WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 6, 967-978. Research Article ISSN 2277–7105

INSILICO DOCKING STUDIES OF COMBINED MEDICINAL PLANTS IN COMPARISON OF THE STANDARD DRUG FOR TREATING KELOIDS

Maria Shirley J.*, Pranesh B. M., Santhosh K., Siva Subramani Bharathi K., Kavinaiya M. and Banupriya R.

School of Pharmacy Sathyabama Institute of Science & Technology, Institution Deemed to be University-U/s 3 of the UGC Act, 1956, Rajiv Gandhi Salai, Chennai – 600119, Tamil Nadu.

Article Received on
25 January 2025,

Revised on 14 Feb. 2025,
Accepted on 06 March 2025

DOI:10.20959/wjpr20256-35895

***Corresponding Author**
Maria Shirley J.
School of Pharmacy Sathyabama Institute of Science & Technology, Institution Deemed to be University-U/s 3 of the UGC Act, 1956, Rajiv Gandhi Salai, Chennai – 600119, Tamil Nadu.

ABSTRACT

Molecular Docking is the computational modeling of the structure of complexes formed by two or more interacting molecules. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. Docking itself only produces plausible candidate structures. The goal of molecular docking is the prediction of the three dimensional structures of interest. The state of the art of various computational aspects of molecular docking based virtual screening of database of small molecules is presented. The goal of ligand-protein docking is to predict the predominant binding mode of a ligand with a protein of known three-dimensional structure. This chapter discusses the background and theory of molecular docking software, as this investigation is to find out how the protein interacts with the combined test compound by comparing it with the standard drug using bio informatics software tools.

KEYWORDS: Molecular docking, Ligand, Test Compound, Standard drug.

INTRODUCTION

MOLECULAR DOCKING

Docking is a method, which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation

in turn may be used to predict the strength of association or binding affinity between two molecules using for example, scoring function. More chemist prefer molecular docking because it is one of the most frequent methods used in rational drug designing as well as to elucidate fundamental biochemical processes. In a simple definition, docking is a molecular modeling technique that is use to predict how a protein (enzyme) interacts with small molecules (ligands). The substrate specificities of protein kinases had found, in many cases, to be determined at least in part by short regions within the substrate known as docking sites. Docking sites are specific and modular, and can dramatically increase the efficiency of phosphorylation. The main objective of molecular docking is to attain ligand-receptor complex with optimized conformation and with the intention of possessing less binding free energy.

Types of docking

Various kind of molecular docking procedure involving either ligand/target flexible or rigid based upon the objectives of docking simulations, docking procedures involving either ligand /target flexible ligand docking (target as rigid molecule),rigid body docking (both the target and ligand as rigid molecules) and flexible docking (both interacting molecules as flexible).

Types of ligand

1. Rigid docking or lock and key.
2. Flexible docking.

Rigid docking or lock and key: In rigid docking, both the internal geometry of the receptor and the ligand is keep fixed during docking.

Flexible docking or induced fit: In this model, both the ligand and side chain of the protein is keep flexible and the energy for different conformations of the ligand fitting into the protein is calculated. For induced fit docking, the main chain also moved to incorporate the conformational changes of the protein upon ligand binding. Through it are time consuming and computationally expensive, yet this method can evaluate many different possible conformations, which make it more exhaustive and possible, simulate real life phenomenon and hence trust worthy.

Different types of interaction

Interaction between particles can defined because of forces between the molecules contained by the particles. These forces are divide into four categories.

- Electrostatic forces: Forces with electrostatic origin due to the changes residing in the matter the most common interaction is charge –dipole and dipole-dipole.
- Electro dynamic Forces: The most widely known is the Van der Waals interactions.
- Steric Force: Steric forces are generating when atoms in different molecules come into very close contact with one another and start affecting the reactivity of each other. The resulting forces can affect chemical reactions and the free energy of a system .
- Solvent related forces: These are forces generated due to chemical reactions between the solvent and the protein or ligand. Examples are Hydrogen bonds (hydrophilic interactions) and hydrophobic interactions.
- Other physical factors: Conformational changes in the protein and the ligand are often necessary for successful docking.

TARGETED DISEASE: KELOID

RECEPTOR: TGF BETA 1

CAUSES: Keloids are thick, raised scars that form due to an overproduction of collagen during the healing process. They extend beyond the original wound boundary and can continue to grow over time. Several factors can contribute to the development of keloids.

- Genetics: Some people are genetically predisposed to keloids. A family history of keloids increases the likelihood of developing them.
- Skin Type: Keloids are more common in individuals with darker skin tones, including people of African, Asian, or Hispanic descent.
- Age: They are more likely to develop in individuals between the ages of 10 and 30.
- Wound Healing: Keloids can form as a result of surgical incisions, acne scars, insect bites, burns, or any trauma that causes damage to the skin.
- Hormonal Changes: Hormonal fluctuations, such as those during pregnancy or puberty, can influence keloid formation.
- Inflammation: Chronic inflammation or infections at the site of a wound can increase the risk of keloid formation.
- Type of Injury: Keloids are more likely to form after deep or significant skin injuries compared to minor wounds.

MECHANISM OF ACTION

Keloid formation is a complex process involving an excessive response to skin injury or trauma, and it primarily revolves around abnormal collagen production and deposition. Here's a detailed look at the mechanisms involved.

- Increased Collagen Production: During wound healing, fibroblasts (cells responsible for collagen production) are activated to repair the damaged skin. In keloids, these fibroblasts produce an excessive amount of collagen. This overproduction results in the formation of a thick, raised scar.
- Imbalance in Collagen Remodeling: Normally, collagen is remodeled and broken down over time as the wound heals. In keloids, this remodeling process is disrupted. The excessive collagen is not broken down properly, leading to the accumulation of fibrous tissue.
- Altered Growth Factor Regulation: Growth factors such as transforming growth factor-beta (TGF-β) play a crucial role in wound healing and collagen production. In keloids, there is often an overexpression of these growth factors, particularly TGF-β, which drives excessive fibroblast activity and collagen synthesis.
- Inflammatory Response: An abnormal inflammatory response can contribute to keloid formation. Chronic inflammation at the wound site can lead to continuous fibroblast activation and collagen deposition.
- Genetic Factors: Genetic predisposition can affect how an individual's body responds to skin injury. Certain genetic variations may influence the inflammatory and fibroblastic responses, making some people more prone to developing keloids.
- Fibroblast Activation: In keloids, fibroblasts are not only overactive but also exhibit increased proliferation and reduced apoptosis (programmed cell death). This leads to an accumulation of fibroblasts and collagen in the scar tissue.

AIM AND OBJECTIVE OF THE STUDY

- ✓ The aim is to study the role of asiaticoside present in gotu kola and wedelolactone present in false daisy in comparison with the standard drug known to be **triamcinolone acetonide** for inhibiting the **TGF- β** protein receptor .
- ✓ The background of our present insilico research investigation is to find out how tgf-β protein interacts with the combined test compound **asiaticoside** with **wedelolactone** using bio informatics software tools.

DRUG PROFILE

STANDARD DRUG: TRIAMCINOLONE ACETONIDE

Molecular Formula: $C_{24}H_{31}FO_6$

Molecular Weight : 434.5 g/mol

CAS : 76-25-5

IUPACName:(1*S*,2*S*,4*R*,8*S*,9*S*,11*S*,12*R*,13*S*)-12-fluoro-11-hydroxy-8-(2-hydroxyacetyl)-6,6,9,13-tetramethyl-5,7-dioxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosa-14,17-dien-16-one

PubChem CID: 6436

STRUCTURE

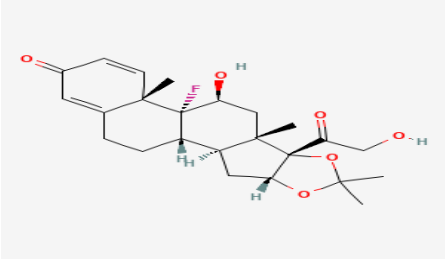

Fig.no:1 Structure of Triamcinolone Acetonide.

1) TEST DRUG: ASIATICOSIDE

Molecular Formula: C48H78O19

Molecular Weight: 959.12 g/mol

CAS: 16830-15-2

IUPAC Name: [(2*S*,3*R*,4*S*,5*S*,6*R*)-6-[[(2*R*,3*R*,4*R*,5*S*,6*R*)-3,4-dihydroxy-6-(hydroxymethyl)-5-[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxyoxan-2-yl]oxymethyl]-3,4,5-trihydroxyoxan-2-yl](1*S*,2*R*,4*aS*,6*aR*,6*aS*,6*bR*,8*aR*,9*R*,10*R*,11*R*,12*aR*,14*bS*)-10,11-dihydroxy-9-(hydroxymethyl)-1,2,6*a*,6*b*,9,12*a*-hexamethyl-2,3,4,5,6,6*a*,7,8,8*a*,10,11,12,13,14*b*-tetradecahydro-1*H*-picene-4*a*-carboxylate

PubChem CID: 11954171

STRUCTURE

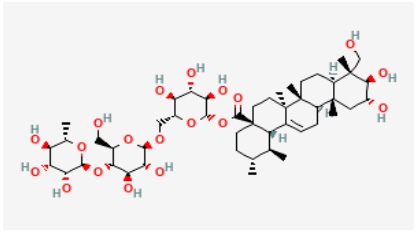

Fig.no. 2: Structure of Asiaticoside.

2) TEST DRUG :WEDELOLACTONE

Molecular Formula: C16H10O7

Molecular Weight: 314.25 g/mol

CAS Number: 5241-44-9

IUPAC Name: 1,8,9-trihydroxy-3-methoxy-[1]benzofuro[3,2-c]chromen-6-one

PubChem CID: 5281813

STRUCTURE

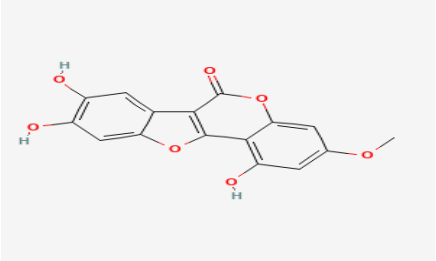

Fig.no. 3: Structure of Wedelolactone.

3) COMBINED FORM OF TEST DRUG:ASIATICOSIDE WITH WEDELOLACTONE

Molecular Formula: C64H88O26N2

Molecular Weight: 1300 g/mol

STRUCTURE

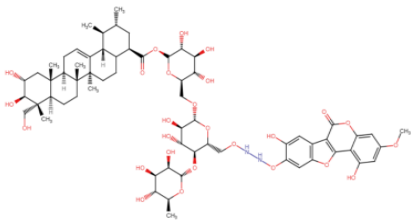

Fig. no. 4: Structure of Asiaticoside with Wedelolactone.

METHODOLOGY

Bioinformatics

Target selection: Based on various clinical literature studies, we chose TGF β1 Receptors which is directly involved in keloid formation Protein 3D Structure prediction: The amino acid sequence of TGF β1 protein was converted into 3D structure using chimeraX version 1.8 software.

Cheminformatics

Drug compound selection

Asiaticoside retrieved from NCBI Pubchem compound database (https://pubchem.ncbi.nlm.nih.gov/compound/Asiaticoside). The retrieved 2D chemical structure was converted into 3D structure using Marvin Sketch (https://marvinjs-demo.chemaxon.com/latest/demo.html)

Wedelolactone retrieved from NCBI Pubchem compound database (https://pubchem.ncbi.nlm.nih.gov/compound/5281813). The retrieved 2D chemical structure was converted into 3D structure using Marvin Sketch (https://marvinjs-demo.chemaxon.com/latest/demo.html**)**

MOLECULAR DRUG DOCKING

The Asiaticoside with Wedelolactone (merged ligands) introduced into the modeled TGF β1 Protein using PyRx – Virtual Screening Tool a protein-ligand docking software.

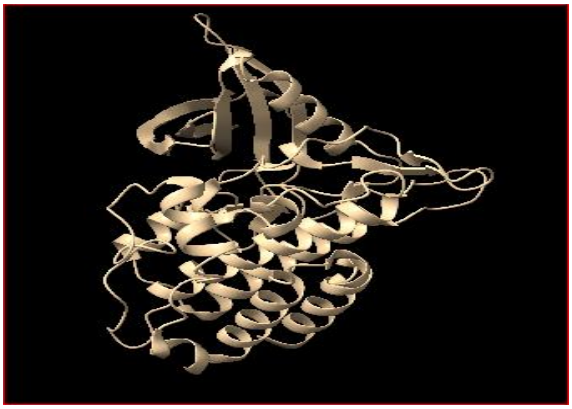

Fig no 5: The above picture represents the 3D Structure of Protein TGF β1.

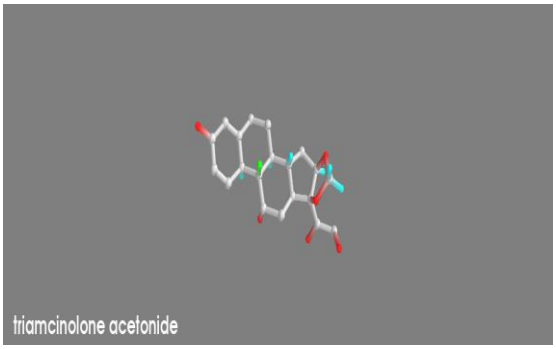

Fig no 6: The above picture represents the structure of the standard drug Triamcilone acitonide.

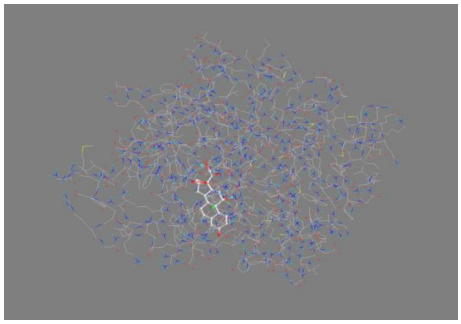

Fig no 7: The above picture represents the Structure of Triamcilone acitonide Introduced Into Tgf B1 Protein.

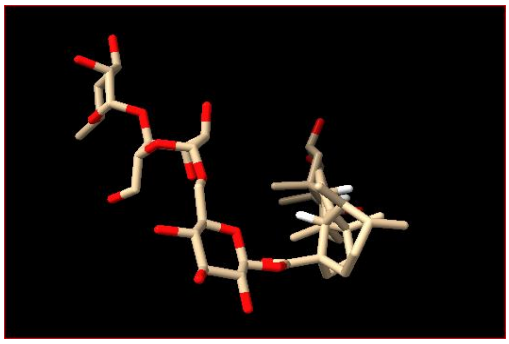

Fig no 8: The above picture represents the 3D Structure of Asiaticoside.

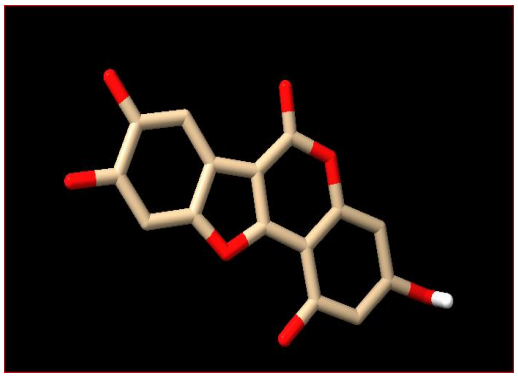

Fig no 9: The above picture represents the 3D Structure of Wedelolactone.

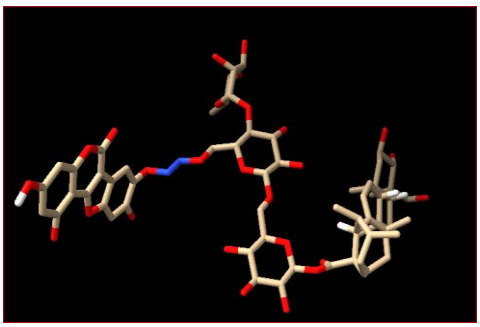

Fig no. 10: The above picture represents the 3D Structure of Asiaticoside with Wedelolactone.

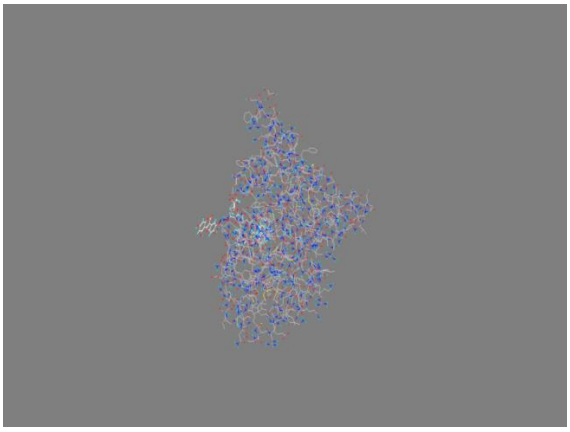

Fig no 11: 3D Structure of Asiaticoside with Wedelolactone Introduced Into Tgf B1 Protein).

The above picture represents Asiaticoside with Wedelolactone ligand molecule docked with TGF β1 Protein using PyRx – Virtual Screening Tool a protein-ligand docking software.

RESULTS AND DISCUSSION

Table 1: Standard drug structure (i.e Triamcilone acitonide) with protein.

Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
5e8t_triamcinolone_acetonide_uff_E=354.27	-8.2	0	0.0	0.0
5e8t_triamcinolone_acetonide_uff_E=354.27	-7.6	1	28.559	30.121
5e8t_triamcinolone_acetonide_uff_E=354.27	-7.3	2	28.689	31.022
5e8t_triamcinolone_acetonide_uff_E=354.27	-7.1	3	20.492	22.619
5e8t_triamcinolone_acetonide_uff_E=354.27	-7.1	4	20.779	23.614
5e8t_triamcinolone_acetonide_uff_E=354.27	-7.0	5	22.363	24.431
5e8t_triamcinolone_acetonide_uff_E=354.27	-6.8	6	15.052	17.027
5e8t_triamcinolone_acetonide_uff_E=354.27	-6.7	7	15.476	16.504
5e8t_triamcinolone_acetonide_uff_E=354.27	-6.7	8	19.728	21.819

Table 2: Asiaticoside with protein.

Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
5e8t_asiaticoside_uff_E=759.50	-9.8	0	0.0	0.0
5e8t_asiaticoside_uff_E=759.50	-9.2	1	5.034	9.757
5e8t_asiaticoside_uff_E=759.50	-9.2	2	12.143	19.158
5e8t_asiaticoside_uff_E=759.50	-9.0	3	5.48	11.347
5e8t_asiaticoside_uff_E=759.50	-8.8	4	11.14	17.745
5e8t_asiaticoside_uff_E=759.50	-8.6	5	17.055	25.065
5e8t_asiaticoside_uff_E=759.50	-8.5	6	10.487	16.69
5e8t_asiaticoside_uff_E=759.50	-8.5	7	5.718	11.555
5e8t_asiaticoside_uff_E=759.50	-8.5	8	22.202	28.97

Table 3: Wedelocatone with protein.

Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
5e8t_wedelolactone_uff_E=438.83	-9.3	0	0.0	0.0
5e8t_wedelolactone_uff_E=438.83	-9.1	1	1.628	6.504
5e8t_wedelolactone_uff_E=438.83	-9.1	2	2.683	6.596
5e8t_wedelolactone_uff_E=438.83	-8.8	3	2.853	4.833
5e8t_wedelolactone_uff_E=438.83	-8.8	4	2.302	6.793
5e8t_wedelolactone_uff_E=438.83	-8.0	5	1.974	2.919
5e8t_wedelolactone_uff_E=438.83	-7.9	6	2.224	6.309
5e8t_wedelolactone_uff_E=438.83	-7.3	7	4.396	8.23
5e8t_wedelolactone_uff_E=438.83	-7.3	8	3.319	5.678

Table 4: 2 Ligand (i.e. Asiaticoside with Wedelolactone) with protein.

Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
5e8t_2ligand_uff_E=1234.95	-10.0	0	0.0	0.0
5e8t_2ligand_uff_E=1234.95	-9.9	1	6.531	13.16
5e8t_2ligand_uff_E=1234.95	-9.8	2	5.338	8.736
5e8t_2ligand_uff_E=1234.95	-9.7	3	2.616	5.094
5e8t_2ligand_uff_E=1234.95	-9.7	4	3.194	13.644
5e8t_2ligand_uff_E=1234.95	-9.7	5	3.558	7.261
5e8t_2ligand_uff_E=1234.95	-9.7	6	2.968	5.181
5e8t_2ligand_uff_E=1234.95	-9.5	7	3.334	6.374
5e8t_2ligand_uff_E=1234.95	-9.5	8	6.469	13.682

RESULTS OF DOCKING STUDIES

Table: Results Of Docking Studies.

S.NO	COMPOUND	BINDING AFFINITY
1.	STANDARD DRUG: (Triamcilonone Acetonide)	-7.5
2.	TEST DRUG (Asiaticoside + Wedelolactone)	-10.7

Based on Insilico results, we report that the docked combined form of test drug (asiaticoside+wedelolactone) would act as an efficient molecule for treating keloid disease. Overall, the drug docking results clearly explain the potential binding affinities between TGF-β receptor and combined drug. This molecule would increase the inhibitory effect of TGF-β receptor in keloid disease.

CONCLUSION

In silico molecular docking was performed to evaluate the binding interactions of Asiaticoside and Wedelolactone with key targets involved in keloid formation. In silico docking studies confirmed strong binding interactions of these bioactive compounds with key molecular targets involved in keloid pathogenesis, suggesting their possible mechanistic role

in fibrosis modulation. The docking results suggested strong affinities, supporting their potential role in modulating fibroblast activity, collagen synthesis, and inflammation.

REFERENCE

1. Udayan Betarbet, MD and Travis W. Blalock, MD Keloids: A Review of Etiology, Prevention, and Treatment J. Clin Aesthet Dermatol, 2020 Feb; 13(2): 33–43.
2. Somesh Gupta, VK Sharma Standard guidelines of care: Keloids and hypertrophic scars. Dermatosurgery Specials, 2011; 77: 1; 94-100
3. Laura A. Walsh, Ellen Wu, David Pontes, Kevin R. Kwan, Sneha Poondru, Corinne H. Miller & Roopal V. Kundu Keloid treatments: an evidence-based systematic review of recent advances, 2023.
4. Elena Arribas-López,1 NazaninZ and,1 Omorogieva Ojo,2,* Martin John Snowden,1 and Tony Kochhar3 A Systematic Review of the Effect of Centella asiatica on Wound Healing. Int J Environ Res Public Health, 2022 Mar; 19(6): 3266.
5. Roberto Cotellese 1 2, Shu Hu 1 2, Gianni Belcaro 3 2, Andrea Ledda 1 2, Beatrice Feragalli 1 2, Mark Dugall 1 2, Morio Hosoi 1 2, Edmondo Ippolito 1 2 Centella asiatica (Centellicum®) facilitates the regular healing of surgical scars in subjects at high risk of keloids, 2018 Apr; 73(2): 151-156. doi: 10.23736/S0026-4733.18.07666-6
6. Kamonwan Jenwitheesuk, Porntip Rojsanga, Bowornsilp Chowchuen, and Palakorn Surakunprapha A Prospective Randomized, Controlled, Double-Blind Trial of the Efficacy Using Centella Cream for Scar Improvement. Evid Based Complement Alternat Med, 2018; 2018: 9525624.
7. Deepak Timalsina and Hari Prasad Devkota, Eclipta prostrata (L.) L. (Asteraceae): Ethnomedicinal Uses, Chemical Constituents, and Biological Activities, 2021 Nov; 11(11): 1738.
8. Thian-Sze Wong John Zeng-Hong Li, Siqi Chen,Jimmy Yu-Wai Chan,and Wei Gao The Efficacy of Triamcinolone Acetonide in Keloid Treatment: A Systematic Review and Meta-analysis, 2016; 3: 71.
9. Marco Morelli Coppola,#* Rosa Salzillo,#* Francesco Segreto, and Paolo Persichetti Triamcinolone acetonide intralesional injection for the treatment of keloid scars: patient selection and perspective, 2018; 11: 387–396.
10. Hui Li, Manting Hou, Ping Zhang, Lutong Ren, Yuanyuan Guo, Liang Zou, Junling Cao, Zhaofang Bai Wedelolactone suppresses breast cancer growth and metastasis via regulating TGF-β1/Smad signaling pathway, 2024.

11. Christopher David Jones,1 Luke Guiot,2 Mike Samy,3 Mark Gorman,1 and Hamid Tehrani4 The Use of Chemotherapeutics for the Treatment of Keloid Scars, 2015 May 21; 7(2): 5880.