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Research Article

Potential Anti-SARS-CoV-2 Effects of Gossypol and AT-101: Molecular Docking Study Against Angiotensin Converting Enzyme 2

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ABSTRACT

This study explores the potential anti-SARS-CoV-2 effects of gossypol (GP) and its AT-101 derivative through *in silico* molecular docking simulations. GP and AT-101 are natural and modified compounds, respectively, with promising biological activities. Using Autodock Vina software, molecular docking simulations were performed to assess the binding interactions between GP, AT-101, and the receptor binding domain of angiotensin-converting enzyme 2 (ACE2) which plays a vital role in facilitating viral entry into host cells. The docking results revealed that GP and AT-101 exhibited favorable interactions with ACE2, suggesting their potential as anti-SARS-CoV-2 agents. GP formed seven hydrogen bonds with ACE2, while AT-101 formed eight, indicating more stable binding and superior interaction. However, it is important to acknowledge that these findings are based on *in silico* modeling and further research is required to validate the antiviral properties of l and AT-101 *in vitro* and *in vivo*. Moreover, the long-term safety and efficacy of these compounds for COVID-19 treatment warrant further investigation through clinical trials. In conclusion, this *in silico* study provides preliminary evidence of the potential anti-SARS-CoV-2 effects of GP and AT-101 by demonstrating their ability to interact with ACE2. However, it is important to acknowledge that these findings are based on *in silico* modeling and further research is required to validate the antiviral properties of GP and AT-101 in vitro and *in vivo*.

1. Introduction

Gossypol (GP) is a natural polyphenol compound found in cottonseeds and the tropical tree *Thespesia populnea* L. [1]. GP has several biological activities including anti-oxidant, anti-viral, anti-parasitic, and anti-bacterial. It hasbeen studied for its potential anticancer properties due to its ability to inhibit the activity of several enzymes involved in cell growth and survival [2]. Despite all its potential activities GP has been found to have toxic side effects, including male infertility and cardiac toxicity, which have limited its clinical use [3]. As a result, researchers have developed a modified form of GP called -/- GP (AT-101) that has reduced toxicity while enhancing its biological activities. AT-101 is a Bcl-2 family inhibitor that has been investigated for its potential use in the treatment of various types of cancer. It works by inhibiting the activity of Bcl-2 protein and other anti-apoptotic proteins, which can lead to apoptosis in cancer cells [4]. Several clinical trials have been conducted to evaluate the safety and efficacy of AT-101 in the treatment of various cancers, including prostate, bladder, ovarian, lung, glioblastoma, leukemia, and multiple myeloma cells with promising results [5–11]. Currently, it is undergoing phase II/III clinical trials for further evaluation [12]. Although its anticancer properties have been widely studied, there is limited research on the antiviral effects of GP. GP is effective in inhibiting other ssRNA viruses, including plant viruses like tobacco

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mosaic virus [13], as well as zoonotic viruses such as avian influenza virus [14], West Nile virus [15], and Hendra virus [16]. One study showed that the GP derivative could be a safe and effective broad-spectrum therapeutic agent to treat diseases caused by Zika and dengue virus infection without toxicity [17]. In a study, authors shed light on the underlying mechanism of GP's action by demonstrating that it likely targets the RNA-dependent RNA polymerase of ssRNA viruses across a broad range of hosts, including plants and animals, which was previously not fully understood [18]. Overall, while there is some preliminary evidence suggesting that GP and its derivatives may have antiviral properties, more research is needed to confirm these findings and to determine whether they could be useful in the treatment of viral infections.

The emergence of SARS-CoV-2 has led to an unprecedented global health crisis, with the virus spreading rapidly across the world and causing significant social and economic disruptions [19]. While vaccines have proven effective in preventing COVID-19, the virus's ability to mutate and the emergence of new variants of concern have raised concerns about the long-term effectiveness of current vaccines. Researchers and healthcare professionals are therefore working tirelessly to develop new treatments and broad-spectrum inhibitors that can effectively combat various SARS-CoV-2 variants [20]. Additionally, as the virus has been found to cause serious damage to both humans and animals [21], there is a pressing need to understand its pathogenic mechanisms and identify potential therapeutic targets to mitigate the effects of COVID-19. Despite the challenges presented by the ongoing pandemic, the scientific community remains committed to developing effective strategies to control the spread of SARS-CoV-2 and protect public health.

The SARS-CoV-2 spike protein is the key protein that enables the virus to enter host cells. The spike protein comprises two subunits, S1 and S2, with the receptor-binding domain (RBD) located on the S1 subunit. The RBD is responsible for binding to the host cell receptor angiotensin-converting enzyme 2 (ACE2), which is present on the surface of human cells [22].

In the present work, to identify possible anti-viral effects to target SARS-CoV-2, the interactions of AT-101 or GP with ACE2 were screened. This methodical computer-aided drug-designing methodology not only helped to learn more about the potential putative targets of the compounds but also revealed structural characteristics of the compounds that are responsible for their bioactivity on the selected target.

2. General Methods

2.1.Receptor preparation

Receptor preparation is an essential step in molecular docking, which involves preparing the three-dimensional structure of the target receptor protein for the docking simulation. The main objective is to ensure that the receptor is in an optimal conformation to interact with ligands. The SARS-CoV-2 main protease ACE2 (PDB ID: 1R42) was selected as the receptor proteins. The three-dimensional (3D) structure of ACE2 was obtained from a reliable source the Protein Data Bank (PDB) in PDB format (https://www.rcsb.org/). The PDB provides experimentally determined structures of proteins, including X-ray crystallography and NMR-derived structures. Autodock Vina 4.2.5.1 software was employed for eliminating water molecules, hydrogenating the proteins, and adjusting the load distribution. Water molecules and other heteroatoms that are not directly involved in the binding site or relevant interactions are typically removed from the receptor structure.

This simplifies the docking process and focuses on the key interactions between the receptor and ligands. By following these steps, the receptor structure is prepared in a state that optimizes its binding site and overall conformation for the subsequent docking simulation with ligands. The prepared receptor is then ready to be used in molecular docking experiments to investigate ligand-receptor interactions and predict binding affinities. A maximum of five cavities were

found using default parameters in order to acquire better potential binding sites.

2.2.Ligand preparation

Ligand preparation is a crucial step in molecular docking, where the three-dimensional structure of the ligand molecule is prepared to ensure its compatibility with the docking software and accurate representation of its chemical properties. The three-dimensional structures of GP and AT-101 were downloaded from Pubchem database as "sdf" format and converted to PDB format. Autodock Vina software was utilized to remove water molecules and adjust the load distribution. By following these steps, the ligand structure is prepared in a suitable form for molecular docking simulations. Proper ligand preparation ensures that the ligand's chemical properties are accurately represented and facilitates the exploration of ligand-receptor interactions, binding modes, and affinity predictions during the docking process.

2.3.Docking

High-throughput molecular docking was performed using Autodock Vina, a widely used software for predicting ligand-receptor interactions. The docking simulations were carried out to investigate the binding of GP or AT-101 to ACE2 receptor. To define the search space for docking, the grid center coordinates and dimensions of the grid box were set. For ACE2, the grid center was set at X=19.81, Y=-5.57, and Z=14.73, with the same grid box dimension. These parameters were determined after careful calibration and optimization.

By utilizing the standardized grid box size and other docking parameters, consistent conditions were maintained for the docking experiments with GP and AT-101. The Autodock Vina software performed an exhaustive sampling of the ligand conformational space within the defined search space, generating a range of possible ligand-receptor binding conformations.

To gain insights into the molecular interactions, the resulting docked conformations were analyzed and visualized using PyMOL software. The docking approach employed in this study enables the exploration of ligand-receptor interactions at the atomic level, providing valuable information for understanding the potential interactions between GP derivatives and ACE2.

2.4.Molecular dynamics (MD) simulations

The docked ligand targets were merged in Discovery Studio Visualizer (DSV) software as a complex. The system was configured to simulate water TIP4P in a 10 Å orthorhombic box. The docked complex, comprising merged ligand targets, was neutralized by the automatic addition of ions calculated by DSV software. Subsequently, the simulation was equilibrated for 1 ns, with trajectory recording at 4.2 ps intervals, using the NPT ensemble class and a temperature of 310 K. The parameters obtained for analysis included root mean square displacement (RMSD) and root mean square fluctuation (RMSF). Docking results were also verified via DSV software.

3. Results and Discussion

The process of testing the pharmacokinetic and pharmacodynamic properties of components for the discovery or design of new drugs is a time-consuming endeavor spanning several years. However, well-established ingredients that have undergone extensive research and development over time possess clearly defined profiles, thereby reducing the need for prolonged preclinical studies [23]. These properties render them highly promising candidates for novel applications.

In recent times, the advent of *in silico* studies, which involve computational methods and simulations, has opened up new possibilities for investigating SARS-CoV-2. Notably, the elucidation of the crystal structure of ACE2 (the cellular receptor for the virus) has provided a valuable perspective for theoretical exploration and analysis of the virus [24]. *In silico* studies have been instrumental in studying the interactions between potential drug candidates and viral targets, aiding in the identification and optimization of compounds with therapeutic potential against SARS-CoV-2 [25]. These computational approaches enable the rapid screening and evaluation of large libraries of

molecules, accelerating the drug discovery process and offering valuable insights for the design of new treatments [26, 27].

Natural products, such as those derived from plants, have historically been a source of potential drugs. They often contain diverse chemical compounds that may exhibit biological activities [28]. Some natural products, such as certain plant extracts or herbal remedies, have been investigated for their antiviral properties in general [29, 30], but their effectiveness against COVID-19 specifically is still being studied. It's worth mentioning that while natural products may have potential therapeutic properties, rigorous scientific investigation, including clinical trials, is necessary to establish their safety and efficacy for COVID-19 treatment.

The findings highlight the diverse capabilities of numerous medicinal plants in employing a multimodal approach, encompassing anti-viral effects for the management of COVID-19 [31]. Previous studies have reported the potential virucidal effects of GP against the influenza virus, indicating that extracts derived from *Gossypium* leaves demonstrated inhibitory effects on viral adsorption and replication within host cells [32, 33]. Although there are many herbs with reported anti-viral effects, and GP and AT-101 (Figure 1) show a wide range of biological effects, there is no information about their potential anti-COVID effects.

The biological properties of a drug molecule at a specific therapeutic target receptor are shaped by its spatial structure. This structure, influenced by the connectivity of the constituent atoms, determines the molecule's geometry. When this spatial arrangement introduces asymmetry, the molecule exhibits optical activity, resulting in the existence of enantiomeric pairs. It is known that enantiomers have different binding pockets due to their different conformations, thus exhibiting differences in binding energies, leading to different conformations within chiral selective structures.

Table 1. Interaction of the ACE2 receptor with GP or AT-101

Protein name	Docking Score (Binding Energy, Kcal/mol)	H Bond	Amino acid Residue
AT-101/ACE2	-118.086	-13.425	Tyr199, Lys187, Asp 509, Trp203, Ser511, Ala99, Leu100, Ser77, Leu73, Gln102, Asn103
Gossypol/ACE2	-96.996	-23.605	Asp382, Glu375, Ala348, Glu402, Asn397, His401, Phe400, Glu398, Gly395, Asp206

Molecular docking studies could identify highly active compounds, based on binding energy scores. The compounds with the lowest binding energy of the docking scores are usually the most effective in inhibiting the target receptor because lower binding energy equates to higher binding affinity [34].

Amino acid residues, H bond, and docking scores corresponding to the binding energies of the screened compounds with ACE2 are presented inTable 1. Each of the compounds effectively docked with ACE2 receptor (Figure 2). Both of them had negative ACE2 binding energy values, indicating positive interactions with the ACE2 active sites. The binding energy of the GP was -96.996 indicating a good binding affinity. Active site residues were Glu375, Ala348, Asn397, His401, Phe400, Gly395, Asp206 (Figure 3A). AT-101 had the impressive binding energy value, which was -118.086 kcal/mol showing effectively docked against ACE2. It established steric contacts with Trp203, Ser77, Gln102, Asn103, hydrogen interactions with Tyr199, Lys187, Asp509, Ser511, Ala99,

Ser77, Leu73 (Figure 3B). It also formed steric interactions with Ala348, Glu402, Asn397, His401.

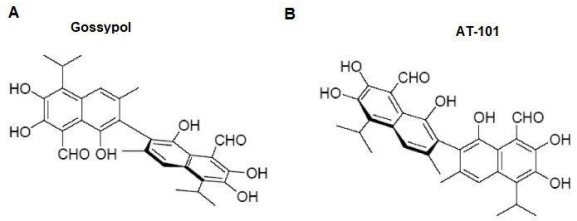

Figure 1. Chemical structures of (A) GP and (B) AT-101

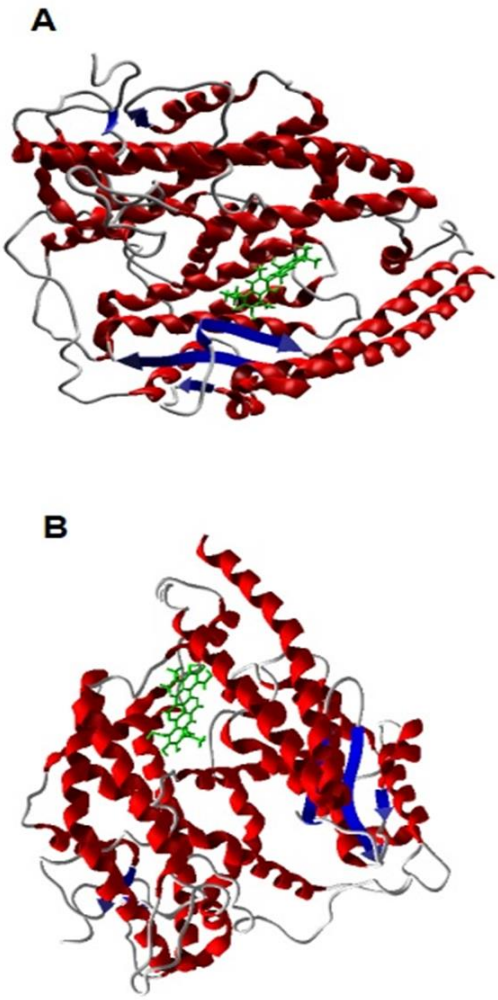

Figure 2. Molecular docking of ACE2 receptor with (A) GP and (B) AT-101

The results clearly show that AT-101 has better binding values. GP was described as an anti-HIV drug in 1989 [35], but no data on its effectiveness in any assays were provided. Novel GP compounds were created and their anti-HIV-1 and anti-H5N1 properties were tested *in vitro* [36]. The virus entrance stage of cell infection may be compromised by these novel GP compounds describing them as a new type of antiviral agent. However, there is no study investigating the anti-viral effect of AT-101.

The stability of protein-ligand interactions relies on the presence of hydrogen bonds (H-bonds), which are intermolecular forces responsible for keeping two or more molecules bound together [37]. H-bond interactions were shown in Figure 3, Based on this analysis, GP has 7 H-bonds with ACE2 and AT-101 has 8 H-bonds with ACE2. The presence of six phenolic hydroxyl groups and two aldehydic groups makes GP chemically reactive. GP, due to the limited rotation of its internaphthyl bond, is classified as a chiral compound. The atropisomeric (-)-gosypol form of GP is AT-101 and formed more H-bonds than GP. Since the two molecules have different binding pockets, their binding affinities and therefore their activities were determined to be different from each other. As our findings are supported, many previous studies have shown that AT-101 is more active and effective than GP in biological systems. The critical role of the interaction between potential antiviral compounds and ACE2 in facilitating virus entry into host cells makes it an important target for therapeutic and vaccine development. Obtaining a comprehensive understanding of the intricate structure of this interaction offers valuable insights into the virus's mechanism of cell entry and potential strategies for prevention. However, further research is necessary to assess its long-term safety and effectiveness.

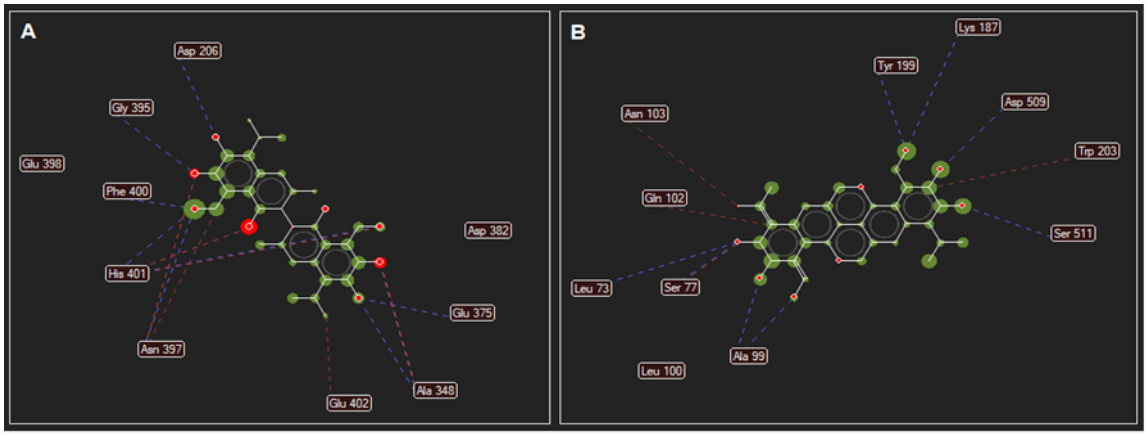

Figure 3. Molecular docking of ACE2 receptor and (A) GP or (B) AT-101 and interactions with key residues

The stability of the docked complex was evaluated by calculating the root mean square deviation (RMSD) of each trajectory record throughout 4.2 picoseconds during the 1.0 nanosecond MD simulation, with respect to the initial position of the docked complex. The plot demonstrates that the RMSD values of GP (A) and AT-101 (B) have a steep increase due to the initial binding to the substrate in the period of approximately 0.01 ns (Figure 4). GP takes 0.2 ns and AT-101 takes 0.15 ns to reach a stabilized conformation. To further confirm the stability of the protein-ligand complex, we also monitored the RMSF of specific residues involved in interactions. RMSF depends on the RMSD graph, where more fluctuations in the RMSF graph generally provide a less stable RMSD graph. An RMSF value exceeding 2.5 Å suggests instability in these particular sites. Based on the results, it is evident that AT-101 exhibits the lowest degree of fluctuation (Figure 5).

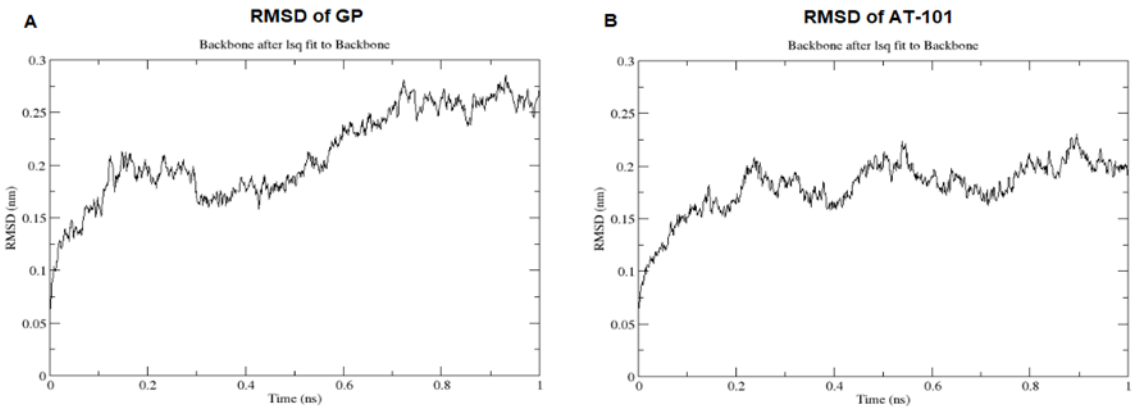

Figure 4. Root mean square deviation (RMSD) for a 1 ns period of MD simulation studies for (A) GP and (B) AT-101

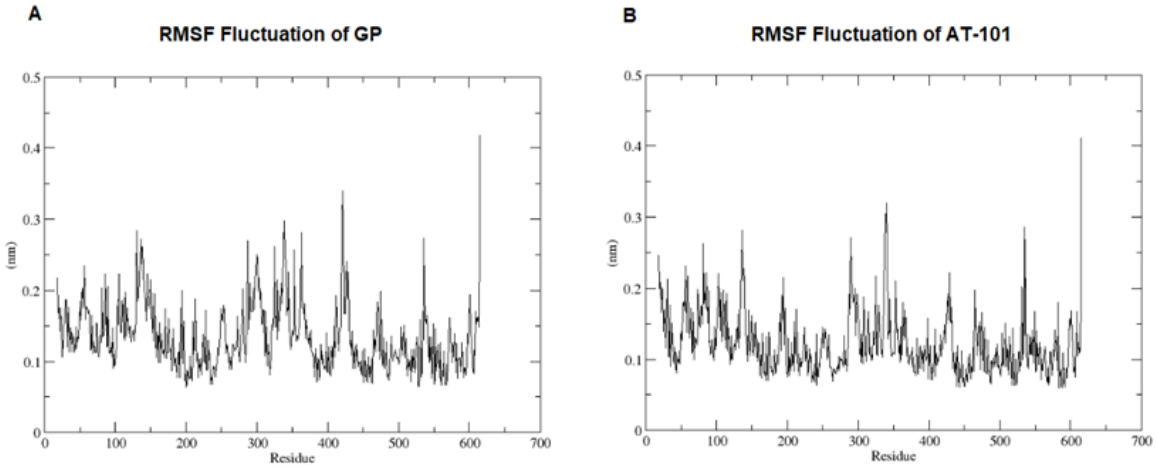

Figure 5. Root mean square fluctuation (RMSF) for (A) GP and (B) AT-101

Moreover, we have investigated the protein-ligand contact simulation results to verify docking scores. For GP, the dominant contribution to the interaction arises from the Asn397 residue where hydrogen bond and water bridge interactions collectively constitute an interaction fraction of 0.6 (equivalent to 60% of the total interaction). The other interactions are given by other residues that help the protein-ligand interaction His401 and Ala348 where the combination of H-bonds and water bridges with interaction fractions of approximately 0.5 and 0.65, respectively. For AT-101, Ala99 residue has the highest interaction overall, with an interaction value of 1.2, and the other contributing residues were Ser77 and Leu73.

4. Conclusion

The anti-viral property of GP has been demonstrated *in silico* and confirmed in vitro. However, there are neither *in silico* nor *in vitro* anti-viral studies on AT-101. The anti-COVID effects of both GP derivatives are not available in the literature. In this study, the anti-COVID capacity of GP and AT-101 was demonstrated for the first time by *in silico* methods.

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The Declaration of Research and Publication Ethics
The authors of the paper declare that they comply with the scientific, ethical and quotation rules of SAUJS in all processes of the paper and that they do not make anfalsification on the data collected. In addition, they declare that Sakarya University Journal of Science and its editorial board have no responsibility for any ethical violations that may be encountered, and that this study has not been evaluated in any academic publication environment other than Sakarya University Journal of Science.

References

[1] D. Pal, P. Sahu, G. Sethi, C. E. Wallace, A. Bishayee, “Gossypol and Its Natural Derivatives: Multitargeted Phytochemicals as Potential Drug

Candidates for Oncologic Diseases," Pharmaceutics, vol. 14, no. 12. 2022.

[2] J. A. Kenar, "Reaction chemistry of gossypol and its derivatives," *JAOCS*, Journal of the American Oil Chemists' Society, vol. 83, no. 4. 2006.

[3] I. C. N. Gadelha, N. B. S. Fonseca, S. C. S. Oloris, M. M. Melo, B. Soto-Blanco, "Gossypol toxicity from cottonseed products," *S*cientific World Journal, vol. 2014. 2014.

[4] I. Marzo J. Naval, "Bcl-2 family members as molecular targets in cancer therapy," Biochemical Pharmacology, vol. 76, no. 8. 2008.

[5] K. Balakrishnan, W. G. Wierda, M. J. Keating, V. Gandhi, "Gossypol, a BH3 mimetic, induces apoptosis in chronic lymphocytic leukemia cells," Blood, vol. 112, no. 5, 2008.

[6] D. Caylioglu, R. J. Meyer, D. Hellmold, C. Kubelt, M. Synowitz, J. Held-Feindt, "Effects of the anti-tumorigenic agent at101 on human glioblastoma cells in the microenvironmental glioma stem cell niche," International Journal of Molecular Science, vol. 22, no. 7, 2021.

[7] X. Pang, Wu, Y., Wu, Y., Lu, B., Chen, J., Wang, J., M., Liu, "(-)-Gossypol suppresses the growth of human prostate cancer xenografts via modulating VEGF signaling-mediated angiogenesis," Molecular Cancer Therapeutics, vol. 10, no. 5, 2011.

[8] M. P. Kline, Rajkumar, S. V., Timm, M. M., Kimlinger, T. K., Haug, J. L., Lust, J. A., S. Kumar, "R-(-)-gossypol (AT-101) activates programmed cell death in multiple myeloma cells," Experimental Hematology, vol. 36, no. 5, 2008.

[9] J. A. Macoska, S. Adsule, K. Tantivejkul, S. Wang, K. J. Pienta, C. T. Lee, "-(-)Gossypol promotes the apoptosis of bladder cancer cells in vitro," Pharmacological research, vol. 58, no. 5–6, 2008.

[10] T. Ren Shan, J., Qing, Y., Qian, C., Li, Q., Lu, G., S. F., Zhou, "Sequential treatment with AT-101 enhances cisplatin chemosensitivity in human non-small cell lung cancer cells through inhibition of apurinic/apyrimidinic endonuclease I-activated IL-6/STAT3 signaling pathway," Drug design, development and therapy, vol. 8, 2014.

[11] G. B. Patil, D. M. Borse, M. P. More, D. A. Patil, "Gossypol-Embedded Casein Nanoparticles for Potential Targeting of Ovarian Cancer: Formulation, Characterization, and Anticancer Activity," Journal of Pharmaceutical Innovation, vol. 12, no.1, 2022.

[12] O. Renner, Mayer, M., Leischner, C., Burkard, M., Berger, A., Lauer, U. M., S. C. Bischoff, "Systematic Review of Gossypol/AT-101 in Cancer Clinical Trials," Pharmaceuticals, vol. 15, no. 2, 2022.

[13] L. Li, Li, Z., Wang, K., Zhao, S., Feng, J., Li, J., Q. Wang, "Design, synthesis, and biological activities of aromatic gossypol schiff base derivatives," Journal of agricultural and food chemistry, vol. 62, no. 46, 2014.

[14] J. Yang Chen, G., Li, L. L., Pan, W., Zhang, F., Yang, J., P. Tien, "Synthesis and anti-H5N1 activity of chiral gossypol derivatives and its analogs implicated by a viral entry blocking mechanism," Bioorganic and medicinal chemistry letters, vol. 23, no. 9, 2013.

[15] A. J. Lopez-Denman, A. Russo, K. M. Wagstaff, P. A. White, D. A. Jans, J. M. Mackenzie, "Nucleocytoplasmic shuttling of the West Nile virus RNA-dependent RNA polymerase NS5 is critical to infection," Cellular Microbiology, vol. 20, no. 8, 2018.

[16] S. C. Atkinson, Audsley, M. D., Lieu, K. G., Marsh, G. A., Thomas, D. R., Heaton, S. M., N. A., Borg, "Recognition by host nuclear transport proteins drives disorder-to-order transition in Hendra virus v," Scientific Reports, vol. 8, no. 1, 2018.

[17] Y. Gao, Tai, W., Wang, X., Jiang, S., Debnath, A. K., Du, L., S. Chen, "A gossypol derivative effectively protects against Zika and dengue virus infection without toxicity," BMC Biology, vol. 20, no. 1, 2022.

[18] W. Wang, Li, W., Wen, Z., Wang, C., Liu, W., Zhang, Y., Li, "Gossypol Broadly Inhibits Coronaviruses by Targeting RNA-Dependent RNA Polymerases," Advanced Science, vol. 9, no. 35, 2022.

[19] Q. Wang, Zhang, Y., Wu, L., Niu, S., Song, C., Zhang, Z., J. Qi, "Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2," Cell, vol. 181, no. 4, 2020.

[20] R. Wang, Zhang, Q., Ge, J., Ren, W., Zhang, R., Lan, J., Zhang, L. "Analysis of SARS-CoV-2 variant mutations reveals neutralization escape mechanisms and the ability to use ACE2 receptors from additional species," Immunity, vol. 54, no. 7, 2021.

[21] E. Song, Zhang, C., Israelow, B., Lu-Culligan, A., Prado, A. V., Skriabine, S., A., Iwasaki, "Neuroinvasion of SARS-CoV-2 in human and mouse brain," Journal of Experimental Medicine, vol. 218, no. 3, 2021.

[22] C. G. K. Ziegler, Allon, S. J., Nyquist, S. K., Mbano, I. M., Miao, V. N., Tzouanas, C. N., K. Zhang, "SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues," Cell, vol. 181, no. 5, 2020.

[23] A. Basu, A. Sarkar, U. Maulik, "Molecular docking study of potential phytochemicals and their effects on the complex of SARS-CoV2 spike protein and human ACE2," Scientific Reports, vol. 10, no. 1, 2020.

[24] Z. Jin, Du, X., Xu, Y., Deng, Y., Liu, M., Zhao, Y., H. Yang, "Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors," Nature, vol. 582, no. 7811, 2020.

[25] A. G. Junior, S. E. L. Tolouei, F. A. dos Reis Lívero, F. Gasparotto, T. Boeing, and P. de Souza, "Natural Agents Modulating ACE-2: A Review of Compounds with Potential against SARS-CoV-2 Infections," Current Pharmaceutical Design, vol. 27, no. 13, 2021.

[26] S. Barage, Karthic, A., Bavi, R., Desai, N., Kumar, R., Kumar, V., K. W., Lee, "Identification and characterization of novel RdRp and Nsp15 inhibitors for SARS-COV2 using computational approach," Journal of Biomolecular Structure and Dynamics, vol. 40, no. 6, 2022.

[27] J. O. Ogidigo, E. A. Iwuchukwu, C. U. Ibeji, O. Okpalefe, M. E. S. Soliman, "Natural phyto, compounds as possible noncovalent inhibitors against SARS-CoV2 protease: computational approach," Journal of Biomolecular Structure and Dynamics, vol. 40, no. 5, 2022.

[28] F. Zhu, Qin, C., Tao, L., Liu, X., Shi, Z., Ma, X., Y. Chen, "Clustered patterns of species origins of nature-derived drugs and clues for future bioprospecting," Proceedings of the National Academy of Sciences, vol. 108, no. 31, 2011.

[29] V. S. L. Goh, C. K. Mok, J. J. H. Chu, "Antiviral natural products for arbovirus infections," Molecules, vol. 25, no. 12. 2020.

[30] M. F. Montenegro-Landívar, Tapia-Quirós, P., Vecino, X., Reig, M., Valderrama, C., Granados, M., J. Saurina, "Polyphenols and their potential role to fight viral diseases: An overview," Science of the Total Environment, vol. 801. 2021.

[31] X. Y. Lim, B. P. Teh, T. Y. C. Tan, "Medicinal Plants in COVID-19: Potential and Limitations," Frontiers in pharmacology, vol. 12, 2021.

[32] L. Li, Z. Li, K. Wang, Y. Liu, Y. Li, Q. Wang, "Synthesis and antiviral, insecticidal, and fungicidal activities of gossypol derivatives containing alkylimine, oxime or hydrazine moiety," Bioorganic Medicinal Chemistry, vol. 24, no. 3, 2016.

[33] L. F. de Lima, J. O. de Oliveira, J. N. P. Carneiro, C. N. F. Lima, H. D. M. Coutinho, M. F. B. Morais-Braga, "Ethnobotanical and antimicrobial activities of the Gossypium (Cotton) genus: A review," Journal of Ethnopharmacology, vol. 279. 2021.

[34] L. Simon, A. Imane, K. K. Srinivasan, L. Pathak, I. Daoud, "In Silico Drug-Designing Studies on Flavanoids as Anticolon Cancer Agents: Pharmacophore Mapping, Molecular Docking, and Monte Carlo Method-Based QSAR Modeling," Interdisciplinary Sciences: Computational Life Sciences, vol. 9, no. 3, 2017.

[35] T. S. Lin, Schinazi, R., Griffith, B. P., August, E. M., Eriksson, B. F., Zheng, D. K., W. H. Prusoff, "Selective inhibition of human immunodeficiency virus type 1 replication by the (-) but not the (+) enantiomer of gossypol," Antimicrobial agents and chemotherapy, vol. 33, no. 12, 1989.

[36] Y. Liu, L. Wang, L. Zhao, Y. Zhang, "Structure, properties of gossypol and its derivatives from physiological activities to drug discovery and drug design," Natural Product Reports, vol. 39, no. 6. 2022.

[37] S. A. Gouhar Z. A. Elshahid, "Molecular docking and simulation studies of synthetic protease inhibitors against COVID-19: a computational study," Journal of Biomolecular Structure and Dynamics, vol. 40, no. 24, 2022.