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Research Article

Towards a predicted anti-aging molecular targets of asiaticoside based on bioinformatics analysis

Maria Violita Sekar Ayu Kencana[1], K. Ariex Widyantara[1], Yosef Alpha Christian[1], Bakti Wahyu Saputra[2], Agustina Setiawati[1]

[1]Department of Pharmaceutical Biology, Faculty of Pharmacy, Sanata Dharma University, Yogyakarta, Indonesia
[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia

Abstract

Objectives: Human skin, the largest organ, serves as a critical barrier against environmental damage and microbial invasion. The skin aging process leads to collagen degradation, reduced elasticity, and wrinkle formation, influenced by intrinsic and extrinsic factors. This process has driven significant interest in the anti-aging market, which is expected to grow to $44.5 billion by 2030. Asiaticoside (AS) has exhibited anti-aging properties by promoting collagen synthesis and fibroblast proliferation.

Methods: This study employed bioinformatics analyses to identify molecular targets and pathways modulated by AS in skin aging. The gene databases were extracted from PubMed (www.ncbi.nlm.nih.gov), OMIM (www.omim.org), and GeneCards (www.genecards.org). Protein-protein interaction (PPI) networks and CytoHubba algorithms (MCC, DMNC, MNC) identified ten key genes implicated in the skin aging cascade. To validate the results, molecular docking was conducted to assess AS's binding affinity to these targets.

Results: This study identified IL-1β, JUN, TGF-β1, CCL-2, MMP-9, STAT-3, MAPK-3, CXCL-8, MMP-2, and KDR as potentially targeted by AS in the skin aging cascade. Molecular docking revealed a strong binding affinity of AS with MMP-9 (-8.16 kcal/mol), indicating its role in inhibiting ECM degradation.

Conclusion: This study highlights AS's potential as a promising anti-aging agent by targeting key proteins and pathways, paving the way for further therapeutic exploration. This prediction of molecular pathways should be further verified by *in vitro* and *in vivo* experiments.

Keywords: Asiaticoside, bioinformatics, molecular docking, pathway, skin aging

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Skin, the outermost and largest organ, serves as a protective layer for underlying tissue from microbial infection and contributes as an essential barrier against environmental damage [1–5]. The human skin is the first organ that exhibits obvious signs of aging, undergoing progressive changes in both morphology and physiology with age [6]. Awareness about skin aging has expanded lately as society becomes more conscious of beauty. Thus, numerous studies on the factors and strategies to slow skin aging have gained popularity in cosmetic medicine nowadays [7]. The global facial rejuvenation market is predicted to elevate significantly from $24.6 billion to approximately $44.5 billion by 2030 due to the increase in aging populations. Thus, technological innovations have greatly improved public interest in beauty and skin health, and attempts to delay skin aging are growing rapidly [8].

Skin aging refers to a natural, multifaceted, and complicated biological degenerative process [6, 7, 9, 10]. Three skin layers—epidermis, dermis, and subcutaneous—experience degenerative alterations due to aging, with dermal changes being the most obvious [11]. Skin aging is identified by features including skin laxity, wrinkles, elasticity loss, and a rough-looking texture [10]. Its aging process is accelerated by

Address for correspondence: Agustina Setiawati, Ph.D. Department of Pharmaceutical Biology, Faculty of Pharmacy, Sanata Dharma University, Yogyakarta, Indonesia
Phone: +628112636672 **E-mail:** nina@usd.ac.id **ORCID:** 0000-0001-6301-3413
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a combination of endogenous and exogenous factors more than in any other body organ [6, 12, 13]. The endogenous factors are characterized by a reduced ability to regenerate, decreased stratum corneum permeability, epidermal atrophy that mostly affects the stratum spinosum, as well as a reduction in fibroblast and collagen levels in the dermis [5, 12]. Collagen is a protein that provides tensile strength, firmness, and elasticity and supports skin integrity [14]. Exogenous factors, mainly resulting from exposure to ultraviolet (UV) rays, lead to progressive skin damage and play a role in the aging process known as photoaging [5, 15–17]. Chronic UV exposure on human skin activates the expression of matrix metalloproteases (MMPs), impacting collagen and elastin fibers in the dermis and ultimately resulting in solar elastosis. Both endogenous and exogenous factors decrease collagen, the primary factor associated with aging skin, which encourages extracellular matrix (ECM) degradation, skin laxity, deep wrinkle formation, and hyperpigmentation [10, 16, 18]. The skin aging process increases dryness, dullness, coarseness, sagging, and loss of elasticity due to a decrease in skin surface hydration [19, 20].

The utilization of biologically active compounds continues to be a rising trend in the 21st century, marked by the growth of the global natural cosmetics market [21]. Biologically active compounds with pharmaceutical properties, often referred to as cosmeceuticals, represent the latest advancement in beauty care products aimed at reducing wrinkles [22]. There are abundant botanical products that have been clinically proven to prevent the skin aging process. Among them, *Centella asiatica* contains natural products such as asiaticoside, madecassoside, asiatic acid, and madecassic acid [10, 23]. Asiaticoside and madecassoside are the two major terpenoid glycosides that have demonstrated anti-skin-aging effects [24, 25].

Asiaticoside (AS) (Fig. 1a) is a major pentacyclic triterpene glycoside (saponin) with similar sugar chains (Glu-Glu-Rha) bonded to its carboxyl groups [10, 26, 27]. Asiaticoside (AS) is synthesized through glycosylation followed by a rhamnosylation reaction of asiatic acid, catalyzed by UDP-glucosyltransferases (UGTs), which initially attach a glucose molecule to the carboxyl group at C-28 [27]. It increased normal human skin cell migration, adhesion, and proliferation [28]. In addition, AS, an active main secondary metabolite in *Centella asiatica*, induces anti-aging properties by promoting collagen levels and encouraging the growth of normal dermal fibroblasts [29–31]. Nevertheless, it is commonly used for cosmetic purposes in topical applications [32]. Previous studies have proven that AS possesses anti-aging properties by inducing collagen synthesis in dermal fibroblasts via the activation of TGF-β signaling pathways [33]. However, the precise mechanisms by which it interferes with skin aging at the molecular level remain uncertain. Since asiaticoside and madecassoside are major biomarkers of triterpenoid glycosides in *Centella asiatica* [34, 10], this study further analyzed both compound combinations for skin anti-aging.

This investigation outlined a molecular pathway related to bioinformatics assessments of AS's effects on skin aging. Over the past few years, bioinformatics analysis has been widely used for generating diverse datasets that analyze protein and gene expression levels, identifying various genes involved in pathways associated with skin aging [20]. Furthermore, bioinformatics assists in determining the molecular mechanisms underlying specific clinical alterations rapidly and precisely [7]. As a result, 10 top genes were ranked as the most influential genes using three network scoring methods: MCC (Maximal Clique Centrality), DMNC (Density of Maximum Neighborhood Component), and MNC (Maximum Neighborhood Component). These algorithms measure centrality by predicting and exploring the distance from the direct neighborhood of a vertex [20, 35].

This study employs molecular docking and simulation approaches for protein-ligand interactions to facilitate the discovery of innovative skin aging treatments. Thus, AS interacts with key molecular pathways associated with skin aging, which can be computationally predicted and validated by molecular docking and bioinformatics tools. Asiaticoside, by acting on MMP-2/9, plays a crucial role in the degradation of the extracellular matrix, making it a promising agent for skin rejuvenation. Furthermore, the combination of asiaticoside and madecassoside targeted metabolic enzymes such as CYP and UGT to protect the skin aging process from environmental oxidative stress. In conclusion, our research has outlined how asiaticoside targets various molecular pathways such as interleukins, growth regulators, metabolic enzymes, and matrix metalloproteinases, all of which are involved in inhibiting skin aging activities. Furthermore, this prediction of molecular pathways should be further verified by *in vitro* and *in vivo* experiments.

Materials and Methods

Data mining and collection

Key proteins and genes involved in the skin aging mechanism were retrieved from public biomedical databases, including PubMed (www.ncbi.nlm.nih.gov), OMIM (www.omim.org), and GeneCards (www.genecards.org), as a preliminary step in the analysis. The targets of asiaticoside, encompassing both direct and indirect influences on these biomolecules, were identified via www.stitch.embl.de. An interactive Venn diagram tool (www.interactivenn.net) was applied to identify the specific proteins and genes influenced by asiaticoside in relation to skin aging [36].

Construction of protein interaction networks and gene clustering

The construction of a protein-protein interaction (PPI) network and gene clustering involved mapping the dynamic, complex interactions among multiple proteins. Direct and indirect protein interactions were extracted using STRING-DB v11.5 (https://string-db.org), forming the basis of the interaction network. Subsequently, gene analysis was performed with Cytoscape 3.10.1 (https://cytoscape.org/), a platform designed to visualize molecular interaction networks effectively [20].

Analysis of hub gene expression levels

The study employed MNC and Degree algorithms from the CytoHubba plugin to identify the top 10 genes with the

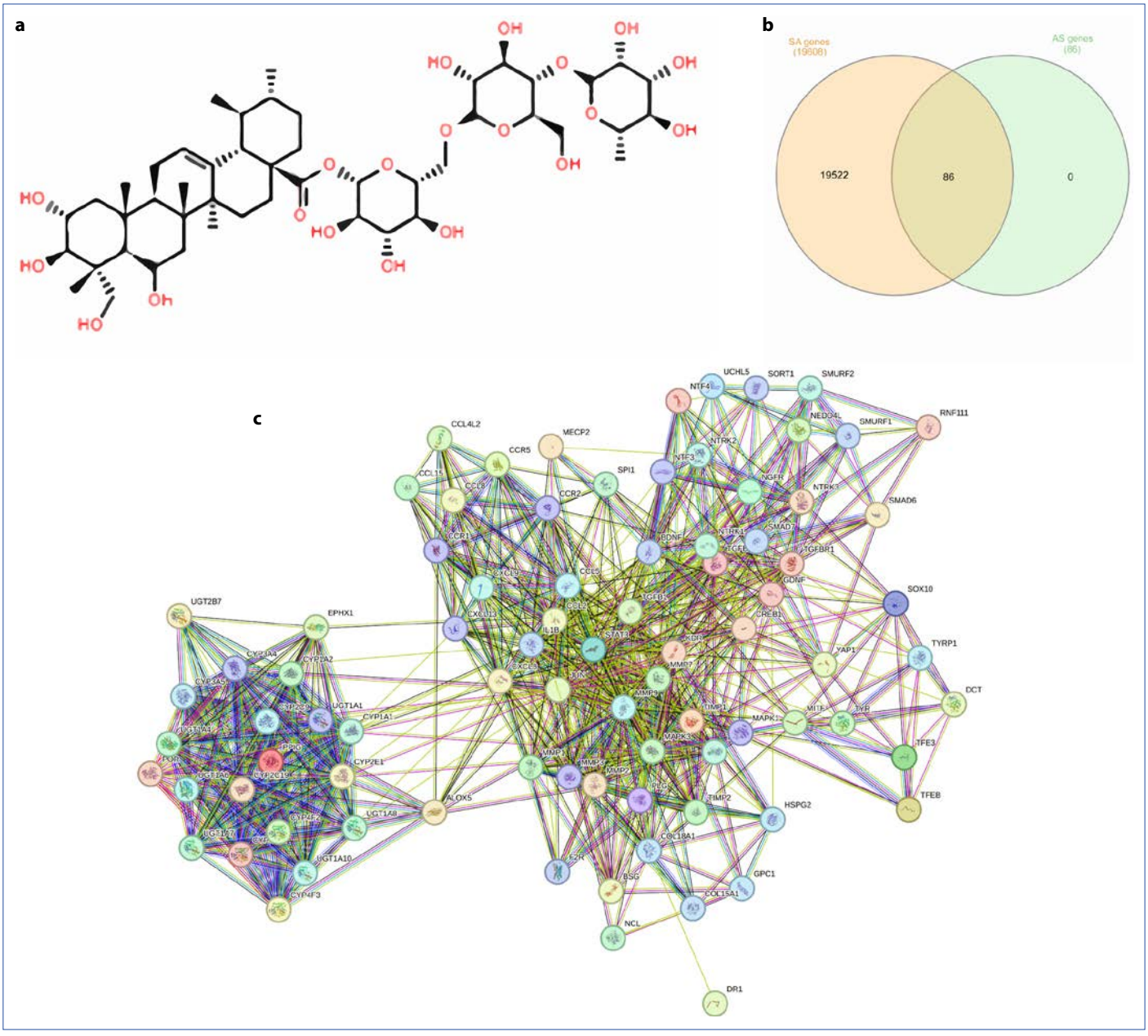

Figure 1. Asiaticoside's top target proteins and genes related to skin aging. (a) Asiaticoside's structure, (b) venn diagram of asiaticoside (AS) and skin aging (SA) interfered genes, (c) protein-protein interaction (PPI) network of the intersecting genes.

highest correlation within the PPI network. These genes, identified as hub genes, are closely associated with skin aging. The bioinformatics analysis was conducted on a system equipped with an 11th Gen Intel Core i3-1115G4 processor at 3.00 GHz and 8 GB of RAM.

Molecular docking

The structures IL1B (6Y8I), MMP9 (1GKC), and CYP3A5 (7LAD) were sourced from the RCSB Protein Data Bank (www.rcsb.org), and the ligand preparation was carried out using BIOVIA Discovery Studio 2021. The study utilized the native ligand as a control, followed by re-docking using AS. The ligand was protonated with Gasteiger charges, while Kollman charges were assigned to the macromolecule using AutoDockTools 1.5.7. The AS compounds were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov). Molecular docking employed a genetic algorithm with 100 GA runs. For the 6Y8I complex, the ligand was positioned at coordinates x=7.425, y=25.105, z=7.064, and for the 1GKC complex at x=65.607, y=31.083, z=117.697, using a grid box size of 40×40×40 and a spacing of 0.375 Å. The complexes were visualized in 3D and superimposed post-docking using BIOVIA Discovery Studio 2021. Docking accuracy was evaluated by calculating the RMSD value, which was 2.0 Å. The results of docking were applied to predict binding energies and protein-ligand interactions.

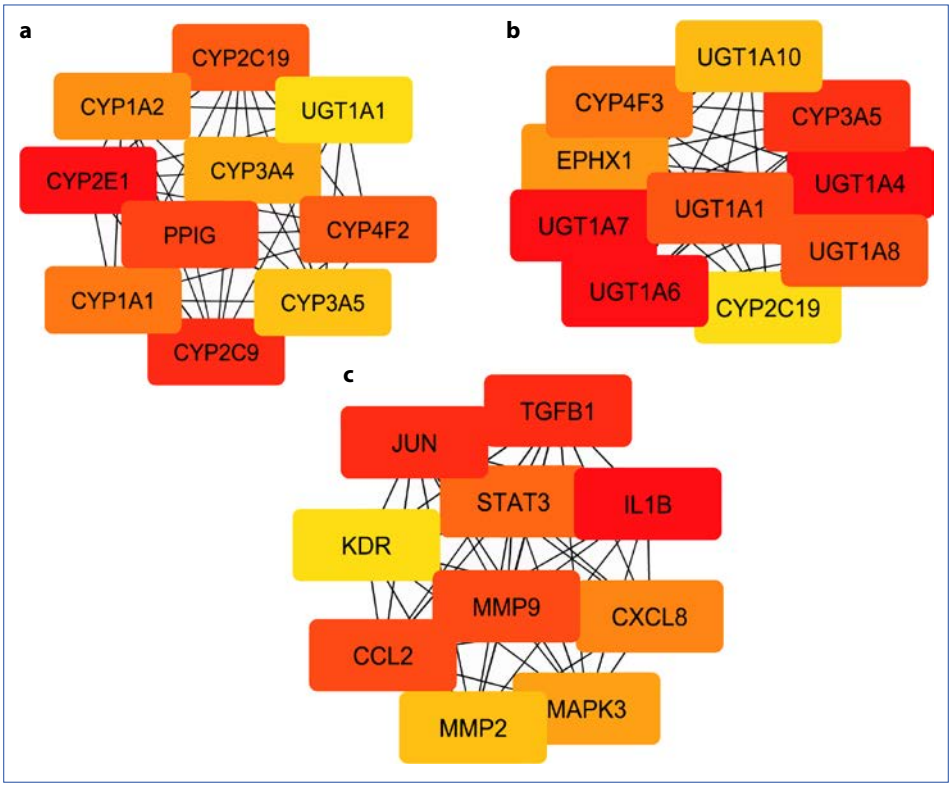

Figure 2. The clustering of the top 10 genes of AS related to skin aging according to MCC (a), DMNC (b), and MNC algorithm (c) in CytoHubba.

AS: Asiaticoside; MCC: Maximal clique centrality; DMNC: Density of maximum neighborhood component; MNC: Maximum neighborhood component.

Results

AS (Fig. 1a) is a saponin glycoside with sugar molecules (glucose-glucose-rhamnose) that are attached to the triterpene group [37]. Using the specified screening criteria, two data sets were generated through the Venn diagram tool. A total of 19,608 genes involved in the skin aging process were compared with 68 genes that interacted with AS. Venn diagram analysis identified 86 genes associated with asiaticoside that are linked to skin aging (Fig. 1b). The PPI network showed that 86 gene targets of AS interact with each other to produce two major interconnected networks (Fig. 1c). Since asiaticoside coexists with madecassoside in plant extract, we further conducted bioinformatics and molecular docking analysis of both compounds in the skin aging process.

Madecassoside (MS) is a triterpenoid saponin (Appendix 1a), which has been studied for its anti-inflammatory and wound-healing properties [10]. AS, in combination with MS, targets 21 genes related to the skin aging process, all of which are metabolic enzymes such as cytochrome P450 (CYP), arachidonate 5-lipoxygenase (ALOX5), UDP-glucuronosyltransferases (UGTs), cytochrome P450 oxidoreductase (POR), and peptidylprolyl isomerase G (PPIG) (Appendix 1b, c). Furthermore, the MCC, DMNC, and MNC methodologies quantify gene interactions based on interaction degree, with each approach identifying the highest-ranking genes within the top 10 results of the analysis. The ranks, shown in Figure 2, sequence the genes most affected by AS that contribute to skin aging. There was only one independent cluster based on each algorithm. The genes targeted by AS with the highest scores based on the MCC algorithm are CYP2E1 and CYP2C9 (Fig. 2a). Meanwhile, based on the DMNC algorithm: UGT1A7, UGT1A6, UGT1A4, and CYP3A5 were identified (Fig. 2b), and based on the MNC algorithm, there are IL-1β, JUN, and TGF-β1 (Fig. 2c). The biological functions of the genes related to skin aging, based on MNC data, are presented and analyzed in Table 1. When combined with MS, the top target genes based on MCC, DMNC, and MNC are subclasses of CYPs (CYP3A5, CYP1A2) (Appendix 2).

Molecular docking studies were conducted to predict the potential binding of AS, and further studies were carried out to investigate the relationship between anti-aging-related genes and AS. We selected IL-1B and MMP-9 as target genes for molecular docking with AS. MMP-9 and AS showed eight H-bonds to Pro421, His401, His411, Leu397, Leu418, Glu402, Leu188, and Ala189 (Fig. 3). UGTs are seen to have multiple hydrophobic bonds with Leu110 at IL-1B and Leu188, Val398, and Tyr423 at MMP9. In this process, AS showed lower binding energy at MMP-9, which is –8.16 kcal/mol, compared to –5.57 kcal/mol at IL-1B (Table 2), where AS has Van der Waals interactions with Asp12, Asn108, and Lys109 on IL-1B, as well as with Phe110, Ala191, His190, His405, Tyr420, Met422, Leu187,

Table 1. Top 10 proteins network interaction ranked by MNC algorithm

No	Gene symbol	Gene/protein name/abbreviation	Biological function related to skin aging	Reference
1	IL-1β	Interleukin 1β	IL-1β is an inflammatory mediator that is induced by main mediators in the inflammatory responses (CCL-2), activating signaling activities of STAT-3. The maturation and release of IL-1β is regulated by an inflammatory signaling platform called inflammasome.	[70–74]
2	JUN	c-Jun	Activated by ERK pathways. Combines with c-Fos to form the transcription factor AP-1 which stimulates MMP-2/9 transcription. Increased MMP transcription accelerates the degradation of collagen.	[39, 45]
3	TGF-β1	Transforming Growth Factor β1	TGF-β1 is a one of TGF-β isoform that induced Smad 2 and Smad 3 phosphorylation which function as a transcriptional activator to induced MMP-2/ 9 transcription.	[50, 54, 58]
4	CCL-2	Chemokine (C-C motif) ligand 2	Also known as monocyte chemotactic/chemoattractant protein 1 (MCP). CCL-2 is an inflammatory chemokine secreted by macrophage that induces activation to promote inflammation after binding to its ligand CCR-2. CCL-2 activates a series of downstream signals such as JAK which then activates phosphorylation STAT 3/5 which then activates phosphorylation IL-1β/CXCL-8.	[75–77]
5	MMP-9	Matrix metalloproteinase 9	MMP-9 is known as gelatinase B. The expression of MMP-9 is stimulated by AP-1 and produced by keratinocytes. MMP-9 can degrade gelatin types I and V, collagen types IV and V, fibronectin in dermal fibroblast cells located in the ECM thereby stimulating skin aging.	[18, 44, 52, 78–81]
6	STAT-3	Signal Transducer and Activator of Transcription 3	Activated by CCL-2 which then lead to upregulation expression of MMP-2/9. The STAT-3 pathway is activated in response to several cytokines, including IL-1β and CXCL-8.	[66, 73, 76, 82]
7	MAPK-3	Mitogen-Activated Protein Kinase 3	Also known as extracellular signal-regulated kinases (ERKs), it is present in the cytoplasm and translocated into the nucleus. MAPK-3 (JNK, ERK, and p38) transfers extracellular signals to the nucleus, thereby activating transcription factors and inducing AP-1 as a downstream activator of MAPK, which then induced and regulates the transcription of MMP 2/9.	[15, 17]
8	CXCL-8	Chemokine (C-X-C motif) ligand 8	Also known as IL-8, activated by CCL-2 signaling pathway which then activates the phosphorylation of JAKs and STAT3.	[67, 77, 83, 84]
9	MMP-2	Matrix Metalloproteinase 2	MMP-2 is known as gelatinase A. The expression of MMP-2 is stimulated by AP-1 and produced by keratinocytes. MMP-2 can degrade gelatin type I, collagen types IV, V, VII, X in dermal fibroblast cells located in the ECM thereby stimulating skin aging.	[18, 42, 52, 78–81]
10	KDR	Kinase insert Domain Receptor	Also referred to as VEGFR-2, VEGF receptor is bound by VEGF-A, activating downstream pathways like MAPK1/3, which then regulates transcription factors AP-1 (c-Jun, c-Fos).	[46, 85, 86]

MNC: Maximum neighborhood component.

Tyr393, and Gly186 on MMP9 (Fig. 3). This study is considered valid based on the calculation of RMSD control, where the value for IL1B was 1.74 Å and for MMP9 was 1.65 Å. These results allow the specific binding of AS to MMP9, where the genes play important roles in the anti-aging pathway.

Furthermore, we conducted molecular docking of AS and MS to CYP3A5 as one of the possible molecular targets based on MCC, DMNC, and MNC algorithms. AS indicated a lower binding energy of –11.82 kcal/mol than MS to CYP3A5 (–10.43 kcal/mol). AS has Van der Waals interactions with Leu108, Ser107, Leu120, Phe220, Gly306, Thr309, Thr310, Val313, Phe367, Pro368, Ala447, Met451, and Leu481. It also formed hydrogen bonds with Arg106, Phe213, Val369, and Glu374. On the other hand, MS interacts with CYP3A5 through hydrogen bonding at Arg106, Ser107, Gly109, Ala305, Thr309, Glu308, Phe304, and Phe434. It binds considerably to Arg105, Leu108, Ser119, Leu120, Phe210, Ile303, Gly306, Tyr307, Val369, Ala370, Arg372, Leu373, Glu374, Arg375, Pro433, Arg439, Asn440, Cys441, Gly435, and Leu481 through Van der Waals interactions (Appendix 3, 4). These findings are validated by confirming the binding energy of clobetasol propionate as the control, with a binding energy value of 8.11 kcal/mol.

Through a literature review, this study predicted the molecular cascade pathway illustrated in Figure 4. TGF-β1 (Transforming Growth Factor-β1), VEGFA (Vascular Endothelial Growth Factor A), EGF (Epidermal Growth Factor), and CCL-2 (Chemokine (C-C motif) ligand 2) bind to their respective receptors, triggering a molecular cascade within the cytoplasm. This cascade eventually leads to the phosphorylation of MMP-2/9 in the ECM, resulting in collagen degradation. AS is predicted to interact with certain molecules, inhibiting skin aging.

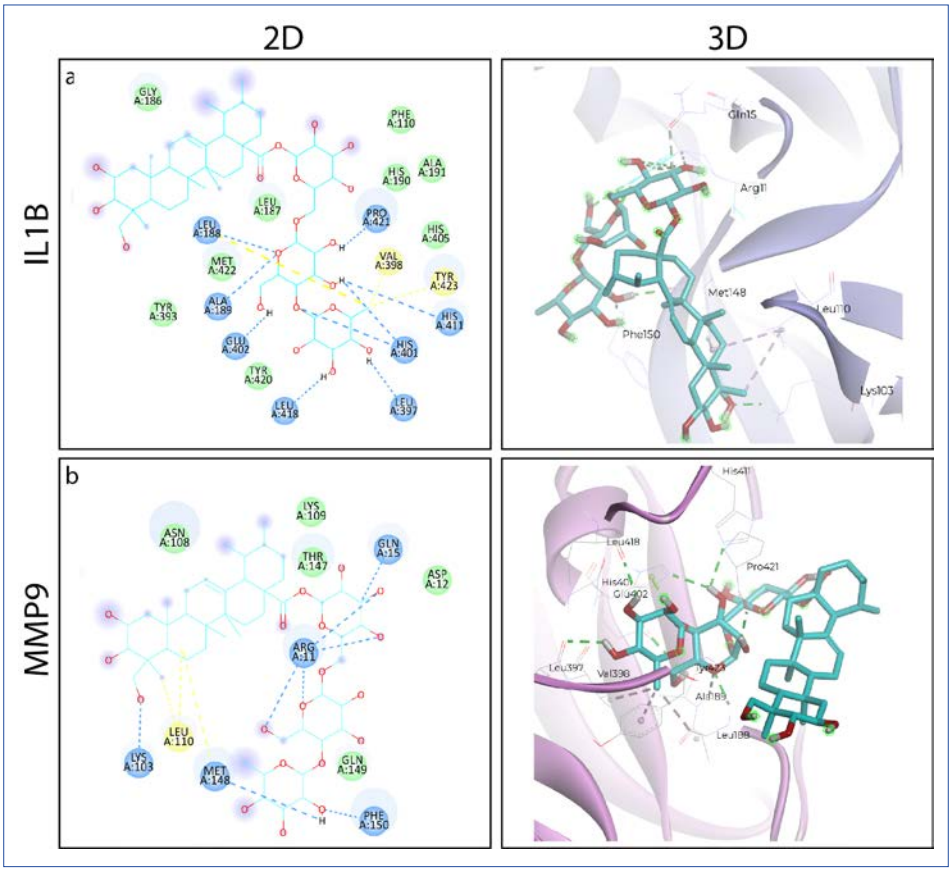

Figure 3. The binding poses of AS in IL1B and MMP-9 binding pocket in 2D and 3D view. Yellow, red, and white indicated carbon, oxygen, and hydrogen atoms. Yellow, blue, and green indicated hydrophobic bond, hydrogen bond, van der waals interaction.

IL1B: Interleukin 1β; MMP: Matrix metalloproteinase; AS: Asiaticoside.

Discussion

This study is the first to explore AS's impact on molecular pathways associated with skin aging, examining upstream and downstream elements within these routes (Fig. 4). The gene targets obtained in this study differed from previous bioinformatics studies of AS in skin aging due to the use of different databases such as PharmMapper, SwissTargetPrediction, CTD, and BATMAN, as well as analysis tools. While Huang and colleagues' study demonstrated that AS targeted apoptosis and inflammation-related signaling pathways [38], our findings suggest that AS targeted both inflammation-related signaling pathways and ECM degradation enzymes.

Skin aging is a complex biological phenomenon linked to the increased expression of genes that contribute to ECM breakdown [11, 39]. Comprising an adaptable, three-dimensional network of macromolecules, the ECM provides both biochemical and structural support to neighboring cells, while its specialized biochemical and biomechanical properties regulate key physiological activities such as cell growth, migration, and homeostasis [40, 41]. One of the cell types that secrete components in the ECM is glycoproteins, which contain proteoglycans, collagen, fibronectin, elastin, and laminins [42].

As the predominant structural protein within the extracellular matrix, collagen is present in substantial quantities and is susceptible to degradation, which then triggers the downregulation of the ECM [43]. Collagen degradation is primarily driven by extrinsic factors, particularly UV radiation [11, 14, 41, 44, 45]. However, even in the absence of sunlight exposure, aging leads to a decline in collagen production, attributed to genetically regulated apoptosis, mitochondrial dysfunction, and diminished antioxidant defense mechanisms [46]. These factors lead to an upregulation of enzymes that break down the ECM [14, 41]. This is due to differences in MMP concentrations and the four protease inhibitors, known as tissue inhibitors of matrix metalloproteinases (TIMPs), that modulate MMP activity [47]. Specifically, MMP expression increases, while the expression of TIMPs decreases [6, 48]. MMPs represent an extensive group of zinc-dependent endopeptidases capable of breaking down ECM proteins [11, 14, 45, 49, 50]. Among them, MMP-2 and MMP-9 are key ECM enzymes essential for ECM degradation, a process driven by endopeptidase activity [11, 40, 48, 51].

The activation of MMPs is triggered by various factors such as TGF-β, VEGF, and epidermal growth factor (EGF) [52]. EGF binds to its receptor (EGFR) on the cell surface and then combines with the Src homology 2 (SH2) domain of the growth-factor-

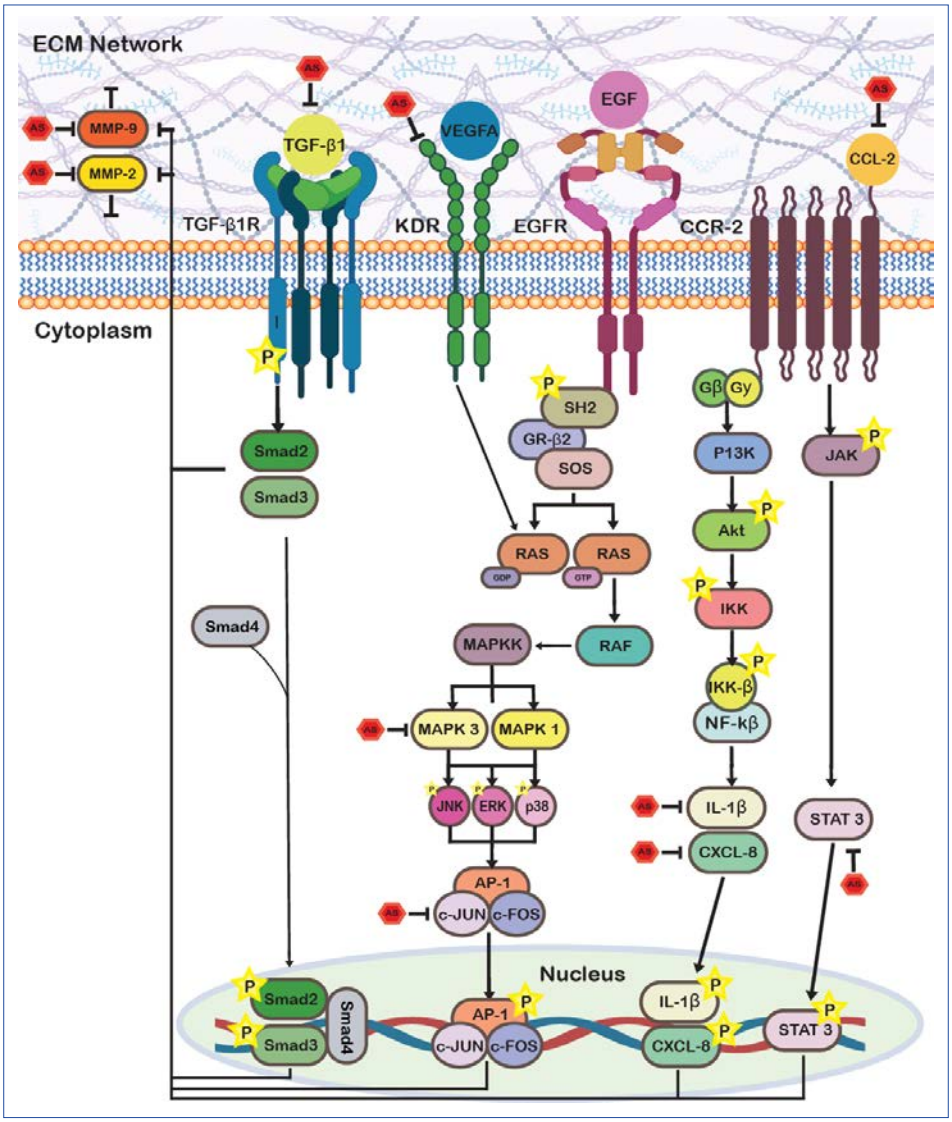

Figure 4. Predicted molecular cascade of AS in skin aging.

IL-1β: Interleukin 1β; JUN: c-Jun; TGF-β1: Transforming growth factor β1; CCL-2: Chemokine (C-C motif) ligand 2; MMP-9: Matrix metalloproteinase 9; STAT-3: Signal transducer and activator of transcription 3; MAPK-3: Mitogen-activated protein kinase 3; CXCL-8: Chemokine (C-X-C motif) ligand 8; MMP-2: Matrix metalloproteinase 2; KDR: Kinase insert domain receptor; AS: Asiaticoside.

receptor-binding protein 2 (GRB2). Simultaneously, GRB2 binds to the ornithine conversion factor, Son of Sevenless (SoS), promoting the activation of the Rat Sarcoma Virus (RAS) protein, a small GTPase. Upon activation, RAS recruits and activates downstream RAF (Rapidly Accelerated Fibrosarcoma) kinases [52, 53]. Subsequently, the activated RAF phosphorylates and triggers mitogen-activated protein kinase kinase (MAPKK) signaling [46]. Activated MAPKK phosphorylates mitogen-ac-

Table 2. Molecular docking of asiaticoside with IL-1β (6Y8I) and MMP-9 (1GKC)

Target protein	Binding energy (kcal/mol)	H-bond residues	Hydrophobic residues	Van der Waals residues
IL-1β	-5.57	Phe150, Met148, Arg11, Lys103, Thr147, Gln15, Gln149	Leu110	Asp12, Asn108, Lys109
MMP-9	-8.16	Pro421, His401, His411, Leu397, Leu418, Glu402, Leu188, Ala189	Val398, Tyr423	Phe110, Ala191, His190, His405, Tyr420, Met422, Leu187, Tyr393, Gly186

IL-1β: Interleukin 1β; MMP-9: Matrix metalloproteinase 9; Phe: Phenylalanine; Met: Methionine; Arg: Arginine; Lys: Lysine; Gln: Glutamine; Leu: Leucine; Asp: Aspartatic acid; Asn: Asparagine; Pro: Proline; His: Histidine; Glu: Glutamic acid; Val: Valine; Tyr: Tyrosine.

tivated protein kinases (MAPKs), such as MAPK-1/3, which subsequently phosphorylate the JNK, ERK, and p38 signaling pathways [41, 54]. This leads to the phosphorylation of the AP-1 complex (c-Fos and c-Jun), which translocates into the nucleus to directly regulate MMP-2/9 expression within the extracellular matrix (ECM) network [5, 39, 41, 44]. AP-1 indirectly suppresses collagen biosynthesis and promotes collagen degradation through multiple mechanisms. It alters the balance between MMPs and TIMPs, favoring MMP dominance. When MMPs prevail over TIMPs, collagen and other fibrillar structures undergo degradation [48]. RAS downstream signaling pathways are also activated by VEGFA binding to its receptor, KDR [55].

Meanwhile, TGF-β1, TGF-β2, and TGF-β3, the three isoforms of the transforming growth factor (TGF-β) subfamily, play distinct roles in various biological processes [56]. TGF-β plays a crucial role in regulating ECM synthesis and managing collagen breakdown through activation of the Smad signaling pathway [11]. TGF-β1 modulates the expression of several MMPs, including MMP-2 and MMP-9, contributing to extracellular matrix remodeling. TGF-β1 increases the activation of MMP-2/9 via phosphorylation of the transcription factors Smad-2/3 (canonical Smad signaling) facilitated by its receptors (TGF-βR1 and TGF-βR2), which assemble into homodimeric and heterodimeric complexes essential for signaling [48, 54, 57]. Smad-2/3 then complexes with Smad4 and translocates to the nucleus, inducing the expression of MMP-2/9 [50, 54, 58].

The upregulation of MMP-2/9 is further initiated by the activation of CCL-2 (MCP-1) [59–62]. CCL-2 plays a critical role in driving disease progression by enabling the attraction of immune cells like monocytes and macrophages to inflammatory sites, thereby enhancing immune cell infiltration and contributing to fibrotic tissue remodeling [62, 63]. Upon binding to its receptor, C-C motif chemokine receptor 2 (CCR-2), CCL-2 activates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) and JAK/STAT pathways [62]. The PI3K/Akt pathway triggers NF-κB, which then moves into the cell nucleus to begin gene transcription, leading to the expression of factors like interleukin-1β (IL-1β) and chemokine (C-X-C motif) ligand 8 (CXCL-8), ultimately resulting in the production and release of these cytokines [41, 52, 59, 63–65]. CCL-2/CCR-2 signaling also activates the JAK/STAT pathway through the stimulation of Janus kinase 2 (JAK-2), which subsequently triggers downstream signaling cascades, including the activation of STAT3/5. This ultimately regulates the transcriptional activation of MMP-2/9, thereby exacerbating the detrimental effects on the skin [64, 66, 67].

Additionally, earlier research has shown that AS reduces TGF-β1 expression by decreasing its mRNA synthesis [10, 29]. Beyond its anti-fibrotic actions, AS also possesses potent anti-inflammatory effects by blocking IL-1β production, further supporting its potential therapeutic role in skin aging and fibrosis [68]. In Figure 4, AS has been shown to inhibit several key molecular targets, including MMP-2/9, CXCL-8, KDR, c-Jun, CCL-2, STAT3, and MAPK3, demonstrating its potential therapeutic role in mitigating skin damage and fibrosis by modulating both upstream and downstream components of these pathways.

Since AS and MS are terpenoid saponins, AS often coexists with MS in plant extract. Both of them inhibit metabolic enzymes related to skin aging, mainly CYPs and UGTs. During the aging process, oxidative stress contributes to the propagation of ROS and reduces enzymatic protection [69]. CYP subclasses are expressed in different skin layers and are responsible for several vitamin metabolisms, including retinoid acid, which contributes to skin aging. One of CYP's AS and MS targets is CYP3A5, which is primarily expressed in the basal layer of the skin epidermis [10]. To date, the findings of this study have initiated further research to confirm *in vitro* and *in vivo* skin aging experiments with the help of network pharmacology analysis through bioinformatics and molecular docking.

Conclusion

Based on bioinformatics analysis, asiaticoside (AS) has been identified to target a wide range of key proteins involved in skin aging. These proteins function collaboratively within various molecular pathways, enhancing the therapeutic potential of AS in combating extracellular matrix (ECM) degradation and inflammation. AS modulates both upstream and downstream signaling mechanisms, including those involving MMP-2/9, TGF-β1, IL-1β, CXCL-8, KDR, c-Jun, CCL-2, STAT3, and MAPK3, to inhibit processes that contribute to skin aging. These findings provide crucial foundational data for further investigation into AS's *in vitro* and *in vivo* activities. AS's ability to regulate multiple molecular targets positions it as a promising candidate for anti-aging therapy. Further exploration of its clinical efficacy is warranted.

Appendix files: https://jag.journalagent.com/ijmb/abs_files/IJMB-26122/IJMB-26122_(2)_IJMB-26122_Appendixes.pdf

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