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Therapeutic Mechanisms of α-/β-Hydroxy Acid Complex on Skin Sebum Balance and Acne via Network Pharmacology

Xiaoyu Ma[1], Jiahong Guo[1], Fernando Bouffard[2], Nianping Feng[3], Sophia Yi Zhang[1, *]

[1]Innoceuticals Research & Development Center of Hundred Splendor Group, Shanghai, China

[2]Innoaesthetics, Barcelona, Spain

[3]Department of Pharmaceutical Sciences, Shanghai University of Traditional Chinese Medicine, Shanghai, China

Email address:

maxiaoyu@inno-sh.cn (Xiaoyu Ma), guojiahong@inno-sh.cn (Jiahong Guo), fernando@innoaesthetics.com (F. Bouffard), npfeng@shutcm.edu.cn (Nianping Feng), yuli26@163.com (Sophia Yi Zhang)

[*]Corresponding author

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Abstract: Acne is a complicated and chronic inflammatory skin disorder, frequently existed at areas with thriving lipid secretion. Among various cosmetic actives, hydroxy acids (HA) emerged as one of the most effective ingredients, and a combination of HAs could provide a synergistic effect and better therapeutic outcome to acne. However, there was no systematic analysis and prediction to explain the synergistic mechanism. The aim of this study was to undercover the overlapping gene targets of formula ingredients and skin diseases, as well as possible interconnected pathways, thus to have a deeper understanding on the function of complex formula. Network pharmacology was utilized to obtain the gene targets of each active against acne and sebum balance. Molecular function, biological process, cellular component and signaling pathway were calculated through protein-protein interaction (PPI) and enrichment analysis. Furthermore, interaction mapping among actives, biological processes and pathways were established by Cytoscape software. 283 targets of HAs-based formula against acne/sebum balance were obtained. 10 hub genes including ALB, EGFR, AKT1, MMP9, SRC, HRAS, CCL5, IL2, CAT and KDR were also achieved. The interaction between hub genes, biological processes and pathways were visualized into network mappings. All the targets contributed to the improvement of acne via sebum modulation, anti-oxidation and immune regulation. Network pharmacology acted as an effective method in exploring the multi-ingredient formula. Through the precise target and pathway analysis, this study showed that HAs-based formula could function in multiple dimensions to regulate the balance of sebum secretion and ameliorate the damage of acne.

Keywords: Hydroxy Acid, Systematic Pharmacology, Acne, Sebum Balance

1. Introduction

Hydroxy acids (HAs), including both α- and β- hydroxy acids (AHAs and BHAs), are naturally-occurring organic acids that endow exfoliation and accelerate epidermal metabolism [1]. AHAs are able to induce bond cleavage between keratinocytes, and expedite cell cycle. BHAs boost the same mechanism of action as AHA, but are more lipophilic. As a result, BHAs have easier access to pilosebaceous unit [2], thus being highly effective in oily skin type. Give that, HAs are especially suitable therapeutic agents in seborrheic keratosis [3], acne [4] and other skin diseases.

However, the selection of HAs is an exquisite process, where concentration, combination and cooperation with other ingredients can greatly influence the ultimate skin functions. For instance, glycolic acid with high dosage exhibited phototoxic behavior, and induced severe skin irritation or chemical burns. Instead, glycolic acid at lower concentration substantially inhibited UVB-induced cytokines and chemokines, providing photoprotection [5]. In another report, it was found that HAs could exert synergistic effect with PAR2

inhibitor in atopic dermatitis [6], proving that complementary actives might further strengthen the efficacy of HAs. In addition, combination peels have already shown its superiority due to its adjustability. Incorporation of lactic acid would endow moisturizing property [7] to the HAs system while BHA such as salicylic acid could regulate the arachidonic acid cascade to present anti-inflammatory capabilities. Given that, it is of great importance to design a rational HAs-based combination to take full advantage of HAs.

Among various HAs, glycolic acid (GA), lactic acid (LA), citric acid (CA) and salicylic acid (SA) stands out as the most commonly employed actives in cosmetic field, especially in skin sebum balance and acne treatment. GA, LA, and CA are first-generation fruit acids, with excellent exfoliating ability to disrupt the cohesion of corneocytes while maintaining unique individual features. As the smallest AHA, GA has great permeability and highly effective in improving hyperkeratinization. CA, a triprotic acid, possesses anti-microbial properties and are not as invasive as GA. LA, however, brings extra skin functions such as moisturizing [8], or acts as probiotic ingredient to offer anti-inflammatory [5] effect by mediating substance P. SA excels other acids due to better penetration into the comedones. Meanwhile, SA is capable of alleviating inflammation [9] and sebum secretion [10]. Apart from HAs, hydroxytyrosol is also an effective ingredient covering multiple functions. It is not only a well-recognized anti-oxidative agent, but also an inflammation regulator via cytokines reduction [11] or autophagy [12]. It is hypothesized that combination of above actives might target a series of biological processes and molecular functions, leading to a more holistic improvement in acne and sebum balance via multiple signal pathways. Nevertheless, there's few studies have investigated the synergistic effect or mechanism of multi-HA formula.

In this study, we incorporated network pharmacology into the HAs-based complex to explore the systematic effect on acne treatment and sebum balance. Hub genes were firstly identified through PPI analysis. Based on the gene information, molecular function, biological process, cellular component and signaling pathway were subsequently acquired through enrichment analysis. The visualized network between actives, biological process, signal pathways and skin symptoms were established to reveal the interconnected mechanism of the formula. This study could provide theoretical insights on the precise targets and mechanisms by meta-data analysis and HA combinations formula design. Moreover, it could deliver a novel guidance for future investigations.

2. Materials and Methods

2.1. Identification of Active Components

α-/β-Hydroxy acid complex designed in this study was composed of glycolic acid, lactic acid, citric acid, salicylic acid and hydroxytyrosol. Each of the above ingredients was retrieved in Pubchem Database to collect the molecular formula, molecular weight, CAS number and 3D structure.

2.2. Target Retrieval of Active Components

PharmMapper, one of the network pharmacology analyzing tool, was employed to predict the function targets of five actives in the complex, where Human Protein Targets Only (v2010, 2241) [13] served as the database. After the screening process, only the top 300 related targets were reserved. The median number was then used to further narrow down the obtained targets. Gene mode in NCBI was subsequently utilized to standardize the target information and generate related target list.

2.3. Target Retrieval of Skin Sebum Balance and Acne

The GENECARD Database [14] was used to search for the potential targets towards sebum balance and acne, two closely related skin symptoms addressed by HAs-based complex. Targets were then collected after screening by median number and deleting the repeated ones.

2.4. Intersection Between Target Genes of Actives and Acne/Sebum Balance

Based on target retrieval from both actives and skin symptoms, a visualized network was then established. Venn diagram was set up to reveal the overlapping target genes. Meanwhile, String Database was used to perform the protein-protein interaction analysis to generate the network diagram.

2.5. Enrichment Analysis

The overlapping targets from both actives and skin symptoms were selected for enrichment analysis, including both Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment, and gene ontology (GO) enrichment. Through enrichment analysis, molecular function (MF), biological process (BP), cellular component (CC) and signaling pathway against acne and sebum balance could be explored. Hypergeometric Distribution Model (1) was applied to evaluate the relevance between target gene set and gene ontology, or biological pathway.

$$P = 1 - \sum_{i=0}^{k-1} \frac{\binom{M}{i}\binom{N-M}{n-i}}{\binom{N}{n}} \quad (1)$$

N represented the total gene number, M was the number of annotated genes in a pathway, n was the targets in designed formula and k was the shared gene number. P value was adjusted through Bonferroni method, revealing the relation between overlapping genes and signaling pathways or GO. When P adjust was less than 0.01, it could be recognized significantly correlated. The software package for enrichment analysis was clusterProfiler package version 3.15.4, based on R platform.

2.6. Construction of "Active Compound-Target-Pathway" Network

Cytoscape [15] software was used to generate the network

of "Active Compound-Target-Pathway". Ten hub genes was first collected by using bioinformatic plug cytoscapehub". The network between hub genes and biological process, as well as the hub genes and signaling pathways were then set up.

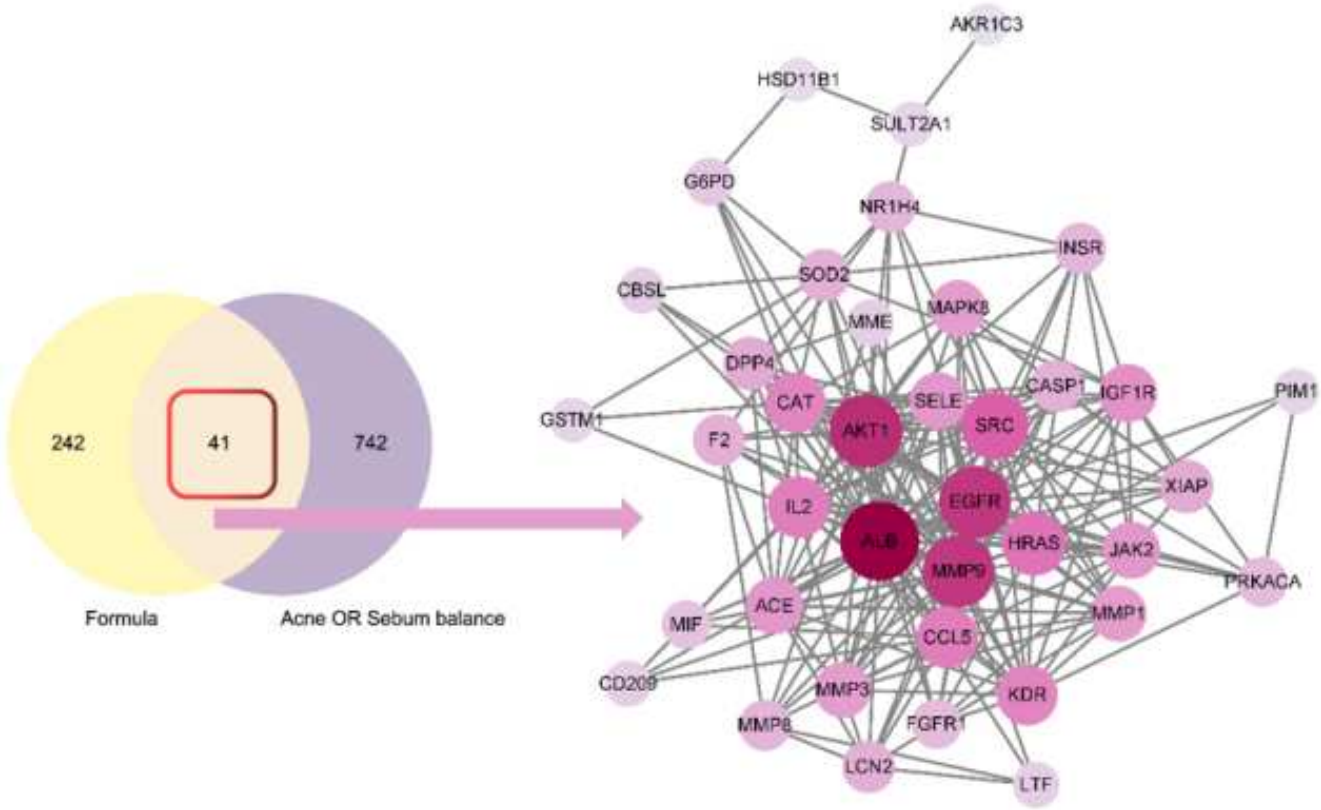

Figure 1. *Venn diagram of the overlapping targets between HAs-based compound and acne/sebum and protein-protein interaction (PPI) network of 41 putative targets.*

3. Results

3.1. Target Identification and PPI Network

Table 1. *Physical and chemical information of HAs-based compound.*

Actives	CAS	Molecular formula	Molecular weight	Molecular structure
Glycolic acid	79-14-1	$C_2H_4O_3$	76.05	
Citric acid	77-92-9	$C_6H_8O_7$	192.12	
Salicylic acid	69-72-7	$C_7H_6O_3$	138.12	
Lactic acid	50-21-5	$C_3H_6O_3$	90.08	
Hydroxyt yrosol	10597-60-1	$C_8H_{10}O_3$	154.16	

The HAs-based compound consisted of five critical ingredients, namely, glycolic acid, lactic acid, citric acid, salicylic acid and hydroxytyrosol. The actives information, including CAS number, molecular formula, molecular weight and 3D molecular structure were collected from PubChem database, as listed in Table 1. After retrieval, 157, 145, 116 targets were identified for glycolic acid, lactic acid and hydroxytyrosol (Norm Fit≥0.3800), 110 targets were screened out for salicylic acid (Norm Fit≥0.3664), and 147 targets were extracted for citric acid (Norm Fit≥0.5576). After deleting the overlapping ones, 283 targets were reserved. At the same time, 783 gene targets (out of 181,708) within acne/sebum balance were also identified. A Venn diagram of the two target sets was then utilized to obtain 41 intersection targets (as shown in Figure 1). Based on the bioinformatic results, the pharmacological targets of HAs-based compound against acne and sebum balance were summarized in Table 2 and the PPI network was thus established in Figure 1 to visualize the target-target interaction.

Table 2. *41 putative targets for HAs-based compound in acne/sebum balance.*

ID	Name	ID	Name
1636	ACE	90459	ERI1
8644	AKR1C3	2147	F2
207	AKT1	2260	FGFR1
213	ALB	2539	G6PD
834	CASP1	2944	GSTM1
847	CAT	3176	HNMT
875	CBS	3265	HRAS
6352	CCL5	3290	HSD11B1

ID	Name	ID	Name
30835	CD209	3480	IGF1R
1803	DPP4	3558	IL2
1956	EGFR	331	XIAP
3643	INSR	4317	MMP8
3717	JAK2	4318	MMP9
3791	KDR	9971	NR1H4
3934	LCN2	5292	PIM1
4057	LTF	5566	PRKACA
5599	MAPK8	6401	SELE
4282	MIF	6648	SOD2
4311	MME	6714	SRC
4312	MMP1	6822	SULT2A1
4314	MMP3		

3.2. Core Targets of HAs-Based Compound in Acne/Sebum Balance

The proteins network was further imported into Cytoscape software to calculate the topological parameters of HAs-based compound against acne/sebum balance targets and function-related proteins. As revealed in Figure 2, ten most important targets were ALB, EGFR, AKT1, MMP9, SRC, HRAS, CCL5, IL2, CAT and KDR.

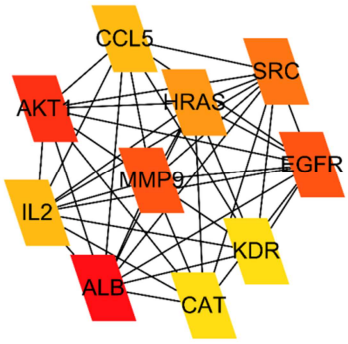

Figure 2. *Ten core targets of HAs-based compound in acne/sebum balance.*

3.3. Core Targets in GO and KEGG Pathway Enrichment

GO and KEGG pathway analysis was utilized on the basis of core genes above. The results were visualized by both bubble diagram and histogram, where the P adjust represented the significance of target enrichment and the area of the bubble represented the count number. According to the findings, there were 67, 762, 19 and 97 annotations on molecular functions, biological process, cellular components and signaling pathways, respectively.

Figure 2 revealed the top 15 enrichment in molecular functions and cellular components. The top 5 related terms in MF were serine hydrolase activity, serine-type peptidase activity, protein tyrosine kinase activity, endopeptidase activity and serine-type endopeptidase activity. The most related terms in CC were membrane region, membrane microdomain, membrane raft, plasma membrane raft and vesicle lumen.

The most related biological process was summarized in Figure 4. It could be seen that the most related process were phosphatidylinositol 3-kiase signaling, inositol lipid-mediated signaling, phosphatidylinositol-mediated signaling, regulation of phosphatidylinositol 3-kinase signaling, cellular response to oxidative stress, protein autophosphorylation, reactive oxygen species metabolic process, response to reactive oxygen species, response to lipopolysaccharide, cellular response to reactive oxygen species, response to oxidative stress, response to molecule of bacterial origin, peptidyl-tyrosine autophosphorylation and peptidyl-tyrosine phosphorylation. Meanwhile, the relation between theses biological processes and core targets of HAs-based compound in acne/sebum balance were demonstrated in Figure 4(C).

The KEGG pathway analysis was also an important indicator in exploring the possible signal pathway and function scenario of HAs-based compound. As showed in Figure 5, the related pathways included lipid and atherosclerosis, longevity regulating pathway-multiple species, endocrine resistance, EGFR tyrosine kinase inhibitor resistance, Relaxin signaling pathway, FoxO signaling pathway, longevity regulating pathway, prostate cancer, proteoglycans in cancer, C-type lectin receptor signaling pathway, chemical carcinogenesis-reactive oxygen species, Ras signaling pathway, bladder cancer, fluid shear stress and atherosclerosis and focal adhesion. The network of pathways and core targets of HAs-based compound against acne/sebum balance were visualized in Figure 5(C). The detailed KEGG enrichment results were listed in Table 3.

Table 3. *KEGG enrichment analysis.*

ID	Description	p.adjust	Count
hsa05417	Lipid and atherosclerosis	2.91E-08	12
hsa04213	Longevity regulating pathway-multiple species	9.03E-07	7
hsa01522	Endocrine resistance	9.03E-07	8
hsa01521	EGFR tyrosine kinase inhibitor resistance	3.43E-06	7
hsa04926	Relaxin signaling pathway	4.44E-06	8
hsa04068	FoxO signaling pathway	4.44E-06	8
hsa04211	Longevity regulating pathway	4.51E-06	7
hsa05215	Prostate cancer	7.16E-06	7
hsa05205	Proteoglycans in cancer	7.45E-06	9
hsa04625	C-type lectin receptor signaling pathway	9.25E-06	7
hsa05208	Chemical carcinogenesis-reactive oxygen species	1.24E-05	9
hsa04014	Ras signaling pathway	1.59E-05	9
hsa05219	Bladder cancer	1.90E-05	5
hsa05418	Fluid shear stress and atherosclerosis	4.67E-05	7
hsa04510	Focal adhesion	4.67E-05	8

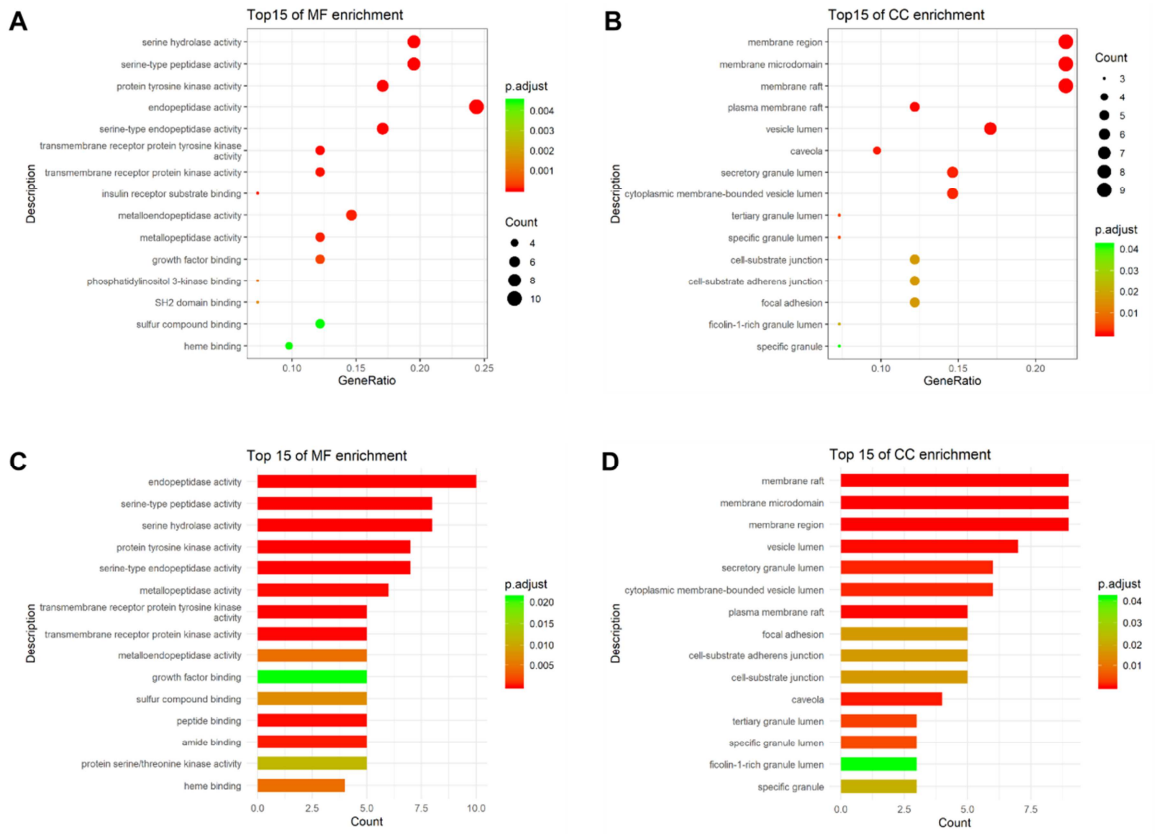

Figure 3. *(A, C) Molecular function and (B, D) cellular component of HAs-based compound.*

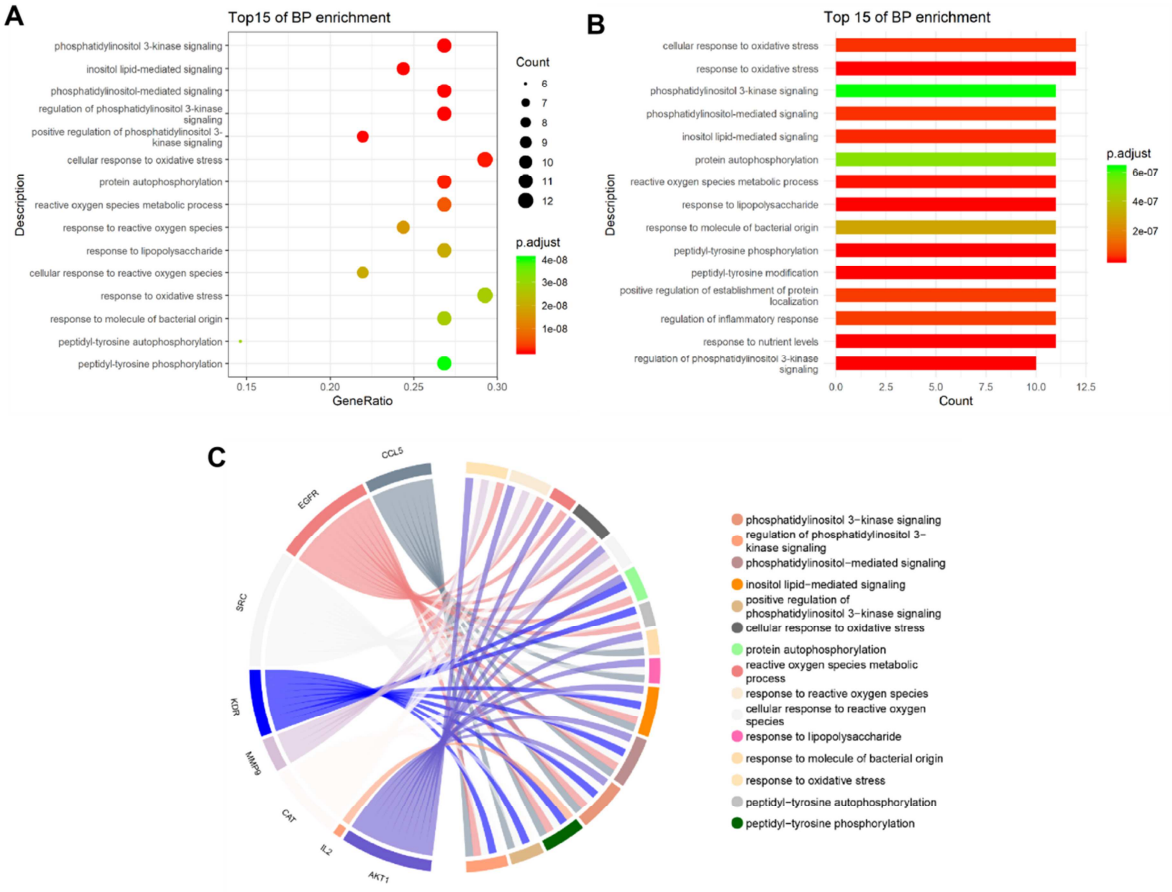

Figure 4. *(A) Bubble diagram, (B) Histogram of the biological process of HAs-based compound and (C) Network of core targets and biological process.*

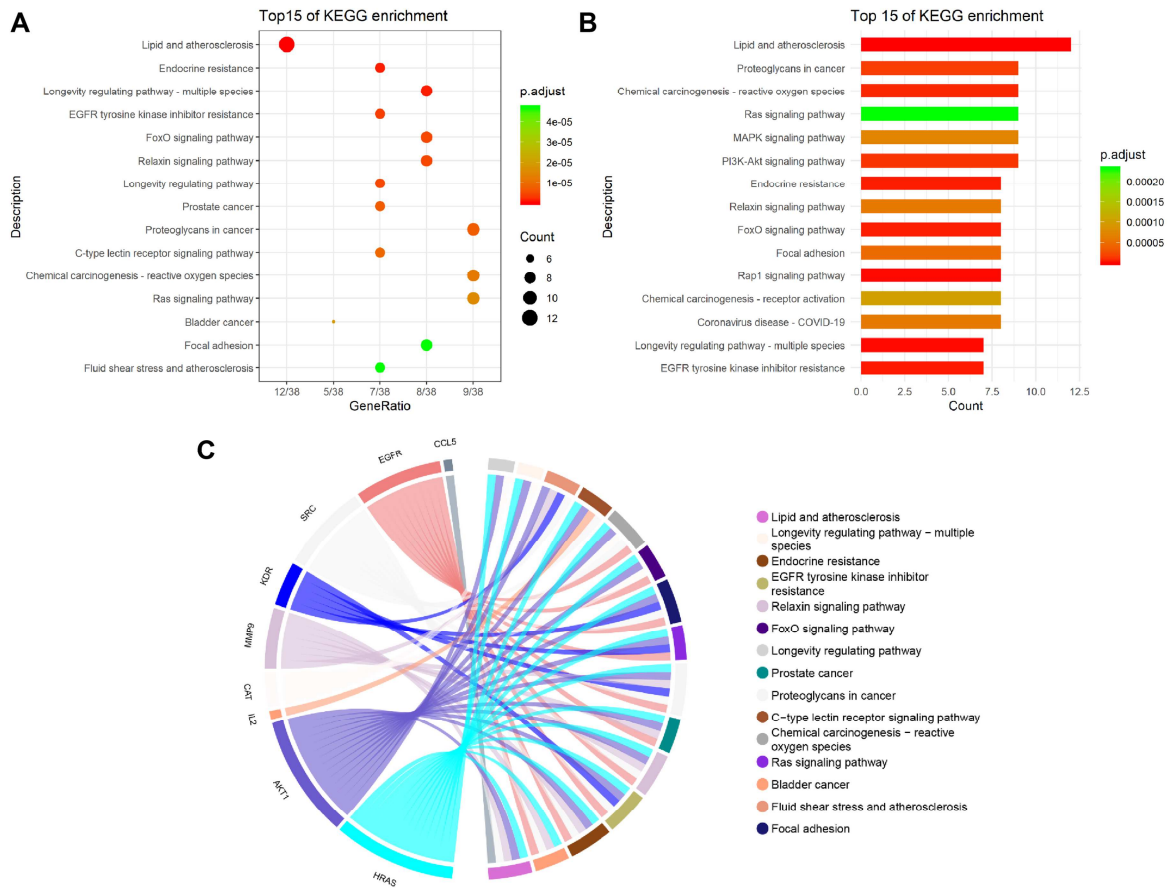

Figure 5. *(A) Bubble diagram, (B) Histogram of the KEGG pathways of HAs-based compound and (C) Network of core targets and signal pathways.*

3.4. Establishment of Network Diagram

Using Cytoscape software, the network of formula ingredients and gene targets in acne/sebum balance was established in Figure 6. At the same time, the interaction mapping of core target, biological process and pathways were generated, as shown in Figure 7. It was obvious that multiple biological processes and pathways were involved in the HA-based compound and contributed to the improvement of acne and sebum balance.

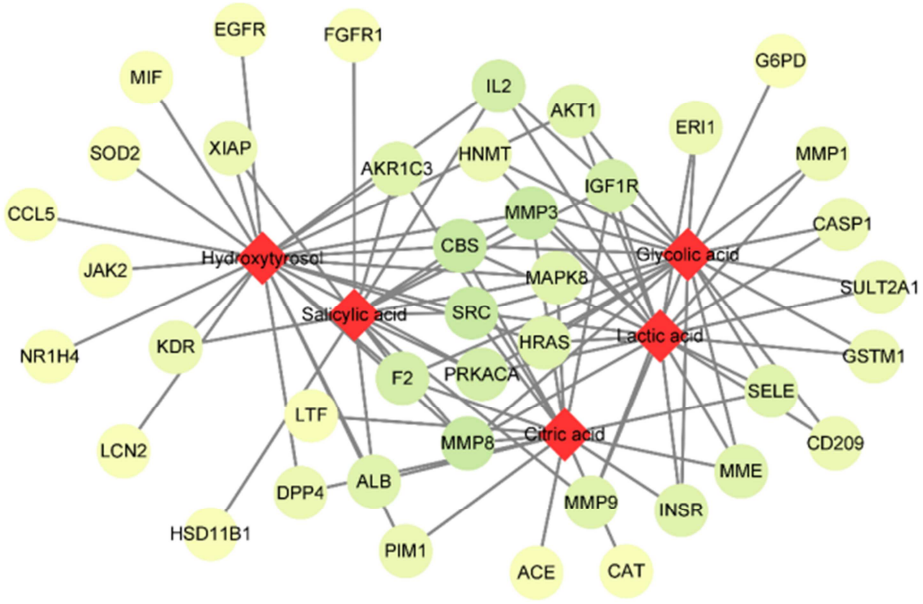

Figure 6. *Network of HAs-based compound against acne/sebum balance targets.*

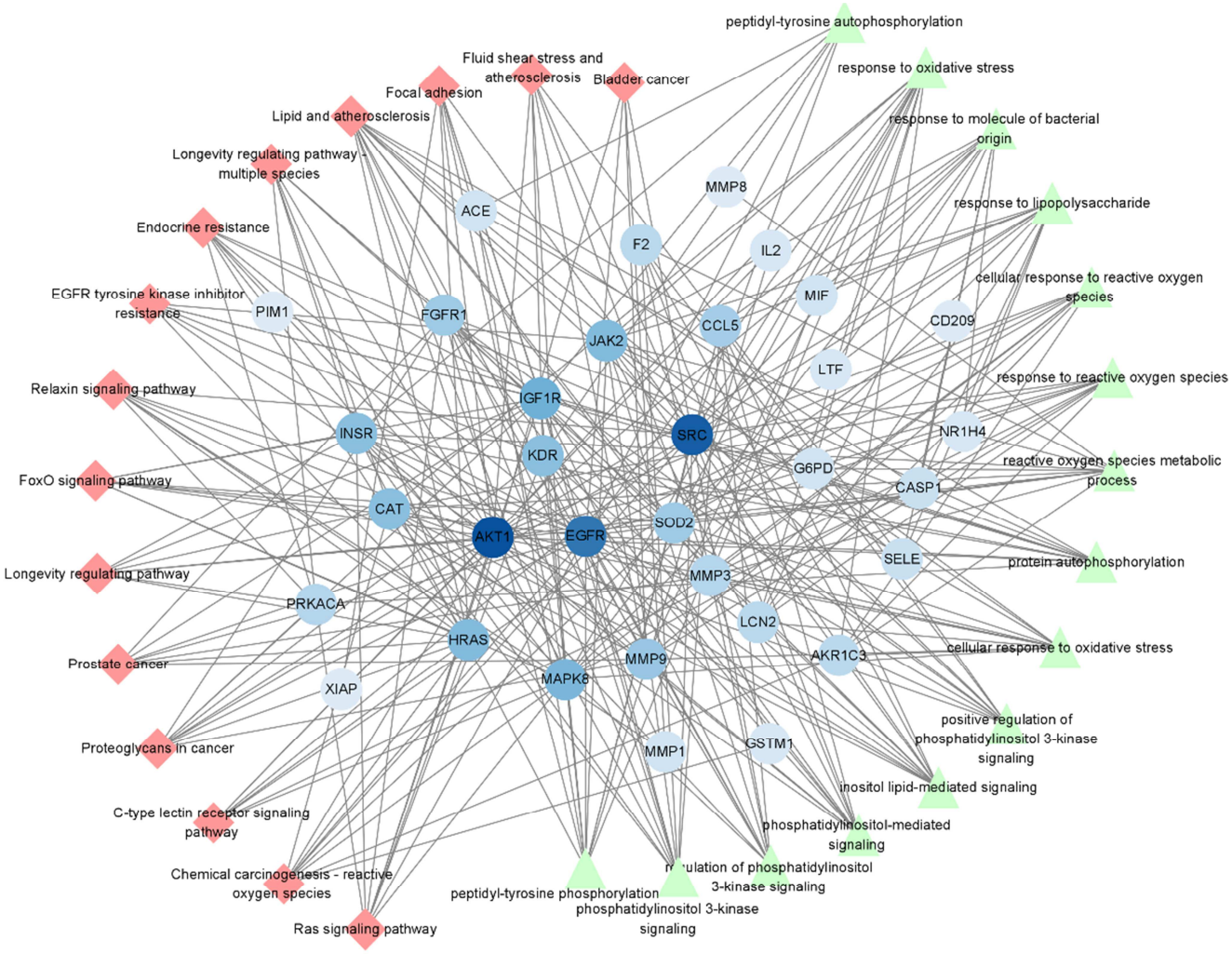

Figure 7. *Network of core target, biological processes and pathways.*

4. Discussion

Acne is a chronic inflammatory skin disorder, frequently existed at areas with thriving lipid secretion. Due to the complexity, a variety of factors contribute to the occurrence of acne, including sebum balance [16], hormone level [17], bacterial infection [18], inflammatory reaction [19]. Among these parameters, sebum secretion stands out as the most closely related one influencing the breakout of acne. Up to now, researchers have already found that the increased sebum secretion, lipid composition such as the ratio of fatty acids, squalene and linoleic acid, or changes in lipid mediator could all lead to the progressing of acne [20]. Therefore, to achieve a sebum balance is of great importance to avoid pathogenesis of acne.

To understand the mechanisms that govern pathological processes relevant to sebaceous glands-related acne, it is imperative to identify the possible targets and signal pathways in sebaceous glands homeostasis. In the previous reports, several regulatory factors, such as EGFR [21], Erbb2 [22], Nrg3 [23], have already been screened out as important targeting site to increased sebum secretion, enlarge sebaceous glands, or induce hyperproliferation. Apart from the core gene targets, various signal pathways were also explored, including ErbB family receptor signaling pathway [24], Wnt signaling pathway [25], or FoxO signaling pathway [26]. As indicated, the complexity of sebum-related gene targets and the multiplicity of the potentially acne-associated sebogenic pathways call for an extended detection on the interconnected anti-acne network.

Treatment with hydroxy acids is one of the most effective therapeutic modalities to manage seborrhea and resultant acne. AHAs and BHAs might play different roles in sebosuppressive activity or superficial peel. However, there’s still no systematic investigation on the precise targets and mechanism exerted by HAs-based compound. In this study, we integrated network pharmacology into the identification and optimization of potential targets, biological processes and signal pathways of HAs combination against acne and sebum balance, thus we would have a clear blueprint before time-consuming in vitro or clinical research.

As shown in Figure 2, ten core targets have been screened out, including ALB, EGFR, AKT1, MMP9, SRC, HRAS, CCL5, IL2, CAT and KDR. ALB is found to have a lower

serum levels in acne patients than in normal population [27]. It is the most abundant circulating protein in plasma and prevent oxidative stress that facilitating acne pathogenesis. EGFR is also an important pharmacological target identified through our research. In previous studies, researchers have confirmed the EGFR immunoreactivity in the peripheral layer of human sebaceous glands [28]. The activation of EGFR stimulate sebaceous glands, promote sebocyte proliferation, and inhibit premature differentiation of sebocytes [29]. AKT1, as an important step in AKT signaling pathway, can inhibit lipid generation in human sebum cells [30]. Anti-oxidative agents such as catechin-3-gallate have been proved to decrease AKT1 level and subsequently alleviate sebum synthesis [31]. In acne lesions, a higher level of MMP-1, MMP-3, and MMP-9 are observed, due to responses from pro-inflammatory cytokines. Anti-oxidative molecules like quercetin endow an inhibitory effect on MMP-9 expression in acne sites [32]. PPARβ/δ is overexpressed in acne skin, accompanied by increased sebum levels [33]. The expression of PPARβ/δ is positively related to SRC, suggesting the possible role of SRC in acne. HRAS is a protooncogene, usually appeared at tumor sites. However, mutation at HRAS gene was identified at severe nodulocystic acne site [34], indicating the potential role of HRAS in acne pathological process. CCL5 is proinflammatory cytokines, which can be up-regulated by bacterium in acne [35]. CCL5 has been reported to attract activated type 1 T cells and macrophages [36], thus causing local inflammation and reversely promoting the sebum secretion. Similarly, as one of the common cytokines involved in immune response, IL2 plays an important role in the inflammatory mechanism of acne. Meanwhile, in hair follicle sebaceous gland units, IL2 receptor exhibits higher expression levels [19]. CAT is an important biomarker, reflecting the antioxidant ability. It is found that the activities of SOD, CAT and total antioxidant capacity are significantly diminished in acne patients [37], impairing the defence against oxygen toxicity. KDR is closely involved in NF-kappaB pathway, and is responsible for transferase activity, transferring phosphorus-containing groups and protein tyrosine kinase activity. KDR tends to be over-expressed in lesional skin and promotes the localization of T cells at sites of inflammation. In conclusion, the above ten hub genes formed a functional cluster through our PPI network analysis, suggesting such cluster played crucial roles in acne pathology.

Based on the hub gene analysis, we could further classify the gene functions into three categories: sebum modulation, anti-oxidation and immune regulation. Genes such as EGFR, AKT1, SRC could target human sebaceous glands by stimulate sebaceous glands, alter lipid generation and adjust sebocyte proliferation. Genes including ALB, CAT, AKT1, MMP9 are associated with the skin oxidation system, disturbance of which would contribute to the imbalance of sebum. Other genes like CCL5, IL2, KDR are immune-related factors, with the ability to coordinate the local inflammation and to exasperate the acne progress or sebum secretion. The hub gene analysis could cover biological processes such as cellular response to oxidative stress, ROS metabolism, and inflammatory response, which is well-accorded with the results we obtain in GO enrichment in Figure 4 and the relation network in Figure 7.

The relation between hub genes and signal pathways are further studied. As indicated by the network relations in Figures 5 and 7, FoxO signaling pathway is closely related to HRAS, AKT1, IL2 and CAT. FoxO is a well-known negative regulator of adipogenesis, and a downstream target of insulin/insulin-like growth factor 1 signalling to regulate lipogenic genes against sebocyte differentiation by inhibiting PPARγ--mediated transcription [38]. EGFR pathway is adjusted by the joint efforts of HRAS, MMP9, KDR, CAT and EGFR. Activation of EGFR signaling in epidermis is reported to result in enlarged, hyperproliferative sebaceous gland [39]. To sum up, it is hinted that multiple pathways might be activated by our HAs-based formula to achieve an improved sebum balance against acne.

The possible gene targets and signal pathways have been identified in our study through network pharmacology, shedding light on the precise functional prediction of the complex HAs-based formula. However, there are still some limitations. The targets and pathways should be further studied in the future via molecular biology or even clinical verification, confirming the effectiveness of network pharmacology and subsequent skin function. High-throughput sequencing technique might be used to practically evaluate our pilot theoretical analysis, and special emphasis could be attached into genes such as KDR and HRAS, which seems to be core factors in acne pathogenesis. Meanwhile, pathways such as longevity regulating pathway and Relaxin signaling pathway are also identified in the study. Investigations on the interplay between these pathway cascades and acne/sebum balance might discover new mechanisms in acne topical treatment. Additionally, the HAs-based compounds may further be incorporated into cosmetic formula, and confirmed its effectiveness in patients with specific acne/sebum balance issues.

5. Conclusion

In this study, we incorporated network pharmacology into the gene targets and signal pathway analysis of multi-ingredient HAs-based formula, to uncover the underlying mechanism against acne through sebum balance adjustment. PPI analysis, GO and KEGG enrichment together established the network relation between HAs-based compounds against acne/sebum balance targets, as well as the relation among hub genes, biological processes and pathways. Our study served as an attempt to disclose the interaction of different hydroxy acids and open up new windows for the future researches.

Conflict of Interest

The authors declare no conflict of interest.

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