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MOLECULAR DOCKING OF PHYTOCHEMICALS FROM ADHATODA VASICA - A SYSTEMATIC SEARCH AND REVIEW

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ABSTRACT

Background

Phytochemicals had always been an important source of therapeutic drugs for mankind. Of innumerable number of drugs, few again more attention for specific purposes. Adhatoda vasica (L.) Nees (AV) is used in India's indigenous medical system. Numerous beneficial properties have been exhibited by AV. However, it is indeed necessary to comprehensively review the information available on adhatoda vasica and its phytochemicals on various targets studied by molecular docking. This review showcases such information for aiding future translator research and development of drugs and devices.

Methodology

The literature search was performed in PubMed, Google Scholar and Cochrane for molecular docking studies involving adhatoda vasica on any target. Only studies that studied molecular docking of phytochemicals from AV were included. Reviews and clinical studies were excluded. The results were screened for duplicates and relevance. The information was tabulated and analyzed.

Results

The molecular docking results are mostly based on AV alone, although a few studies have tried to compare AV to other plant extracts. Multiple phytoconstituents from AV were compared and assessed for binding energy and affinity in the majority of the papers. Numerous papers describe both in vitro and in vivo effects.

Conclusion

As evidenced from the search results, so far results are reported for molecular docking of AV for Sars-CoV-2 virus, Rheumatoid arthristis, bronchitis, inflammation, asthma, cancer and anti-tubercular actions.

Kry Words:

Adhatoda Vasica, Molecular Docking, Review.

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Introduction

Phytochemicals had always been an important source of therapeutic drugs for mankind. Every culture around the world has its own set of curative drugs, apart from major healing systems like Ayurveda, siddha and unani etc. Current century is seen as a golden period of herbal medicine as ancient and traditional preparations are now being documented according to modern scientific techniques. In this regard, the complete documentation involved identifying the therapeutic pathways, determining the dose and toxicity. Of these, dry lab work involves molecular docking of these drugs to known human, animal and microbial targets to determine the pharmaceutical activity.

Of innumerable number of drugs, few again more attention for specific purposes. Adhatoda vasica (L.) Nees (Acanthaceae), is a shrub native to the Indian peninsula. The plant is used in India's indigenous medical system and is a well-known expectorant in both the Ayurvedic and Unani systems of medicine. alaria, chronic fever, intrinsic haemorrhage, cough, asthma, leprosy, skin diseases, and piles are all treated with the leaves.3 The plant is said to have abortifacient, antimicrobial, and cough suppressant activities. crude extract of A. vasica foliage was found to have significant antifeedant and toxic effects on S. littoralis larvae.8 Vasicine, deoxyvasicine, vasicinone, vasicol, vasicinol and adhatodinine are among the alkaloids found in the plant.9 Vasicine is has bronchodilatory and uterine stimulant effects.10 Vasicine acetate has antimycobacterial activity .11Furthermore, essential oils of A. vasica leaves are known to contain ketone, terpene, and phenolic ether, which have antitumor, antimutation, antioxidant, antiaging and sedative effects; essential oils' high phenolic content contributes to their antimicrobial properties.

However, it is indeed necessary to comprehensively review the information available on adhatoda vasica and its phytochemicals on various targets studied by molecular docking. This review showcases such information for aiding future translator research and development of drugs and devices.

Methodology

The literature search was performed in PubMed, Google Scholar and Cochrane for molecular docking studies involving adhatoda vasica on any target. The search criteria was: ("justicia"[MeSH Terms] OR "justicia"[All Fields] OR ("adhatoda"[All Fields] AND "vasica"[All Fields]) OR "adhatoda vasica"[All Fields]) AND ("molecular docking simulation"[MeSH Terms] OR ("molecular"[All Fields] AND "docking"[All Fields] AND "simulation"[All Fields]) OR "molecular docking simulation"[All Fields] OR ("molecular"[All Fields] AND "docking"[All Fields]) OR "molecular docking"[All Fields])

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Translations

Adhatoda Vasica: "justicia"[MeSH Terms] OR "justicia"[All Fields] OR ("adhatoda"[All Fields] AND "vasica"[All Fields]) OR "adhatoda vasica"[All Fields]

Molecular docking: "molecular docking simulation"[MeSH Terms] OR ("molecular"[All Fields] AND "docking"[All Fields] AND "simulation"[All Fields]) OR "molecular docking simulation"[All Fields] OR ("molecular"[All Fields] AND "docking"[All Fields]) OR "molecular docking"[All Fields]

Only studies that studied molecular docking of phytochemicals from AV were included. Reviews and clinical studies were excluded. The results were screened for duplicates and relevance. The information was tabulated and analysed.

Results

Author	Phytochemical	Receptor	Activity	Clinical Usage
Thangaraju et al.,(2022)[12]	vasicine	Thromboxane A2 receptor	platelet amplification potential	treat the thrombocytopenia of dengue
Dagur et al.,(2022)[13]	taraxerol, friedelanol, anisotine, and adhatodine	Mpro of SARS-COV-2	immunoreaction enrichment, inflammatory reaction suppression	Anti-Covid 19 drug
Ghanta et al.,(2022)[14]	Vasicine, vasicinone and deoxyvasicine	5-LOX	Antiinflammatory	Anti bronchitic
Iftikhar et al.,(2022)[15]	vasicinol and vasicine	γ-Globin Gene	gene reactivation	management of β-thalassemia

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Siva et al.,(2022)[15]	vasicine, vasicinone, vasicinolone, vasicol, vasicolinone, adhatodine, adhavasicinone, aniflorine, anisotine, vasnetine, and orientin from	SARS-CoV-2 Main Protease Enzyme	Inhibition	Anti covid 19
Tehreem et al.,(2021)[17]	Vascinol	Angiotensin converting enzyme	Inhibition	Antihypertensive drug
Patel et al.,(2021)[18]	--	Angiotensin converting enzyme	Competes with Sars-CoV-2 for binding with ACE	Anti covid 19
Ghosh et al.,(2021)[2190]	Vasicoline, Vasicolinone, Vasicinone, Vasicine, Adhatodine, Anisotine	SARS CoV-2 Mpro	Inhibits Sars-CoV-2 Virus	Anti covid 19
Gowrishankar et al.,(2021)[20]	vasicolinone and anisotine	3CLpro, ACE-2, spike glycoprotein and RdRp	Inhibits Sars-CoV-2 Virus	Anti covid 19
Selvaraj et al.,(2021)[21]	Pyrazinamide, Anisotine, Vasicinone, Vasicoline	Cornulin	Binding	Anticancer
Selvaraj et al.,(2021)[22]	Stigmasterol, Pyrazinamide, Vasicinone and Ethambutol	E3 ubiquitin-protein ligase WWP1	Binding	Anti-Oral cancer

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Thangaraju et al.,(2021)[23]	vasicine	ACE 2 Receptor, 3CL protease and Spike protein SARS HR1 motif	Inhibition	Anti covid 19
Wang et al.,(2020)[24]	53 compounds	Rhematoid arthritis pathways	inhibition	Anti-Rheumatoid Arthritis
Balachandran et al.,(2017)[25]	2 Acetyl Benzyl amine	JAK-2, AKT1, FLT3 and Bcl-2	Inhibition	Anti cancer
Chaliha et al.,(2016)[26]	Vasicine	Antigen 85C	Inhibition	Anti-tuberculosios
Swain et al.,(2015)[27]	5 compounds	triosephosphate isomerase	Binding	Anti-malarial
Jha et al.,(2012)[28]	vasicoline, vasicolinone, vasicinone, vasicine, adhatodine and anisotine	β-ketoacyl-acyl-carrier protein synthase III	Binding	Anti Tubercular
Ali et al.,(2016)[29]	Vasicine	acetylcholinesterase	Inhibition	Alzheimers Disease treatment
Gheware et al.,(2021)[30]	Numerous compounds from whole extract	HIF-1α, IFN-γ, IL-6, TNF-α, TGF-β, JAK-1, and JAK-3 proteins		Antiinflammatory and antiasthmatic

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Discussion

The molecular docking method can be used to simulate the relationship between a biomolecule and a protein at the atomic level, allowing us to characterize small molecule behaviour in target protein binding sites as well as elucidate fundamental biochemical pathways.31 The docking process consists of two basic steps: predicting the ligand shape as well as its orientation and position within these sites (known as pose) and assessing the binding affinity. These two steps are linked to sampling techniques and scoring schemes.32

Understanding the position of the binding site prior to docking processes improves docking efficiency significantly. In many cases, the binding site is known before ligands are docked into it. In addition, information about the sites can be gained by comparing the target protein to a family of proteins with similar functions or proteins co-crystallized with the other ligands. Cavity detection programmes or online servers, such as GRID, POCKET, SurfNet, PASS, and MMC, can be used to identify putative active sites within proteins in the absence of knowledge about the binding sites. Blind docking refers to docking without making any assumptions about the binding site.32

The molecular docking results are mostly based on AV alone, although a few studies have tried to compare AV to other plant extracts. Multiple phytoconstituents from AV were compared and assessed for binding energy and affinity in the majority of the papers. Numerous papers describe both in vitro and in vivo effects, say like Balachandran et al., (2017), who conducted in vitro and in vivo experiments in addition to docking.25 However, because the current review's goal is to analyze evidence from molecular docking alone, these results have not been summarized.

Further, the goal of this paper to analyze molecular docking alone is to look at the phytochemicals of AV from the rock bottom of drug discovery. It is common in research to find a lot of evidence at this level which has not been followed up till clinical translation. Therefore, it is essential to periodically analyse the evidence to direct the future research in proper direction.

Moreover, despite in vitro and in vivo analysis, molecular docking is essential to determine the structure activity relationship that makes repurposing of drugs possible.

In this regard, numerous papers are seen regarding Sars-CoV-2 binding. This is obviously due to the pressing need for fighting the pandemic. Almost all papers in the past 2 years have focused exclusively on this aspect. Pre-Covid era papers have focused on other aspects such as asthma, cancer and so on.

As evidenced from the search results, so far results are reported for molecular docking of AV for Sars-CoV-2 virus, Rheumatoid arthristis, bronchitis, inflammation, asthma, cancer and anti-tubercular actions. It has been observed by molecular docking that the phytochemicals from AV bind

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to selected targets with binding energy and affinity similar to synthetics drugs currently used for the said purpose. Therefore, it serves as starting point for preparation of next generation drugs. Already some anti-asthmatics are available.33, 34 In these directions, there appears to be a promising future for adhatoda vasica derived phytochemicals.

Conclusion

As far as molecular docking results for AV is concerned, it apparently has numerous promising phytochemicals that can be starting points for future generations of drugs. This regard, it is essential to explore newer possibilities like determining the spectrum of action of AV derived phytochemicals in the molecular level. This effort would bring the huge advantage of lost traditional wisdom to lime light, saving and comforting innumerable number of lives.

REFERENCES

1) Chopra RN. Glossary of Indian medicinal plants. (1956)
2) Kapoor LD. CRC Handbook of ayurvedic medicinal plants. CRC press; 2018 Jan 18.
3) Sharma PV. Classical uses of medicinal plants. Chaukhambha Visvabharati; 1996.
4) Wakhloo RL, Wakhloo D, Gupta OP, Atal CK. Vasicine hydrochloride, a new drug for interruption of pregnancy. Journal of Obstetrics and Gynaecology of India. 1979; 29:939-40.
5) Doshi JJ, Patel VK, Venkatakrishna-Bhatt H. Effect of Adhatoda vasica massage in pyorrhoea. International Journal of Crude Drug Research. 1983 Jan 1;21(4):173-6.
6) Mathew AS, Patel KN, Shah BK. Investigation on antifeedant and anthelmintic potential of Adhatoda vasica Nees. Indian J nat prod. 1998;14(1):11-6.
7) Dhuley JN. Antitussive effect of Adhatoda vasica extract on mechanical or chemical stimulation-induced coughing in animals. Journal of Ethnopharmacology. 1999 Nov 30;67(3):361-5.
8) Sadek MM. Antifeedant and toxic activity of Adhatoda vasica leaf extract against Spodoptera littoralis (Lep., Noctuidae). Journal of applied entomology. 2003 Aug;127(7):396-404.
9) Claeson UP, Malmfors T, Wikman G, Bruhn JG. Adhatoda vasica: a critical review of ethnopharmacological and toxicological data. Journal of ethnopharmacology. 2000 Sep 1;72(1-2):1-20.
10) Gupta OP, Sharma ML, Ghatak BJ, Atal CK. Potent uterine activity of alkaloid vasicine. The Indian journal of medical research. 1977 Nov;66(5):865-71.
11) Ignacimuthu S, Shanmugam N. Antimycobacterial activity of two natural alkaloids, vasicine acetate and 2-acetyl benzylamine, isolated from Indian shrub Adhatoda vasica Ness. leaves. Journal of biosciences. 2010 Dec; 35:565-70.
12) Thangaraju P, N G, Ar V, Gurunthalingam MP, Ty SS, Venkatesan S, Thangaraju E. Molecular docking analysis of Adhatoda Vasica withThromboxane A2 receptor (TXA2R) (6IIU) and Antiviral molecules for possible dengue complications. Infect Disord Drug Targets. 2022 Jul 18. doi: 10.2174/1871526522666220718101544. Epub ahead of print. PMID: 35850647.

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13) Dagur P, Rakshit G, Sheikh M, Biswas A, Jha P, Al-Khafaji K, Ghosh M. Target prediction, computational identification, and network-based pharmacology of most potential phytoconstituent in medicinal leaves of Justicia adhatoda against SARS-CoV-2. J Biomol Struct Dyn. 2022 Apr 12:1-17.
14) Ghanta P, Sinha S, Doble M, Ramaiah B. Potential of pyrroquinazoline alkaloids from Adhatoda vasica Nees. as inhibitors of 5-LOX - a computational and an in-vitro study. J Biomol Struct Dyn. 2022 Apr;40(6):2785-2796.
15) Iftikhar F, Rahman S, Khan MBN, Khan K, Khan MN, Uddin R, Musharraf SG. In Vitro and In Vivo Studies for the Investigation of γ-Globin Gene Induction by Adhatoda vasica: A Pre-Clinical Study of HbF Inducers for β-Thalassemia. Front Pharmacol. 2022 Mar 29; 13:797853.
16) Siva Kumar B, Anuragh S, Kammala AK, Ilango K. Computer Aided Drug Design Approach to Screen Phytoconstituents of Adhatoda vasica as Potential Inhibitors of SARS-CoV-2 Main Protease Enzyme. Life (Basel). 2022 Feb 20;12(2):315.
17) Tehreem S, Rahman S, Bhatti MS, Uddin R, Khan MN, Tauseef S, El-Seedi HR, Bin Muhsinah A, Uddin J, Musharraf SG. A UPLC-DAD-Based Bio-Screening Assay for the Evaluation of the Angiotensin Converting Enzyme Inhibitory Potential of Plant Extracts and Compounds: Pyrroquinazoline Alkaloids from Adhatoda vasica as a Case Study. Molecules. 2021 Nov 18;26(22):6971.
18) Patel CN, Goswami D, Jaiswal DG, Parmar RM, Solanki HA, Pandya HA. Pinpointing the potential hits for hindering interaction of SARS-CoV-2 S-protein with ACE2 from the pool of antiviral phytochemicals utilizing molecular docking and molecular dynamics (MD) simulations. J Mol Graph Model. 2021 Jun; 105:107874.
19) Ghosh R, Chakraborty A, Biswas A, Chowdhuri S. Identification of alkaloids from Justicia adhatoda as potent SARS CoV-2 main protease inhibitors: An in-silico perspective. J Mol Struct. 2021 Apr 5; 1229:129489.
20) Gowrishankar S, Muthumanickam S, Kamaladevi A, Karthika C, Jothi R, Boomi P, Maniazhagu D, Pandian SK. Promising phytochemicals of traditional Indian herbal steam inhalation therapy to combat COVID-19 - An in-silico study. Food Chem Toxicol. 2021 Feb; 148:111966.
21) Selvaraj J, Jh SF, Sivabalan V, Rekha UV, Ponnulakshmi R, Vishnupriya V, Kullappan M, Sreekandan RN, Mohan SK, Vijayalakshmi P. Molecular modeling of cornulin (CRNN) for docking with phytocompounds from Justicia adhatoda L. Bioinformation. 2021 Jan 31;17(1):200-205.
22) Selvaraj J, Rekha UV, Jh SF, Sivabalan V, Ponnulakshmi R, Priya VV, Kullappan M, Sreekandan RN, Mohan SK. Molecular docking data of E3 ubiquitin-protein ligase WWP1 with compounds from a medicinal plant Justicia adhatoda L. Bioinformation. 2021 Jan 31;17(1):162-166.
23) Thangaraju P, Sudha Ty S, Pasala PK, Hari Ty S, Venkatesan S, Thangaraju E. The Role of Justicia adhatoda as Prophylaxis for COVID-19 - Analysis Based on Docking. Infect Disord Drug Targets. 2021;21(8): e160921190441.
24) Wang W, Zhang Y, Luo J, Wang R, Tang C, Zhang Y. Virtual Screening Technique Used to Estimate the Mechanism of Adhatoda vasica Nees for the Treatment of Rheumatoid Arthritis Based on Network Pharmacology and Molecular Docking. Evid Based Complement Alternat Med. 2020 Sep 29; 2020:5872980.

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25) Balachandran C, Arun Y, Sangeetha B, Duraipandiyan V, Awale S, Emi N, Ignacimuthu S, Perumal PT. In vitro and in vivo anticancer activity of 2-acetyl-benzylamine isolated from Adhatoda vasica L. leaves. Biomed Pharmacother. 2017 Sep; 93:796-806.
26) Chaliha AK, Gogoi D, Chetia P, Sarma D, Buragohain AK. An In Silico Approach for Identification of Potential Anti-Mycobacterial Targets of Vasicine and Related Chemical Compounds. Comb Chem High Throughput Screen. 2016;19(1):14-24.
27) Swain SS, Sahu MC, Padhy RN. In silico attempt for adduct agent(s) against malaria: Combination of chloroquine with alkaloids of Adhatoda vasica. Comput Methods Programs Biomed. 2015 Oct;122(1):16-25.
28) Jha DK, Panda L, Lavanya P, Ramaiah S, Anbarasu A. Detection and confirmation of alkaloids in leaves of Justicia adhatoda and bioinformatics approach to elicit its anti-tuberculosis activity. Appl Biochem Biotechnol. 2012 Nov;168(5):980-90.
29) Ali SK, Hamed AR, Soltan MM, El-Halawany AM, Hegazy UM, Hussein AA. Kinetics and molecular docking of vasicine from Adhatoda vasica: An acetylcholinesterase inhibitor for Alzheimer's disease. South African Journal of Botany. 2016 May 1; 104:118-24.
30) Gheware A, Panda L, Khanna K, Bhatraju NK, Jain V, Sagar S, Kumar M, Singh VP, Kannan S, Subramanian V, Mukerji M. Adhatoda vasica rescues the hypoxia-dependent severe asthma symptoms and mitochondrial dysfunction. American Journal of Physiology-Lung cellular and molecular physiology. 2021 May 1;320(5): L757-69.
31) McConkey BJ, Sobolev V, Edelman M. The performance of current methods in ligand-protein docking. Current Science. 2002; 83:845–855
32) Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach for structure-based drug discovery. Curr Comput Aided Drug Des. 2011 Jun;7(2):146-57.
33) Rayees S, Satti NK, Mehra R, Nargotra A, Rasool S, Sharma A, Sahu PK, Gupta VK, Nepali K, Singh G. Anti-asthmatic activity of azepino [2, 1-b] quinazolones, synthetic analogues of vasicine, an alkaloid from Adhatoda vasica. Medicinal Chemistry Research. 2014 Sep; 23:4269-79.
34) Mahindroo N, Ahmed Z, Bhagat A, Lal Bedi K, Kant Khajuria R, Kumar Kapoor V, Lal Dhar K. Synthesis and structure-activity relationships of vasicine analogues as bronchodilatory agents. Medicinal Chemistry Research. 2005 Sep; 14:347-68.