This narrative review aims to summarize the chemical composition, biological activities, and applications of paper mulberry in cosmetics. Method: The literature for this article was acquired from the PubMed, Web of Science, and Google Scholar databases before September 2022. The keywords for searching included "paper mulberry", "*Broussonetia papyrifera*", "skin-lightening", "skin-whitening", "depigmentation", "pharmacological activity", and "biological activity". Results: Paper mulberry consists of various components, including flavonoids, tannins, alkaloids, phenols, saponins, coumarins, glycosides, and polysaccharides, which possess a wide range of pharmacological properties. Apart from its anti-tyrosinase activity, paper mulberry and its compounds exhibited anti-inflammatory, antioxidant, antimicrobial, antiviral, anticancer, antidiabetic, anticholinesterase, antigout, antinociceptive, and hepatoprotective effects. Phenols and flavonoids were demonstrated to be the main contributors to the biological activities of paper mulberry. Paper mulberry is widely applied in cosmetics for skin lightening and skin moisturizing purposes and shows potential for application in hair care products due to the hair nourishing effects. The safety of paper mulberry for topical application was proven in clinical studies. Conclusion: The current review provides a better understanding of paper mulberry's properties and allows us to extend the application of this plant and its bioactive components in cosmetics.

Keywords: paper mulberry; *Broussonetia papyrifera*; skin-lightening; tyrosinase; pharmacological activities

Citation: Nguyen, L.T.H. Biological Activities of Paper Mulberry (*Broussonetia papyrifera*): More than a Skin-Lightening Agent. *Cosmetics* **2022**, *9*, 112. https://doi.org/10.3390/cosmetics9060112

Academic Editor: Enzo Berardesca

Received: 7 October 2022
Accepted: 31 October 2022
Published: 2 November 2022

1. Introduction

Skin lightening is a lucrative industry with a global market size valued at USD 9.96 billion in 2021, and estimated up to USD 16 billion in 2030, according to statistics from Grand View Research [1]. Skin lightening, also known as skin whitening or depigmentation, is a cosmetic procedure to lighten dark skin areas and achieve a lighter skin complexion using laser treatment or skin-lightening products [2,3]. Dark skin or skin hyperpigmentation is a result of exposure to ultraviolet light or chemical irritants, and also is a manifestation in several skin disorders such as melasma, solar lentigines, or post-inflammatory hyperpigmentation [4]. The use of skin-lightening agents aims to reduce the level of melanin, the main pigment in the skin, resulting in a brighter skin tone [5,6].

Melanogenesis, a process of melanin production and distribution by melanocytes, is regulated by several melanogenic enzymes, including tyrosinase, tyrosinase-related protein 1 (TRP1), and tyrosinase-related protein 2 (TRP2) [7]. Tyrosinase catalyzes the rate-limiting conversion of L-tyrosine to L-3-4 dihydroxyphenylalanine (L-DOPA), and subsequently to L-dopaquinone and dopachrome [8,9]. In the next step, TRP2 (dopachrome tautomerase) converts dopachrome to 5,6-dihydroxyindole-2-carboxylic acid and 5,6-dihydroxyindole, which are further converted to eumelanin (black or brown pigment) by tyrosinase or TRP1 [10,11]. Different tyrosinase isozymes might play different roles in the regulation of melanin formation. The soluble isozymes T1, T2, and T3 showed blocking activities, while the isozyme T4, the only isozyme found in melanosomes, accelerates the

conversion of dopachrome into melanin [12]. In the presence of cysteine, L-dopaquinone reacts with cysteine, leading to the formation of cysteinyl-dopa and the production of pheomelanin (red or yellow pigment) [13]. TRP1 has been demonstrated to increase the eumelanin/pheomelanin ratio [14]. In addition, the precursors of melanin, L-tyrosine and L-DOPA might act as hormone-like bioregulators of melanin pigmentation by binding to their specific receptors or stimulating melanocyte-stimulating hormone receptors to positively regulate melanogenesis [9,15]. Melanin has diverse regulatory effects on cellular processes. Eumelanin showed protective effects against radiation and photodamage through antioxidant activity, while pheomelanin was thought to induce oxidative stress and DNA damage, contributing to melanoma progression [16]. A previous study suggested that the inhibition of tyrosinase, TRP1, and TRP2 was associated with a reduction in melanin content in human skin cells [17]. However, after the dopaquinone formation stage, melanin formation might proceed with the velocity of the reaction regulated by metal cations and pH, instead of enzyme involvement [18,19]. Therefore, among these three melanogenic enzymes, tyrosinase might play the most important role in melanin biosynthesis, and skin-lightening agents majorly regulate the production and activity of tyrosinase to reduce the melanin content in the skin [5].

Paper mulberry (*Broussonetia papyrifera* (L.)) is a common plant in the Asia-Pacific region [20]. Many parts of the paper mulberry plant, such as the root, bark, leaves, and fruits, have been used in traditional herbal medicines for the treatment of various diseases, including skin disorders and ophthalmic diseases [21]. Paper mulberry contains numerous chemical components, such as flavonoids, polyphenols, alkaloids, coumarins, and saponins, which possess a wide range of biological and pharmacological effects [22]. Paper mulberry extracts and their constituents showed strong inhibitory effects on the activity of tyrosinase enzyme, and have bene applied in cosmetics as skin-whitening ingredients [23]. Apart from its anti-tyrosinase activity, paper mulberry and its derived compounds have been reported to exert various biological effects, including anti-inflammatory, antioxidant, antimicrobial, anticancer, and other activities [24–26]. This narrative review aims to summarize the chemical composition, biological activities, as well as applications of paper mulberry in cosmetics.

2. Materials and Methods

This article provides a narrative review of the biological activities of paper mulberry and its application in cosmetics. PubMed, Web of Science, and Google Scholar databases were used for searching the published literature up until September 2022 for this review article. The main keywords included "paper mulberry", "*Broussonetia papyrifera*", "skin-lightening", "skin-whitening", "depigmentation", "pharmacological activity", and "biological activity". Original articles and patents in English were analyzed in this article.

3. Results

3.1. Chemical Composition of Paper Mulberry

Paper mulberry consists of various chemical constituents, with the main bioactive compounds including flavonoids, tannins, alkaloids, phenols, saponins, coumarins, glycosides, and polysaccharides (Table S1) [22,27–31]. These compounds are derived from different parts of the paper mulberry, such as the bark, roots, twigs, leaves, flowers, and fruits. Table 1 summarizes the major bioactive components found in paper mulberry.

Table 1. Chemical composition of paper mulberry.

Part	Compound	Reference
Root	(−)-(2S)-kazinol I	[32]
	(2R)-7,3′,4′-trihydroxy-6-prenylflavanone	[32]
	3,3′,4′,5,7-pentahydroxyflavone	[33]

Table 1. *Cont.*

Part	Compound	Reference
Root	3,4-dihydroxyisolonchocarpin	[34–36]
	3′-(3-methylbut-2-enyl)-3′,4′,7-trihydroxyflavane	[33,34,36–39]
	4-hydroxyisolonchocarpin	[34–36,38]
	7,8-dihydroxy-6-(3-methylbut-2-en-1-yl)-2H-chromen-2-one	[40]
	8-(1,1-dimethylallyl)-5′-(3-methylbut-2-enyl)-3′,4′,5,7-tetrahydroxyflanvonol	[32,33,36,37,41]
	Brossoflurenone A	[41]
	Brossoflurenone B	[41]
	Betulin	[42]
	Betulinic acid	[42]
	Broussoaurone A	[43]
	Broussochalcone A	[25,32–36,38,39]
	Broussochalcone B	[34–38]
	Broussochalcone C	[32]
	Broussocoumarin A	[40]
	Broussoflavan A	[32,34,36,38,39,43]
	Broussoflavanonol A	[32]
	Broussoflavonol B	[32,36,40,41]
	Broussoflavonol C	[32]
	Broussoflavonol F	[40,43]
	Broussoflavonol G	[43]
	Broussoflavonol H	[40]
	Broussoflavonol I	[40]
	Broussoflavonol J	[40]
	Broussoflavonol K	[40]
	Broussonin A	[32]
	Broussonin B	[32]
	Broussonol D	[32]
	Broussonol G	[32]
	Daphnegiravan H	[32]
	Glycyrrhiza flavonol A	[40]
	Isolicoflavonol	[40]
	Kazinol A	[32,34,36–38]
	Kazinol B	[25,32,34,36,38]
	Kazinol E	[34,36]
	Kazinol F	[32,38,39]
	Kazinol J	[32,38,39]
	Kazinol V	[32]
	Kazinol W	[32]
	Oleanolic acid	[42]
	Papyriflavonol A	[25,36,37,39–41,44]
	Ursolic acid	[42]

Table 1. *Cont.*

Part	Compound	Reference
Bark	3,4,5-trimethoxyphenyl-1-O-β-D-xylopyranosyl-β-D-glucopyranoside	[45]
	4,5-dicaffeoylquinic acid	[45]
	5,7,3′,4′-tetrahydroxy-3-methoxy-8,5′-diprenylflavone	[46]
	5,7,3′,4′-tetrahydroxy-3-methoxy-8-geranylflavone	[46]
	7,4′-dihydroxy-3′-prenylflavan	[47]
	Broussochalcone A	[46]
	Broussochalcone B	[47]
	Broussoflavonol B	[46,47]
	Broussonin A	[47]
	Broussonin B	[47]
	Caffeic acid	[26]
	Cathayanon H	[47]
	Chlorogenic acid	[45]
	cis-form-5-coffee acylchlorogenic acid	[45]
	Coumaric acid	[26]
	Cryptochlorogenic acid	[45]
	Epicatechin	[26]
	Glyasperin A	[47]
	Isoliquiritigenin	[47]
	Isoquercetin	[45]
	Kaempferol	[26]
	Marmesin	[47]
	Papyriflavonol A	[46]
	Quercetin	[26,48]
	Uralenol	[46]
	Vomifoliol	[47]
Branch/twig	(S)-8-methoxymarmesin	[49]
	3,5,7,4′-tetrahydroxy-3′-(2-hydroxy-3-methylbut-3-enyl) flavone	[48]
	5,7,3′,4′-tetrahydroxy-3-methoxy-8,5′-diprenylflavone	[49]
	5,7,3′,4′-tetrahydroxy-3-methoxyflavone	[48]
	5,7,3′,5′-tetrahydroxyflavanone	[48]
	Brossoflurenone C	[49]
	Broussin	[49]
	Broussoflavonol A	[49]
	Broussoflavonol B	[49]
	Broussoflavonol F	[48]
	Fipsotwin	[49]
	Isolicoflavonol	[48]
	Isoliquiritigenin	[48]
	Kazinol B	[49]
	Kazinol N	[49]

Table 1. *Cont.*

Part	Compound	Reference
Branch/twig	Kazinol M	[49]
	Kazinol Q	[49]
	Luteolin	[48]
	Marmesin	[49]
	Papyriflavonol A	[48]
	Quercetin	[48]
	threo-dadahol A	[49]
	threo-dadahol B	[49]
	Uralenol	[48]
Fruit	2-(4-hydroxyphenyl) propane-1,3-diol-1-O-β-D-glucopyranoside	[50]
	3,4-dihydroxybenzoic acid	[50]
	3-[2-(4- hydroxyphenyl)-3-hydroxymethyl-2,3-dihydro-1-benzofuran-5-yl]propan-1-ol	[51]
	4-hydroxybenzaldehyde	[50]
	7-hydroxycoumarin	[52]
	8,11-Octadecadienoic acid	[53]
	8-Octadecenoic acid	[53]
	Arbutine	[50]
	Betulin	[42]
	Betulinic acid	[42]
	Broussonpapyrine	[54,55]
	Chelerythrine	[54]
	Chushizisin A	[51]
	Chushizisin B	[51]
	Chushizisin C	[51]
	Chushizisin D	[51]
	Chushizisin E	[51]
	Chushizisin F	[51]
	Chushizisin G	[51]
	Chushizisin H	[51]
	Chushizisin I	[51]
	cis-coniferin	[50]
	cis-syringin	[50]
	Coniferyl alcohol	[50]
	Curculigoside C	[50]
	Curculigoside I	[50]
	Dihydroconiferyl alcohol	[50]
	Dihydrosanguinarine	[54]
	Epicatechin	[52]
	erythro-1-(4-hydroxy-3-methoxyphenyl)-2-{4-[(E)-3-hydroxy-1-propenyl]-2-methoxyphenoxy}-1,3-propanediol	[51]
	erythro-1-(4-hydroxyphenyl) glycerol	[50]
	Ferulic acid	[50]

Table 1. *Cont.*

Part	Compound	Reference
Fruit	Linolenic acid	[53]
	Liriodenine	[54,55]
	Nitidine	[54,55]
	N-Norchelerythrine	[54]
	Oleanolic acid	[42]
	Oleic acid	[53]
	Oxyavicine	[54,55]
	Palmitic acid	[53]
	p-coumaraldehyde	[50]
	Polysaccharides	[56]
	Protocatechuic acid	[52]
	Stearic acid	[53]
	threo-1-(4-hydroxy-3-methoxyphenyl)-2-{4-[(E)-3-hydroxy-1-propenyl]-2-methoxyphenoxy}-1,3-propanediol	[51]
	threo-1-(4-hydroxyphenyl) glycerol	[50]
	Ursolic acid	[42]
Seed	Caryophyllene	[57]
	Heptadecene-8-carbonic acid	[57]
	Hexadecanoic acid	[57]
Leaf	(+)-pinoresinol-4′-O-β-D-glucopyranosyl-4″-O-β-D-apiofuranoside	[58]
	3,5,4′-trihydroxy-bibenzyl-3-O-β-D-glucoside	[58]
	4-Caffeoylquinic acid	[59]
	4-Feruloylquinic acid	[59]
	5-Caffeoylquinic acid	[59]
	Apigenin	[60,61]
	Apigenin-6-C-β-D-glucopyranside	[58]
	Apigenin-7-glucoside	[59]
	Apigenin-7-O-glucuronide	[59]
	Apigenin-7-O-β -D-glucoside	[61]
	Broussonetone A	[60]
	Broussonetone B	[60]
	Broussonetone C	[60]
	Broussoside A	[61]
	Broussoside B	[61]
	Broussoside C	[61]
	Broussoside D	[61]
	Broussoside E	[61]
	Chrysoriol-7-O-β-D-glucoside	[61]
	Cosmosiin	[58]
	Coumaric acid	[61]
	Dihydrosyringin	[61]
	Flacourtin	[61]

Table 1. *Cont.*

Part	Compound	Reference
Leaf	Gentisoyl hexoside	[59]
	Isoorientin	[61]
	Isovitexin	[59,61]
	Liriodendrin	[58]
	Luteolin	[61]
	Luteolin-7-O-glucuronide	[59]
	Luteolin-7-O-β-D-glucopyranoside	[58]
	Luteoloside	[61]
	Orientin	[59,61]
	Pinoresinol-4′-O-β-D-glucopyranoside	[61]
	Poliothyrsoside	[61]
	Polysaccharides	[30]
	Syringaresinol-4′-O-β-D-glucoside	[61]
	Vitexin	[59–61]
Whole plant	(2S)-2′,4′-dihydroxy-2″-(1-hydroxy-1-methylethyl) dihydrofuro [2,3-h] flavanone	[62]
	(2S)-abyssinone II	[62]
	3′-[γ-hydroxymethyl-(E)-γ-methylallyl]-2,4,2′,4′-tetrahydroxychalcone 11′-O-coumarate	[62]
	5,7,2′,4′-tetrahydroxy-3-geranylflavone	[62]
	Demethylmoracin I	[62]
	Isogemichalcone C	[62]
	Isolicoflavonol	[62]

3.2. Biological Activities of Paper Mulberry and Its Components

Previous studies have demonstrated that paper mulberry and its components possess a wide range of biological activities, such as antityrosinase, anti-inflammatory, antioxidant, and antimicrobial effects, as listed below (Table 2).

Table 2. Biological activities of paper mulberry.

Biological Activity	Part	Compound	Model	Dose	Detailed Effects	Reference
Antityrosinase	Leaf	n/a	In vitro	IC50 = 17.68 ± 5.3 μg/mL	Inhibit mushroom tyrosinase	[63]
	Leaf	n/a	In vitro	66.67~666.67 μg/mL	Inhibit mushroom tyrosinase	[64]
	Leaf	Broussonetones A-C	In vitro	IC50 = 0.317 ~ 0.323 mM	Inhibit mushroom tyrosinase	[60]
	Twig	Broussoflavonol F, 3,5,7,4′-tetrahydroxy-3′-(2-hydroxy-3-methylbut-3-enyl)flavone, uralenol, quercetin	In vitro	IC50 = 49.5~96.6 μM	Inhibit mushroom tyrosinase	[48]
	Root	Broussoflavonol B/F/H-K, papyriflavonol A, isolicofavonol, glycyrrhiza flavonol	In vitro	IC50 = 9.29~31.74 μM	Inhibit mushroom tyrosinase	[40]

Table 2. *Cont.*

Biological Activity	Part	Compound	Model	Dose	Detailed Effects	Reference
Anti-inflammatory	Bark	n/a	RAW264.7 cells	10~200 μg/mL	Inhibit NO and iNOS production	[24]
	Bark	n/a	RAW264.7 cells	10~80 μg/mL	Inhibit production of NO, iNOS, TNF-α, and IL-1β	[65]
	Fruit	8,11-octadecadienic acid, palmitic acid, linolenic acid, 8-octadecenoic acid, stearic acid, oleic acid	RAW264.7 cells	6~100 μg/mL	Reduce NO production	[53]
	Root	Broussoflavonol B, kazinol J	Mice, 3T3-L1 adipocytes	40 mg/kg, 3~40 μg/mL	Decrease TNF-α-induced inflammation by inhibiting the NF-κB pathway via AMPK activation	[66]
	Root	(2R)-7,3′,4′-trihydroxy-6-prenylflavanone, broussochalcone C, broussoflavanonol A/B, kazinol V/W	RAW264.7 cells	2.5~40 μM	Inhibit production of NO, iNOS, COX-2, TNF-α, and IL-6	[32]
	Root	Broussochalcone A	RAW264.7 cells	1~20 μM	Inhibit production of NO, iNOS, TNF-α, and IL-1β	[67]
	Branch, twig	Kazinol M, broussoflavonol A/B	THP-1 cells	1 μM	Reduce production of IL-1β and TNF-α by suppressing NF-κB/AP-1 activation	[49]
	Root	Broussoflavonol H	Jurkat cells	IC50 = 9.95 μM	Decrease IL-2 production	[40]
	Root, fruit	Betulin, betulinic acid	Rat	0.6, 1, 2 g/kg	Reduce edema	[42]
	Root	Broussochalcone A, papyriflavonol A	Rat, MH-S cells	200 mg/kg, 5~50 μg/mL	Combined with *Lonicera japonica* to inhibit the production of NO, TNF-α, and IL-6 in macrophages, reduce pleural cavity inflammation and bronchitis	[68]
	n/a	Papyriflavonol A	Rat	12.5~50 mg/kg	Inhibit IgE-induced passive cutaneous anaphylaxis	[69]
Antioxidant	Leaf	4-Caffeoylquinic acid, 5-Caffeoylquinic acid, apigenin-7-O-glucuronide, isovitexin, luteolin-7-O-glucuronide, orientin, vitexin	1~10 mM	In vitro	Radical-scavenging activities in DPPH and ABTS assays	[59]
	Leaf	Luteolin, luteoloside, orientin, isoorientin	10 μg/mL	In vitro	Radical-scavenging activities in DPPH and ABTS assays	[61]
	Leaf	Broussonetones A−C, apigenin, vitexin	IC50 = 43.89~107.7 μM	In vitro	Antioxidant effects in SOD-like effect assays	[60]
	Root	n/a	0.1~2.5 mg/mL	SH-SY5Y cells	Decrease extracellular peroxide levels, improve activities of SOD, CAT, glutathione peroxidase, and glutathione reductase	[70]

Table 2. *Cont.*

Biological Activity	Part	Compound	Model	Dose	Detailed Effects	Reference
Antioxidant	Bark, wood	Epicatechin, caffeic acid, coumaric acid, quercetin, kaempferol	10~50 mg/mL	In vitro	Superoxide anion radical and hydroxyl radical scavenging activities	[26]
	Flower	n/a	0.5~5 mg/mL	In vitro	Scavenging activity of DPPH radical	[29]
	Fruit	2-(4-hydroxyphenyl)propane-1,3-diol-1-O-β-D-glucopyranoside, 4-hydroxybenzaldehyde, 3,4-dihydroxybenzoic acid, arbutine, dihydroconiferyl alcohol, coniferyl alcohol, ferulic acid, p-coumaraldehyde, cis-syringin, cis-coniferin, erythro1-(4-hydroxyphenyl)glycerol, threo-1-(4-hydroxyphenyl)glycerol, curculigoside C/I	0.16~100 mM	SH-SY5Y cells	Scavenging activity of DPPH radical and neuroprotective effects against H_2O_2-induced SY5Y cell injury	[50]
	Branch, twig	Kazinol M, broussoflavonol A/B	THP-1 cells	1 μM	Reduce CAA values	[49]
	Root	Broussochalcone A	RAW264.7 cells	1~20 μM	Inhibit production of NO, iNOS, TNF-α, and IL-1β	[67]
	Root	Broussoflavan A, broussoflavonol F/G, broussoaurone A	In vitro	IC50 = 1.0~2.7 μM	Inhibit oxidative stress caused by Fe^{2+} in rat brain homogenate	[43]
	Fruit	Chushizisins A−I, threo-1-(4-hydroxy-3-methoxyphenyl)-2-{4-[(E)-3-hydroxy-1-propenyl]-2-methoxyphenoxy}-1,3-propanediol, erythro-1-(4-hydroxy-3-methoxyphenyl)-2-{4-[(E)-3-hydroxy-1-propenyl]-2-methoxyphenoxy}-1,3-propanediol	PC12 cells	0.16~100 μM	Scavenging activity of DPPH radical and antioxidant effects against H_2O_2-induced impairment in PC12 cells	[51]
	Whole plant	Lignins	In vitro	10~100 mg/L	Scavenging activity of DPPH radical	[71]
	Aerial part	n/a	Beef cattle	5~15% in food	Increase SOD concentration, total antioxidant capacity	[72]
	Aerial part	n/a	Dairy cow	5~15% in food	Increase the concentration of CAT, SOD, and TAC and decrease the serum concentration of 8-OHdG	[73]
	Leaf	n/a	Piglet	150, 300 g/t	Increase concentration of CAT, SOD, glutathione peroxidase	[74]

Table 2. *Cont.*

Biological Activity	Part	Compound	Model	Dose	Detailed Effects	Reference
Anti-microbial	Leaf	n/a	In vitro	MIC = 1~7.5 mg/mL	Inhibit growth of bacteria (*Enterococcus faecalis*, *Vibrio cholera*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klibsella pneumonia*) and fungi (*Aspergilus niger*, *A. flavus*)	[75]
	Seed	Hexadecanoic acid, heptadecene-8-carbonic acid, caryophyllene	In vitro	0.125~1%	Antibacterial activity against *Staphylococcus aureus*, *Proteus vulgaris*, *B. cereus*, *Enterobacter aerogenes*	[57]
	Aerial part	Daphnegiravan F, 5,7,3′,4′-tetrahydroxy-3-methoxy-8,5′-diprenylflavone	In vitro	MIC = 3.9~250 ppm	Anti-oral microbial effect against Gram-positive strains (*Actinomyces naeslundii*, *A. viscosus*, *Streptococcus mutans*, *S. sanguinis*, *S. sorbrinus*) and Gram-negative strains (*Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*)	[76]
	Root	Papyriflavonol A, kazinol B, broussochalcone A	In vitro	MIC = 12.5~45 μg/mL	Antifungal effect against *Candida albicans* and *Saccharomyces cerevisiae*, antibacterial activity against *Escherichia coli*, *Salmonella typhimurium*, *S. epidermis*, *S. aureus*	[25]
	Root	Papyriflavonol A	In vitro	MIC = 10~25 μg/mL	Antifungal effect against *C. albicans* and *S. cerevisiae*	[44]
	Fruit	Polysaccharides	In vitro	0.4~2.0 mg/mL	Antibacterial activity against *E. coli*, *P. aeruginosa*, *B. subtilis*, *S. aureus*	[56]
	Root	Broussochalcone A/B, broussoflavan A, 3′-(3-methylbut-2-enyl)-3′,4′,7-trihydroxyflavane, 3,4-dihydroxyisolonchocarpin, 8-(1,1-dimethylallyl)-5′-(3-methylbut-2-enyl)-3′,4′,5,7-tetrahydroxyflanvonol, daphnegiravan I, kazinol A/B/E, 4-hydroxyisolonchocarpin, papyriflavonol A, broussoflavonol B	In vitro	IC50 = 0.7~54 μM	Inhibit bacterial neuraminidase	[36]

Table 2. *Cont.*

Biological Activity	Part	Compound	Model	Dose	Detailed Effects	Reference
Antiviral	Root	Broussochalcone A/B, 4-hydroxyisolonchocarpin, papyriflavonol A (4), 3′-(3-methylbut-2-enyl)-3′,4,7-trihydroxyflavane, kazinol A/B/F/J, broussoflavan A	In vitro	IC50 = 9.2~66.2 μM	Inhibit papain-like protease	[38]
Anticancer	Bark	n/a	HT-29 cells	50~200 μg/mL	Induce apoptosis-related DNA fragmentation, increase the expression of p53, caspase 3, Bax, inhibit cell proliferation	[24]
	Bark	Papyriflavonol A, broussoflavonol B, broussochalcone A, uralenol, 5,7,3′,4′-tetrahydroxy-3-methoxy-8,5′-diprenylflavone	MCF-7 cells	5~25 μM	Anti-proliferation effects on estrogen receptor-positive breast cancer MCF-7 cells	[46]
	Bark, leaf, fruit	n/a	MCF-7, HeLa, HepG2 cells	31.25~1000 μg/mL	Cytotoxic activity against cancer cells	[77]
	Root	Broussoflavonol F/H/I/K, isolicofavonol, glycyrrhiza flavonol A, papyriflavonol A	NCI-H1975, HepG2, MCF-7 cells	IC50 = 0.9~2.0 μM	Growth inhibition activity against three cancer cell lines	[40]
	Root	Kazinol A	T24, T24R2 cells		Inhibit cell growth through G0/1 arrest mediated by a decrease in cyclin D1 and an increase in p21	[37]
	n/a	Broussochalcone A	HEK293, HCT116, SW480, SNU475 cells	5~20 μM	Induce apoptosis in colon and liver cancer cells	[78]
	n/a	Broussochalcone A	HepG2 cells	5 μM	Cytotoxic effects against human hepatoma HepG2 cells with activation of apoptosis-related proteins	[79]
	Fruit	N-norchelerythrine, dihydrosanguinarine, oxyavicine, broussonpapyrine, nitidine, chelerythrine, liriodenine	BEL-7402, Hela cells	IC50 = 5.97~47.41 μg/mL	Inhibit cancer cell growth	[54]
Antidiabetic	Root	Broussoflavonol B, kazinol J	Mice	40 mg/kg	Improve glucose tolerance	[66]
	Root	8-(1,1-dimethylallyl)-5′-(3-methylbut-2-enyl)-3′,4′,5,7-tetrahydroxyflanvonol, uralenol, 3,3′,4′,5,7-pentahydroxyflavone, broussochalcone A	In vitro	IC50 = 4.3~36.8 μM	Inhibit the activity of PTP1B	[33]

Table 2. *Cont.*

Biological Activity	Part	Compound	Model	Dose	Detailed Effects	Reference
Antidiabetic	Root	Broussochalcone A/B, 3,4-Dihydroxyisolonchocarpin, 4-Hydroxyisolonchocarpin, 3′-(3-Methylbut-2-enyl)-3′,4′,7-trihydroxyflavane, kazinol A/B/E, 8-(1,1-Dimethylallyl)-5′-(3-methylbut-2-enyl)-3′,4′,5,7-tetrahydroxyflanvonol, papyriflavonol A, brossoflurenone A	In vitro	IC50 = 2.1~75.7 μM	Inhibit the activity of α-glucosidase	[35]
Anticho-linesterase	Root	8-(1,1-Dimethylallyl)-5′-(3-methylbut-2-enyl)-3′,4′,5,7-tetrahydroxyflanvonol, papyriflavonol A, broussoflavonol B, brossoflurenone A/B	In vitro	IC50 = 0.5~24.7 μM	Inhibit human acetylcholinesterase and butyrylcholinesterase	[41]
Antigout	Root	3,4-dihydroxyisolonchocarpin, broussochalcone A	*In vitro*	IC50 = 0.6~1.8 μM	Inhibit the activity of xanthine oxidase	[34]
Antinociceptive	Root, fruit	Betulin, betulinic acid	Rat	1, 2 g/kg	Inhibit writhing responses	[42]
Hepato-protective	Leaf	Polysaccharides	Mice	100~400 mg/kg	Improve acetaminophen-induced liver damage, reduce liver apoptosis, enhance the detoxification ability of the liver to acetaminophen	[30]
	Root	Broussoflavonol B, kazinol J	Mice	40 mg/kg	Suppress hepatic steatosis by decreasing lipogenic gene expression and increasing AMPK phosphorylation	[66]

n/a: not applicable; IC50: half-maximal inhibitory concentration; MIC: minimum inhibitory concentration; NO: nitric oxide; iNOS: inducible nitric oxide synthase; TNF-α: tumor necrosis factor-alpha; IL: interleukin; COX-2: cyclooxygenase-2; NF-κB: nuclear factor-kappa B; AP-1: activator protein 1; AMPK: AMP-activated protein kinase; CAA: cellular antioxidant activity; SOD: superoxide dismutase; CAT: catalase; TAC: total antioxidant capacity; DPPH: 1,1-diphenyl-2-picrylhydrazyl; ABTS: 2,2′-azino-bis-3-ethylbenzthiazoline-6-sulfonic acid; 8-OHdG: 8-Hydroxyguanosine.

3.2.1. Antityrosinase Activity

Paper mulberry is one of the most well-known skin-lightening ingredients with tyrosinase inhibitory effects. An ethanolic extract from the leaves of paper mulberry exhibited inhibitory activity in mushroom tyrosinase assays, with a IC50 value of 17.68 ± 5.3 μg/mL. Moreover, the antityrosinase effect of paper mulberry leaf extract was stable over two months at 4 °C or room temperature [63]. Another study demonstrated that methanolic extracts of the leaves or bark of paper mulberry inhibited tyrosinase activity by 90–100% at 666.67 μg/mL [64]. The antityrosinase effect of paper mulberry might be related to the flavonoids and diterpenes in its composition. Flavonoid derivatives from paper mulberry, including broussoflavonol B/F/H-K, papyriflavonol A, isolicofavonol, glycyrrhiza flavonol, 3,5,7,4′-tetrahydroxy-3′-(2-hydroxy-3-methylbut-3-enyl)flavone, uralenol, and quercetin, showed strong inhibition effects on mushroom tyrosinase with IC50 values less than 100 μM [40,48]. Three ent-kaurane diterpenes, broussonetones A–C, from paper mulberry leaves exerted more stable inhibitory activities on mushroom tyrosinase than the positive control, kojic acid [60]. Kazinol F, a compound derived from paper mulberry, also inhibited mushroom tyrosinase activity [80]. All published studies have reported the inhibitory

effects of paper mulberry and its components on mushroom tyrosinase, not on human tyrosinase or human melanocytes. Hence, further studies should be conducted to provide strong scientific evidence for the application of paper mulberry as a depigmentation agent in the beauty industry.

3.2.2. Anti-Inflammatory Activity

The anti-inflammatory effect of paper mulberry and its components has been indicated in numerous studies using both in vitro and in vivo models. Butanol and hexane fractions from the stem bark of paper mulberry showed anti-inflammatory activity by suppressing the production of pro-inflammatory mediators, including nitric oxide (NO), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α), as well as decreasing the expression of inducible NO synthase (iNOS) in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages [24,65]. Similarly, treatment with oil from paper mulberry fruits also reduced NO production in LPS-activated RAW 264.7 cells [53]. A methanolic extract of the root bark of paper mulberry and its main bioactive compounds broussoflavonol B and kazinol J significantly reduced TNF-α-induced inflammation in 3T3-L1 adipocytes and adipose tissues by inhibiting the NF-κB pathway via AMPK activation [66]. Flavonoids from the root bark of paper mulberry, including broussochalcone A/C, broussoflavanonol A/B, kazinol V/W, and (2R)-7,3′,4′-trihydroxy-6-prenylflavanone, reduced the expression of NO, iNOS, and pro-inflammatory cytokine (TNF-α and IL-6) in LPS-induced macrophages [32,67]. In a similar study, kazinol M and broussoflavonol A/B inhibited the production of IL-1β and TNF-α by suppressing NF-κB/AP-1 activation in LPS-stimulated THP-1 cells [49]. Another study showed that broussoflavonol H decreased IL-2 production in Jurkat induced by PHA and PMA (IC50 = 9.95 μM) [40]. Root and fruit extracts from paper mulberry also exerted in vivo anti-inflammatory effects by suppressing carrageenan-induced edema in rats [42]. Paper mulberry (*B. papyrifera*) combined with *Lonicera japonica* exhibited inhibitory effects on lung inflammation in LPS-treated rats and alveolar macrophages by downregulating the production of NO and pro-inflammatory cytokines [68]. Papyriflavonol A, a flavonoid from paper mulberry, showed in vivo anti-inflammatory effects by inhibiting IgE-induced passive cutaneous anaphylaxis in rats [69]. The anti-inflammatory effects of paper mulberry and its bioactive components might be effective for the prevention of post-inflammatory hyperpigmentation and other inflammatory diseases.

3.2.3. Antioxidant Activity

Paper mulberry and its bioactive components possess antioxidant activities both in vitro and in vivo. Extracts from paper mulberry leaves exhibited radical-scavenging activities in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2′-azino-bis-3-ethylbenzthiazoline-6-sulfonic acid (ABTS) assays, and phenols, particularly flavonoids, might be the main contributors to this antioxidant effect [59,61]. Another study indicated that the broussonetones A−C, apigenin, and vitexin from the leaves of paper mulberry showed antioxidant effects in SOD-like effect assays [60]. Paper mulberry stem bark, wood, fruit, and flower extracts also exerted strong radical scavenging activities due to their high contents of total phenols and flavonoids [26,29,50]. A root extract of paper mulberry showed inhibitory effects against H_2O_2-induced oxidative stress in SH-SY5Y cells by reducing extracellular peroxide levels and improving the activities of SOD, catalase, glutathione peroxidase, and glutathione reductase [70]. Kazinol M, broussoflavonol A, and 5,7,3′,4′-tetrahydroxy-3-methoxy-8,5′-diprenylflavone exhibited strong antioxidant effects in cellular antioxidant activity assays [49]. Broussochalcone A exerted a strong radical-scavenging activity in a diphenyl-2-picrylhydrazyl assay system [67]. Broussoflavan A, broussoflavonol F/G, and broussoaurone A from paper mulberry roots inhibited the oxidative stress caused by Fe^{2+} in rat brains [43]. In addition, lignans and lignins from paper mulberry also showed high antioxidant activities in DPPH and ABTS assays [51,71]. In vivo, paper mulberry extracts significantly enhanced antioxidant capacities in dairy cows, beef cattle,

and piglets [72–74]. These findings imply the protective effect of paper mulberry against oxidative stress, suggesting potential in the treatment of various diseases.

3.2.4. Anti-Microbial Activity

A previous study indicated that a methanolic extract of paper mulberry leaves showed inhibitory effects against bacteria (*Enterococcus faecalis*, *Vibrio cholera*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klibsella pneumonia*) and fungi (*Aspergilus niger*, *A. flavus*) [75]. The seed oil of paper mulberry exerted antibacterial activities against *Staphylococcus aureus*, *Proteus vulgaris*, *Bacillus cereus*, and *Enterobacter aerogenes,* but did not affect fungal strains [57]. Extracts from the aerial parts of paper mulberries and the derived compounds, daphnegiravan F and 5,7,3′,4′-tetrahydroxy-3-methoxy-8,5′-diprenylflavone, exhibited an anti-oral microbial effect on both Gram-positive and Gram-negative bacteria [76]. Prenylated flavonoids from paper mulberry also possess antimicrobial activities. Papyriflavonol A showed antifungal effects against *Candida albicans* and *Saccharomyces cerevisiae*, as well as antibacterial activity against *Escherichia coli*, *Salmonella typhimurium*, *S. epidermis*, and *S. aureus* [25,44]. Kazinol B exerted inhibitory effects on *S. cerevisiae*, *S. epidermis,* and *S. aureus*, while broussochalcone A was only effective on *C. albicans* [25]. The antibacterial effects of these flavonoids might occur through inhibiting bacterial neuraminidase [36]. Paper mulberry polysaccharides showed antibacterial activities against *E. coli*, *P. aeruginosa*, *B. subtilis*, and *S. aureus* in a dose-dependent manner [56]. These findings suggest the potential application of paper mulberry and derived compounds for the treatment of diseases caused by bacterial and fungal infections.

3.2.5. Anti-Viral Activity

Polyphenols from paper mulberry were demonstrated to exert antiviral activities, particularly against coronavirus. The isolated phenolic compounds, including broussochalcone. A/B, 4-hydroxyisolonchocarpin, papyriflavonol A (4), 3′-(3-methylbut-2-enyl)-3′,4,7-trihydroxyflavane, kazinol A/B/F/J, and broussoflavan A, exhibited inhibitory effects against papain-like protease, a crucial enzyme for the replication of coronavirus [38]. In another study, molecular docking analysis revealed that broussochalcone A, papyriflavonol A, 3′-(3-methylbut-2-enyl)-3′,4′,7-trihydroxyflavane, kazinol F/J, and broussoflavan A showed a strong binding affinities with the main protease of severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) [39].

3.2.6. Anti-Cancer Activity

A dichloromethane fraction of paper mulberry stem bark induced apoptosis-related DNA fragmentation, and increased the expression of p53, caspase 3, and Bax, as well as inhibiting the proliferation of human colon cancer HT-29 cells [24]. Extracts from barks, leaves, and fruits of paper mulberry showed cytotoxic effects against three cancer cell lines, MCF-7, HepG2, and HeLa cells [77]. Broussoflavonol B downregulated the expression of estrogen receptor-α (ER-α) and inhibited the proliferation of both ER-positive and ER-negative breast cancer cells [46,81,82]. Uralenol and 5,7,3′,4′-tetrahydroxy-3-methoxy-8,5′-diprenylflavone also suppressed the growth of ER-positive breast cancer MCF-7 cells [46]. Broussoflavonol F/H/I/K, glycyrrhiza flavonol A, papyriflavonol A, and isolicofavonol showed inhibitory effects against human lung, liver, and breast cancer cells [40,46]. Similarly, broussochalcone A exerted anti-cancer activities against colon and liver cancer cells in vitro [78,79]. Another flavonol from paper mulberry, kazinol A, induced cytotoxic effects in T24 and cisplatin-resistant T24R2 human bladder cancer cells [37]. Total alkaloids and seven isoquinoline alkaloids (N-norchelerythrine, dihydrosanguinarine, oxyavicine, broussonpapyrine, nitidine, chelerythrine, liriodenine) from paper mulberry fruits showed strong inhibitory effects on the growth of BEL-7402 and Hela cell lines, suggesting their anti-cancer potential [37]. Hence, paper mulberry and its components might be promising candidates for cancer therapy.

3.2.7. Anti-Diabetic Activity

A paper mulberry root extract exerted antidiabetic activities by improving glucose tolerance in high-fed diet (HFD)-induced C57BL/6 mice [66]. Protein-tyrosine phosphatase 1B (PTP1B) is the key enzyme involved in the dephosphorylation of the insulin receptor, resulting in insulin resistance. PTP1B inhibitors might be effective for the treatment of type 2 diabetes [83]. Several compounds isolated from paper mulberry, including uralenol, 8-(1,1-dimethylallyl)-5′-(3-methylbut-2-enyl)-3′,4′,5,7-tetrahydroxyflanvonol, 3,3′,4′,5,7-pentahydroxyflavone, and broussochalcone A, exhibited PTP1B-inhibitory activities [33]. Another study reported that a chloroform extract of paper mulberry root and 12 derived polyphenolic compounds showed inhibitory activities against α-glucosidases, a key enzyme family in glucose metabolism [35,84]. Among these 12 polyphenols, papyriflavonol A was the most potent α-glucosidase inhibitor, with an IC50 value of 2.1 μM [35]. These findings provide evidence for the potential of using paper mulberry in diabetes treatment.

3.2.8. Anti-Cholinesterase Activity

Acetylcholinesterase plays a crucial role in cholinergic transmission by catalyzing the hydrolysis reaction of acetylcholine. Acetylcholinesterase and the related enzyme butyrylcholinesterase have been demonstrated to be involved in the pathogenesis of Alzheimer's disease by directly interacting with amyloid-beta (Aβ) and triggering the formation of Aβ plaques [85,86]. Paper mulberry ethanol extracts with prenylated flavonoids as the main active components exerted inhibitory effects on both human acetylcholinesterase and butyrylcholinesterase, suggesting their potential for the treatment of Alzheimer's disease [41].

3.2.9. Anti-Gout Activity

An ethanolic extract of paper mulberry root bark showed antigout potential by inhibiting the activity of xanthine oxidase (XOD), an enzyme that synthesizes uric acid from hypoxanthine [34,87]. Two phenolic compounds, broussochalcone A and 3,4-dihydroxyisolonchocarpin, were found to be the main contributors to the XOD-inhibitory effects of the paper mulberry extract [34].

3.2.10. Antinociceptive Activity

A previous study demonstrated that the administration of extracts from the roots, stems, leaves, and fruits of paper mulberry (2 g/kg) exerted antinociceptive activity by inhibiting the acetic acid-induced writhing response in rats [42].

3.2.11. Hepatoprotective Activity

Polysaccharides from paper mulberry ameliorated acetaminophen-induced liver damage, reduced liver apoptosis, enhanced antioxidant capacity, and improved the detoxification ability of the liver to acetaminophen by regulating the intestinal microbiota in mice [30]. An extract of paper mulberry root significantly suppressed hepatic steatosis in HFD-induced obese mice by decreasing lipogenic gene expression and increasing AMPK phosphorylation in the liver [66]. These data suggest the application of paper mulberry for the treatment of hepatic diseases.

3.3. Application of Paper Mulberry in Cosmetics

3.3.1. Skin Lightening and Moisturizing

Paper mulberry is commonly used as a skin-lightening agent in cosmetics. Paper mulberry might prevent skin hyperpigmentation by inhibiting the activity of tyrosinase and melanin formation [88]. Extracts from paper mulberry are included in many skin-whitening compositions for external application [89,90]. Paper mulberry combined with *Styela clava* extract is blended into a facial mask sheet for the whitening purpose [91]. A mask pack containing paper mulberry showed moisturizing effects on the skin [92]. Paper mulberry combined with white ginseng was incorporated in a cosmetic composition for skin moisturizing and smoothing [93]. A study conducted on 24 male participants demonstrated

that kazinol F, a compound derived from paper mulberry, showed a significant depigmentation effect against ultraviolet B (UVB) radiation. Even though melanin pigmentation was considered a response of the skin to UV radiation and the inhibition of melanogenesis may increase the skin's vulnerability to the damage [94], the lotion containing kazinol F did not only reduce skin darkness, but it also alleviated UV-induced erythema in human skin. This effect was assessed using three different instruments (Chromameter CR200, Dermaspectrometer, and Mexamter MX16) and was comparable with hydroquinone, a common skin-lightening agent [95]. Paper mulberry has been widely applied in the cosmetic industry in Europe and South America; however, there have been limited clinical trials to prove its skin-lightening effects in humans [96].

3.3.2. Hair Protection and Hair Growth

A previous study showed that the application of formulations containing paper mulberry root extract exerted hair-protective effects by improving the tensile strength, optical absorption, and luster of damaged hair [97]. Another study on 11 healthy subjects indicated that using a leaf extract of paper mulberry for 12 weeks showed beneficial effects on hair growth, indicated by increased total hair count as compared with the start date of the trial. The underlying mechanism might be through regulating the WNT-β-catenin and STAT6 pathways to promote the proliferation of dermal papilla cells [98]. These data suggest the potential application of paper mulberry in hair-care products in cosmetics.

3.4. Safety Assessment of Paper Mulberry for Cosmetic Topical Application

The safety of paper mulberry for topical application was assessed in previous studies. A microemulsion formulation containing paper mulberry leaf extract was applied for human skin irritation tests in the form of single-application closed-patch tests in 30 women without any skin symptoms. The results showed that transepidermal water loss and erythema values were not significantly different between microemulsions containing paper mulberry and the placebo, suggesting that paper mulberry did not cause skin irritation in humans [99]. Another report indicated that a skin composition containing paper mulberry showed no adverse effects on human skin [89]. The application of a lotion product containing kazinol F, a component of paper mulberry, did not show any irritation or sensitization effects on human skin [80]. These findings suggest the safety of paper mulberry for application in skin-lightening products.

4. Conclusions

Paper mulberry is a common skin-lightening ingredient in the cosmetic industry. Extracts from different parts of the paper mulberry contain various bioactive components, such as phenols, flavonoids, alkaloids, and tannins, which possess a wide range of biological activities. Among them, antityrosinase, antioxidant, antimicrobial, and anti-inflammatory effects are considered the typical pharmacological properties, which can be utilized for cosmetic applications. Although paper mulberry is demonstrated to be safe for topical application and has been used in many cosmetic preparations, there is a lack of clinical studies to prove its skin-lightening effects in humans. Hence, more research on paper mulberry as well as the combination of paper mulberry with other agents might be helpful to expand the applications of paper mulberry in cosmetics.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cosmetics9060112/s1, Table S1: Chemical structure of compounds in paper mulberry.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Grand View Research. Skin Lightening Products Market Size, Share & Trends Analysis Report By Product (Creams, Cleanser, Mask), by Nature, by Region, and Segment Forecasts, 2022–2030. Available online: https://www.grandviewresearch.com/industry-analysis/skin-lightening-products-market (accessed on 6 October 2022).
2. Rendon, M.I.; Gaviria, J.I. Review of skin-lightening agents. *Dermatol. Surg.* **2005**, *31*, 886–890. [CrossRef] [PubMed]
3. Briganti, S.; Camera, E.; Picardo, M. Chemical and instrumental approaches to treat hyperpigmentation. *Pigment Cell Res.* **2003**, *16*, 101–110. [CrossRef] [PubMed]
4. Draelos, Z.; Dahl, A.; Yatskayer, M.; Chen, N.; Krol, Y.; Oresajo, C. Dyspigmentation, skin physiology, and a novel approach to skin lightening. *J. Cosmet. Dermatol.* **2013**, *12*, 247–253. [CrossRef] [PubMed]
5. Kamakshi, R. Fairness via formulations: A review of cosmetic skin-lightening ingredients. *J. Cosmet. Sci.* **2012**, *63*, 43–54. [PubMed]
6. Mehta, R.C.; Makino, E.T.H.; Sonti, S.D.; Garruto, J.A. Melanin Modification Compositions and Methods of Use. U.S. Patent No 8,236,288, 7 August 2012. Available online: https://patents.google.com/patent/EP2661264B1/en (accessed on 6 October 2022).
7. D'Mello, S.A.; Finlay, G.J.; Baguley, B.C.; Askarian-Amiri, M.E. Signaling pathways in melanogenesis. *Int. J. Mol. Sci.* **2016**, *17*, 1144. [CrossRef] [PubMed]
8. Hearing, V.J. Biochemical control of melanogenesis and melanosomal organization. *J. Investig. Dermatol. Symp. Proc.* **1999**, *4*, 24–28. [CrossRef] [PubMed]
9. Slominski, A.; Zmijewski, M.A.; Pawelek, J. L-tyrosine and L-dihydroxyphenylalanine as hormone-like regulators of melanocyte functions. *Pigment Cell Melanoma Res.* **2012**, *25*, 14–27. [CrossRef]
10. Aroca, P.; Solano, F.; Salina, C.; García-Borrón, J.C.; Lozano, J.A. Regulation of the final phase of mammalian melanogenesis: The role of dopachrome tautomerase and the ratio between 5,6-dihydroxyindole-2-carboxylic acid and 5,6-dihydroxyindole. *Eur. J. Biochem.* **1992**, *208*, 155–163. [CrossRef]
11. Jiménez-Cervantes, C.; Solano, F.; Kobayashi, T.; Urabe, K.; Hearing, V.J.; Lozano, J.A.; García-Borrón, J.C. A new enzymatic function in the melanogenic pathway. The 5,6-dihydroxyindole-2-carboxylic acid oxidase activity of tyrosinase-related protein-1 (TRP1). *J. Biol. Chem.* **1994**, *269*, 17993–18000. [CrossRef]
12. Hearing, V.J.; Korner, A.M.; Pawelek, J.M. New Regulators of Melanogenesis Are Associated with Purified Tyrosinase Isozymes. *J. Invest. Dermatol.* **1982**, *79*, 16–18. [CrossRef]
13. Schallreuter, K.; Slominski, A.; Pawelek, J.; Jimbow, K.; Gilchrest, B. What controls melanogenesis? *Exp. Dermatol.* **1998**, *7*, 143–150. [CrossRef] [PubMed]
14. Videira, I.F.d.S.; Moura, D.F.L.; Magina, S. Mechanisms regulating melanogenesis. *An. Bras. Dermatol.* **2013**, *88*, 76–83. [CrossRef] [PubMed]
15. Slominski, A.; Tobin, D.J.; Shibahara, S.; Wortsman, J. Melanin Pigmentation in Mammalian Skin and Its Hormonal Regulation. *Physiol. Rev.* **2004**, *84*, 1155–1228. [CrossRef] [PubMed]
16. Slominski, R.M.; Sarna, T.; Płonka, P.M.; Raman, C.; Brożyna, A.A.; Slominski, A.T. Melanoma, Melanin, and Melanogenesis: The Yin and Yang Relationship. *Front. Oncol.* **2022**, *12*, 842496:1–842496:18. [CrossRef]
17. Kim, S.S.; Kim, M.-J.; Choi, Y.H.; Kim, B.K.; Kim, K.S.; Park, K.J.; Park, S.M.; Lee, N.H.; Hyun, C.-G. Down-regulation of tyrosinase, TRP-1, TRP-2 and MITF expressions by citrus press-cakes in murine B16 F10 melanoma. *Asian Pac. J. Trop. Biomed.* **2013**, *3*, 617–622. [CrossRef]
18. Ancans, J.; Tobin, D.J.; Hoogduijn, M.J.; Smit, N.P.; Wakamatsu, K.; Thody, A.J. Melanosomal pH controls rate of melanogenesis, eumelanin/phaeomelanin ratio and melanosome maturation in melanocytes and melanoma cells. *Exp. Cell Res.* **2001**, *268*, 26–35. [CrossRef]
19. Ito, S.; Wakamatsu, K. Chemistry of mixed melanogenesis—Pivotal roles of dopaquinone. *Photochem. Photobiol.* **2008**, *84*, 582–592. [CrossRef]
20. Peñailillo, J.; Olivares, G.; Moncada, X.; Payacán, C.; Chang, C.-S.; Chung, K.-F.; Matthews, P.J.; Seelenfreund, A.; Seelenfreund, D. Sex distribution of paper mulberry (*Broussonetia papyrifera*) in the Pacific. *PLoS ONE* **2016**, *11*, e0161148. [CrossRef]
21. Chen, Y.R.; Wang, L.; Liu, X.; Wang, F.L.; An, Y.; Zhao, W.; Tian, J.L.; Kong, D.G.; Zhang, W.R.; Xu, Y.; et al. The Genus Broussonetia: An Updated Review of Phytochemistry, Pharmacology and Applications. *Molecules* **2022**, *27*, 5344. [CrossRef]
22. Qureshi, H.; Anwar, T.; Khan, S.; Fatimah, H.; Waseem, M. Phytochemical constituents of *Broussonetia papyrifera* (L.) L′He′r. ex Vent: An overview. *J. Indian Chem. Soc.* **2020**, *97*, 55.
23. Shivhare, S.; Malviya, K.; Malviya, K.S.; Jain, V. A Review: Natural skin lighting and nourishing agents. *Res. J. Top. Cosmet. Sci.* **2013**, *3*, 11–15.
24. Wang, L.; Son, H.J.; Xu, M.-L.; Hu, J.-H.; Wang, M.-H. Anti-inflammatory and anticancer properties of dichloromethane and butanol fractions from the stem bark of *Broussonetia papyrifera*. *J. Korean Soc. Appl. Biol. Chem.* **2010**, *53*, 297–303. [CrossRef]
25. Sohn, H.Y.; Son, K.H.; Kwon, C.S.; Kwon, G.S.; Kang, S.S. Antimicrobial and cytotoxic activity of 18 prenylated flavonoids isolated from medicinal plants: *Morus alba* L., *Morus mongolica* Schneider, *Broussnetia papyrifera* (L.) Vent, *Sophora flavescens* Ait and *Echinosophora koreensis* Nakai. *Phytomedicine* **2004**, *11*, 666–672. [CrossRef] [PubMed]

26. Xu, M.-L.; Wang, L.; Hu, J.-H.; Lee, S.K.; Wang, M.-H. Antioxidant activities and related polyphenolic constituents of the methanol extract fractions from *Broussonetia papyrifera* stem bark and wood. *Food Sci. Biotechnol.* **2010**, *19*, 677–682. [CrossRef]
27. Amir, M.K.; Rizwana, A.Q.; Faizan, U.; Syed, A.G.; Asia, N.; Sumaira, S.; Muhammad, K.L.; Muhammad, Y.L.; Ishtiaq, H.; Waheed, M. Phytochemical analysis of selected medicinal plants of Margalla Hills and surroundings. *J. Med. Plant. Res.* **2011**, *5*, 6055–6060. [CrossRef]
28. Sirita, J.; Chomsawan, B.; Yodsoontorn, P.; Kornochalert, S.; Lapinee, C.; Jumpatong, K. Antioxidant activities, phenolic and tannin contents of paper mulberry (*Broussonetia papyrifera*) extract. *Med. Plants—Int J. Phytomed. Relat. Ind.* **2020**, *12*, 371–375. [CrossRef]
29. Sun, J.; Zhang, C.S.; Yu, L.N.; Bi, J.; Liu, S.F.; Zhu, F.; Yang, Q.L. Antioxidant activity and total phenolics of *Broussonetia papyrifera* flower extracts. *Appl. Mech. Mater.* **2012**, *140*, 263–267. [CrossRef]
30. Xu, B.; Hao, K.; Chen, X.; Wu, E.; Nie, D.; Zhang, G.; Si, H. *Broussonetia papyrifera* Polysaccharide Alleviated Acetaminophen-Induced Liver Injury by Regulating the Intestinal Flora. *Nutrients* **2022**, *14*, 2636. [CrossRef]
31. Qureshi, H.; Arshad, M.; Bibi, Y. Toxicity assessment and phytochemical analysis of *Broussonetia papyrifera* and *Lantana camara*: Two notorious invasive plant species. *J. Biodivers Environ. Sci.* **2014**, *5*, 508–517.
32. Ryu, H.W.; Park, M.H.; Kwon, O.K.; Kim, D.Y.; Hwang, J.Y.; Jo, Y.H.; Ahn, K.S.; Hwang, B.Y.; Oh, S.R. Anti-inflammatory flavonoids from root bark of *Broussonetia papyrifera* in LPS-stimulated RAW264.7 cells. *Bioorg. Chem.* **2019**, *92*, 103233. [CrossRef]
33. Chen, R.M.; Hu, L.H.; An, T.Y.; Li, J.; Shen, Q. Natural PTP1B inhibitors from *Broussonetia papyrifera*. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3387–3390. [CrossRef]
34. Ryu, H.W.; Lee, J.H.; Kang, J.E.; Jin, Y.M.; Park, K.H. Inhibition of xanthine oxidase by phenolic phytochemicals from *Broussonetia papyrifera*. *J. Korean Soc. Appl. Biol. Chem.* **2012**, *55*, 587–594. [CrossRef]
35. Ryu, H.W.; Lee, B.W.; Curtis-Long, M.J.; Jung, S.; Ryu, Y.B.; Lee, W.S.; Park, K.H. Polyphenols from *Broussonetia papyrifera* displaying potent alpha-glucosidase inhibition. *J. Agric. Food Chem.* **2010**, *58*, 202–208. [CrossRef] [PubMed]
36. Park, M.H.; Jung, S.; Yuk, H.J.; Jang, H.J.; Kim, W.J.; Kim, D.Y.; Lim, G.; Lee, J.; Oh, S.R.; Lee, S.U.; et al. Rapid identification of isoprenylated flavonoids constituents with inhibitory activity on bacterial neuraminidase from root barks of paper mulberry (*Broussonetia papyrifera*). *Int J. Biol. Macromol.* **2021**, *174*, 61–68. [CrossRef] [PubMed]
37. Park, S.; Fudhaili, A.; Oh, S.S.; Lee, K.W.; Madhi, H.; Kim, D.H.; Yoo, J.; Ryu, H.W.; Park, K.H.; Kim, K.D. Cytotoxic effects of kazinol A derived from *Broussonetia papyrifera* on human bladder cancer cells, T24 and T24R2. *Phytomedicine* **2016**, *23*, 1462–1468. [CrossRef] [PubMed]
38. Park, J.Y.; Yuk, H.J.; Ryu, H.W.; Lim, S.H.; Kim, K.S.; Park, K.H.; Ryu, Y.B.; Lee, W.S. Evaluation of polyphenols from *Broussonetia papyrifera* as coronavirus protease inhibitors. *J. Enzym. Inhib. Med. Chem.* **2017**, *32*, 504–515. [CrossRef] [PubMed]
39. Ghosh, R.; Chakraborty, A.; Biswas, A.; Chowdhuri, S. Identification of polyphenols from *Broussonetia papyrifera* as SARS CoV-2 main protease inhibitors using in silico docking and molecular dynamics simulation approaches. *J. Biomol. Struct. Dyn.* **2021**, *39*, 6747–6760. [CrossRef]
40. Tian, J.L.; Liu, T.L.; Xue, J.J.; Hong, W.; Zhang, Y.; Zhang, D.X.; Cui, C.C.; Liu, M.C.; Niu, S.L. Flavanoids derivatives from the root bark of *Broussonetia papyrifera* as a tyrosinase inhibitor. *Ind. Crops Prod.* **2019**, *138*, 111445. [CrossRef]
41. Ryu, H.W.; Curtis-Long, M.J.; Jung, S.; Jeong, I.Y.; Kim, D.S.; Kang, K.Y.; Park, K.H. Anticholinesterase potential of flavonols from paper mulberry (*Broussonetia papyrifera*) and their kinetic studies. *Food Chem.* **2012**, *132*, 1244–1250. [CrossRef]
42. Lin, L.W.; Chen, H.Y.; Wu, C.R.; Liao, P.M.; Lin, Y.T.; Hsieh, M.T.; Ching, H. Comparison with various parts of *Broussonetia papyrifera* as to the antinociceptive and anti-inflammatory activities in rodents. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 2377–2384. [CrossRef]
43. Ko, H.H.; Yu, S.M.; Ko, F.N.; Teng, C.M.; Lin, C.N. Bioactive constituents of Morus australis and *Broussonetia papyrifera*. *J. Nat. Prod.* **1997**, *60*, 1008–1011. [CrossRef] [PubMed]
44. Sohn, H.Y.; Kwon, C.S.; Son, K.H. Fungicidal effect of prenylated flavonol, papyriflavonol A, isolated from *Broussonetia papyrifera* (L.) vent. against Candida albicans. *J. MicroBiol. Biotechnol.* **2010**, *20*, 1397–1402. [CrossRef] [PubMed]
45. Dou, C.Z.; Liu, Y.F.; Zhang, L.L.; Chen, S.H.; Hu, C.Y.; Liu, Y.; Zhao, Y.T. Polyphenols from *Broussonetia papyrifera* Induce Apoptosis of HepG2 Cells via Inactivation of ERK and AKT Signaling Pathways. *Evid. Based Complement. Altern. Med.* **2021**, *2021*, 8841706. [CrossRef]
46. Guo, F.; Feng, L.; Huang, C.; Ding, H.; Zhang, X.; Wang, Z.; Li, Y. Prenylflavone derivatives from *Broussonetia papyrifera*, inhibit the growth of breast cancer cells in vitro and in vivo. *Phytochem. Lett.* **2013**, *6*, 331–336. [CrossRef]
47. Chang, C.-F.; Wang, C.-H.; Lee, T.-H.; Liu, S.-M. Bioactive compounds from the bark of *Broussonetia papyrifera* after solid fermentation with a white rot fungus Perenniporia tephropora. *J. Wood Chem. Technol.* **2020**, *40*, 317–330. [CrossRef]
48. Zheng, Z.-P.; Cheng, K.-W.; Chao, J.; Wu, J.; Wang, M. Tyrosinase inhibitors from paper mulberry (*Broussonetia papyrifera*). *Food Chem.* **2008**, *106*, 529–535. [CrossRef]
49. Malaník, M.; Treml, J.; Leláková, V.; Nykodýmová, D.; Oravec, M.; Marek, J.; Šmejkal, K. Anti-inflammatory and antioxidant properties of chemical constituents of *Broussonetia papyrifera*. *Bioorg. Chem.* **2020**, *104*, 104298. [CrossRef]
50. Zhou, X.J.; Mei, R.Q.; Zhang, L.; Lu, Q.; Zhao, J.; Adebayo, A.H.; Cheng, Y.X. Antioxidant phenolics from *Broussonetia papyrifera* fruits. *J. Asian Nat. Prod. Res.* **2010**, *12*, 399–406. [CrossRef]
51. Mei, R.Q.; Wang, Y.H.; Du, G.H.; Liu, G.M.; Zhang, L.; Cheng, Y.X. Antioxidant Lignans from the Fruits of *Broussonetia papyrifera*. *J. Nat. Prod.* **2009**, *72*, 621–625. [CrossRef]

52. Sun, J.; Liu, S.F.; Zhang, C.S.; Yu, L.N.; Bi, J.; Zhu, F.; Yang, Q.L. Chemical composition and antioxidant activities of *Broussonetia papyrifera* fruits. *PLoS ONE* **2012**, *7*, e32021. [CrossRef]
53. Hongfang, Z.; Linzhang, H.; Luping, Q.; Baokang, H. Antioxidative and anti-inflammatory properties of Chushizi oil from Fructus Broussonetiae. *J. Med. Plant. Res.* **2011**, *5*, 6407–6412. [CrossRef]
54. Pang, S.Q.; Wang, G.Q.; Lin, J.S.; Diao, Y.; Xu, R.A. Cytotoxic activity of the alkaloids from *Broussonetia papyrifera* fruits. *Pharm. Biol.* **2014**, *52*, 1315–1319. [CrossRef] [PubMed]
55. Pang, S.-Q.; Wang, G.-Q.; Huang, B.-K.; Zhang, Q.-Y.; Qin, L.-P. Isoquinoline alkaloids from *Broussonetia papyrifera* fruits. *Chem. Nat. Compd.* **2007**, *43*, 100–102. [CrossRef]
56. Han, Q.H.; Wu, Z.L.; Huang, B.; Sun, L.Q.; Ding, C.B.; Yuan, S.; Zhang, Z.W.; Chen, Y.E.; Hu, C.; Zhou, L.J.; et al. Extraction, antioxidant and antibacterial activities of *Broussonetia papyrifera* fruits polysaccharides. *Int. J. Biol. Macromol.* **2016**, *92*, 116–124. [CrossRef]
57. Kumar, N.N.; Ramakrishnaiah, H.; Krishna, V.; Deepalakshmi, A. GC-MS analysis and antimicrobial activity of seed oil of *Broussonetia papyrifera* (L.) Vent. *Int. J. Pharm. Sci. Res.* **2015**, *6*, 3954. [CrossRef]
58. Ran, X.K.; Wang, X.T.; Liu, P.P.; Chi, Y.X.; Wang, B.J.; Dou, D.Q.; Kang, T.G.; Xiong, W. Cytotoxic constituents from the leaves of *Broussonetia papyrifera*. *Chin. J. Nat. Med.* **2013**, *11*, 269–273. [CrossRef]
59. Cao, X.; Yang, L.; Xue, Q.; Yao, F.; Sun, J.; Yang, F.; Liu, Y. Antioxidant evaluation-guided chemical profiling and structure-activity analysis of leaf extracts from five trees in *Broussonetia* and *Morus* (Moraceae). *Sci Rep.* **2020**, *10*, 4808. [CrossRef]
60. Ko, H.H.; Chang, W.L.; Lu, T.M. Antityrosinase and antioxidant effects of ent-kaurane diterpenes from leaves of *Broussonetia papyrifera*. *J. Nat. Prod.* **2008**, *71*, 1930–1933. [CrossRef]
61. Yang, C.; Li, F.; Du, B.; Chen, B.; Wang, F.; Wang, M. Isolation and characterization of new phenolic compounds with estrogen biosynthesis-inhibiting and antioxidation activities from *Broussonetia papyrifera* leaves. *PLoS ONE* **2014**, *9*, e94198. [CrossRef]
62. Lee, D.; Bhat, K.P.; Fong, H.H.; Farnsworth, N.R.; Pezzuto, J.M.; Kinghorn, A.D. Aromatase inhibitors from *Broussonetia papyrifera*. *J. Nat. Prod.* **2001**, *64*, 1286–1293. [CrossRef]
63. Thungmungmee, S.; Ingkaninan, K.; Pitaksuteepong, T. Stability study of *Broussonetia papyrifera* leaf extract. *Thai J. Pharm. Sci.* **2012**, *36*, 197–200.
64. Hwang, J.-H.; Lee, B.M. Inhibitory effects of plant extracts on tyrosinase, L-DOPA oxidation, and melanin synthesis. *J. Toxicol. Environ. Health A* **2007**, *70*, 393–407. [CrossRef]
65. Wu, W.-T. Evaluation of anti-inflammatory effects of *Broussonetia papyrifera* stem bark. *Indian J. Pharmacol.* **2012**, *44*, 26. [CrossRef] [PubMed]
66. Lee, J.M.; Choi, S.S.; Park, M.H.; Jang, H.; Lee, Y.H.; Khim, K.W.; Oh, S.R.; Park, J.; Ryu, H.W.; Choi, J.H. *Broussonetia papyrifera* Root Bark Extract Exhibits Anti-inflammatory Effects on Adipose Tissue and Improves Insulin Sensitivity Potentially Via AMPK Activation. *Nutrients* **2020**, *12*, 773. [CrossRef] [PubMed]
67. Cheng, Z.; Lin, C.; Hwang, T.; Teng, C. Broussochalcone A, a potent antioxidant and effective suppressor of inducible nitric oxide synthase in lipopolysaccharide-activated macrophages. *Biochem. Pharmacol.* **2001**, *61*, 939–946. [CrossRef]
68. Ko, H.J.; Jin, J.H.; Kwon, O.S.; Jong Taek Kim, K.H.S.; Kim, H.P. Inhibition of experimental lung inflammation and bronchitis by phytoformula containing *Broussonetia papyrifera* and Lonicera japonica. *Korean Soc. Appl. Pharmacol.* **2011**, *19*, 324–330. [CrossRef]
69. Kwak, W.J.; Moon, T.C.; Lin, C.X.; Rhyn, H.G.; Jung, H.; Lee, E.; Kwon, D.Y.; Son, K.H.; Kim, H.P.; Kang, S.S.; et al. Papyriflavonol A from *Broussonetia papyrifera* inhibits the passive cutaneous anaphylaxis reaction and has a secretory phospholipase A2-inhibitory activity. *Biol. Pharm. Bull.* **2003**, *26*, 299–302. [CrossRef]
70. Tsai, F.H.; Lien, J.C.; Lin, L.W.; Chen, H.Y.; Ching, H.; Wu, C.R. Protective effect of *Broussonetia papyrifera* against hydrogen peroxide-induced oxidative stress in SH-SY5Y cells. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1933–1939. [CrossRef]
71. Yao, L.; Xiong, L.; Yoo, C.G.; Dong, C.; Meng, X.; Dai, J.; Ragauskas, A.J.; Yang, C.; Yu, J.; Yang, H. Correlations of the physicochemical properties of organosolv lignins from *Broussonetia papyrifera* with their antioxidant activities. *Sustain. Energy Fuels* **2020**, *4*, 5114–5119. [CrossRef]
72. Tao, H.; Si, B.; Xu, W.; Tu, Y.; Diao, Q. Effect of *Broussonetia papyrifera* L. silage on blood biochemical parameters, growth performance, meat amino acids and fatty acids compositions in beef cattle. *Asian Australas J. Anim. Sci.* **2020**, *33*, 732–741. [CrossRef]
73. Si, B.; Tao, H.; Zhang, X.; Guo, J.; Cui, K.; Tu, Y.; Diao, Q. Effect of *Broussonetia papyrifera* L. (paper mulberry) silage on dry matter intake, milk composition, antioxidant capacity and milk fatty acid profile in dairy cows. *Asian Australas J. Anim. Sci.* **2018**, *31*, 1259–1266. [CrossRef] [PubMed]
74. Chen, G.; Shui, S.; Chai, M.; Wang, D.; Su, Y.; Wu, H.; Sui, X.; Yin, Y. Effects of Paper Mulberry (*Broussonetia papyrifera*) Leaf Extract on Growth Performance and Fecal Microflora of Weaned Piglets. *Biomed. Res. Int.* **2020**, *2020*, 6508494. [CrossRef] [PubMed]
75. Amir, M.K.; Rizwana, A.Q.; Syed, A.G.; Faizan, U. Antimicrobial activity of selected medicinal plants of Margalla hills, Islamabad, Pakistan. *J. Med. Plants Res.* **2011**, *5*, 4665–4670. [CrossRef]
76. Geng, C.-A.; Yan, M.-H.; Zhang, X.-M.; Chen, J.-J. Anti-oral microbial flavanes from *Broussonetia papyrifera* under the guidance of bioassay. *Nat. Prod. Bioprospect.* **2019**, *9*, 139–144. [CrossRef] [PubMed]
77. Kumar, N.N.; Ramakrishnaiah, H.; Krishna, V.; Radhika, M. Cytotoxic activity of *Broussonetia papyrifera* (L.) Vent on MCF-7, HeLa and HepG2 cell lines. *Int. J. Pharm. Pharm. Sci.* **2014**, *6*, 339–342.

78. Shin, S.; Son, Y.; Liu, K.H.; Kang, W.; Oh, S. Cytotoxic activity of broussochalcone a against colon and liver cancer cells by promoting destruction complex-independent β-catenin degradation. *Food Chem. Toxicol.* **2019**, *131*, 110550. [CrossRef]
79. Park, S.H.; Lee, J.; Shon, J.C.; Phuc, N.M.; Jee, J.G.; Liu, K.H. The inhibitory potential of Broussochalcone A for the human cytochrome P450 2J2 isoform and its anti-cancer effects via FOXO3 activation. *Phytomedicine* **2018**, *42*, 199–206. [CrossRef]
80. Jang, D.; Lee, B.-G.; Jeon, C.; Jo, N.; Park, J.; Cho, S.; Lee, H.; Koh, J. Melanogenesis inhibitor from paper mulberry. *Cosmet. Toilet.* **1997**, *112*, 59–64.
81. Guo, M.; Wang, M.; Zhang, X.; Deng, H.; Wang, Z.Y. Broussoflavonol B restricts growth of ER-negative breast cancer stem-like cells. *Anticancer Res.* **2013**, *33*, 1873–1879. [PubMed]
82. Guo, M.; Wang, M.; Deng, H.; Zhang, X.; Wang, Z.Y. A novel anticancer agent Broussoflavonol B downregulates estrogen receptor (ER)-α36 expression and inhibits growth of ER-negative breast cancer MDA-MB-231 cells. *Eur. J. Pharmacol.* **2013**, *714*, 56–64. [CrossRef] [PubMed]
83. Eleftheriou, P.; Geronikaki, A.; Petrou, A. PTP1b Inhibition, A Promising Approach for the Treatment of Diabetes Type II. *Curr. Top. Med. Chem.* **2019**, *19*, 246–263. [CrossRef] [PubMed]
84. Kumar, S.; Narwal, S.; Kumar, V.; Prakash, O. α-glucosidase inhibitors from plants: A natural approach to treat diabetes. *Pharmacogn. Rev.* **2011**, *5*, 19–29. [CrossRef] [PubMed]
85. Rees, T.M.; Brimijoin, S. The role of acetylcholinesterase in the pathogenesis of Alzheimer's disease. *Drugs Today* **2003**, *39*, 75–83. [CrossRef] [PubMed]
86. Darvesh, S. Butyrylcholinesterase as a Diagnostic and Therapeutic Target for Alzheimer's Disease. *Curr. Alzheimer Res.* **2016**, *13*, 1173–1177. [CrossRef] [PubMed]
87. Kong, L.D.; Cai, Y.; Huang, W.W.; Cheng, C.H.K.; Tan, R.X. Inhibition of xanthine oxidase by some Chinese medicinal plants used to treat gout. *J. Ethnopharmacol.* **2000**, *73*, 199–207. [CrossRef]
88. D'Amelio, F.; Mirhom, Y. Paper mulberry and its preparations as tyrosinase inhibitors and skin lightening agents. *Cosmet. Toiletr. Manufact. Worldw.* **2000**, *2000*, 31–34.
89. Lee, J.Y.; Lim, H.J.J. Skin-Whitening Composition Containing Extracts from Trees Including Paper Mulberry. U.S. Patent 14/478,195, 25 December 2014. Available online: https://patents.google.com/patent/WO2012002783A3/en (accessed on 6 October 2022).
90. Lee, J.Y.; Lim, H.J. Skin-Whitening Composition for External Application on Skin Containing Extracts from Paper Mulberry Flowers and Fruits. U.S. Patent 13/807,904, 2 May 2013. Available online: https://patents.google.com/patent/SG186891A1/en (accessed on 6 October 2022).
91. Yun, W.; Lee, Y.; Kim, D.; Kim, J.; Sung, J.; Lee, H.; Son, H.; Hwang, D.; Jung, Y. The preparation of mask-pack sheet blended with Styela clava tunics and natural polymer. *Text. Color. Finish.* **2017**, *29*, 45–54. [CrossRef]
92. Kwon, S.S.; Yeom, M.H.; Park, C.M.; Kim, D.H.; Kim, H.K. Mask Pack Comprising Cosmetic Cotton-Like Material Prepared from Paper Mulberry. U.S. Patent No 8,329,234, 11 December 2012. Available online: https://patents.google.com/patent/WO2010062142A2/en (accessed on 6 October 2022).
93. Go Un, H.; Soon Sang, K.; Sun Young, P.; Jeong Cheol, H.; Youn Joon, K.; Sang Hoon, H. Antioxidant Cosmetic Composition Containing White Ginseng Powder and White Paper Powder. PubChem. Patent KR-20110035265-A, 2009. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/KR-20110035265-A (accessed on 6 October 2022).
94. Slominski, A.T.; Zmijewski, M.A.; Plonka, P.M.; Szaflarski, J.P.; Paus, R. How UV Light Touches the Brain and Endocrine System Through Skin, and Why. *Endocrinology* **2018**, *159*, 1992–2007. [CrossRef]
95. Ha, J.; Jo, N.; Lee, H.; Kim, J.; Lee, B.; Park, W. The depigmentation effect of a new material extracted from Paper Mulberry and its comparison by three colorimetric instruments. *J. Soc. Cosmet. Sci. Korea* **1996**, *22*, 9–19.
96. Rendon, M.I.; Vazquez, Y.; Micciantuono, S. Cosmeceutical Skin Lighteners. In *Cosmeceuticals and Cosmetic Practice*; John Wiley & Sons Ltd.: West Sussex, UK, 2014; p. 218.
97. Kim, J.-S.; Kim, J.-S. Effect of paper mulberry extract on damaged hair. *Asian J. Beauty Cosmetol.* **2021**, *19*, 175–182. [CrossRef]
98. Lee, Y.H.; Nam, G.; Kim, M.-K.; Cho, S.-C.; Choi, B.Y. *Broussonetia papyrifera* Promotes Hair Growth Through the Regulation of β-Catenin and STAT6 Target Proteins: A Phototrichogram Analysis of Clinical Samples. *Cosmetics* **2020**, *7*, 40. [CrossRef]
99. Thungmungmee, S.; Ingkaninan, K.; Tuntijarukorn, P.; Pitaksuteepong, T. Skin Lightening Microemulsion Formulation of *Broussonetia papyrifera* Leaf Extract and Human Skin Irritation Test. *J. Interdiscip. Netw.* **2013**, *2*, 71–76.