Research Article

Türk Fen ve Sağlık Dergisi
Turkish Journal of Science and Health

Volume 2
Number 2
Year 2021
Pages 40-47

e-ISSN: 2717-7173 https://dergipark.org.tr/tr/pub/tfsd

Received: 28.12.2020 Accepted: 09.04.2021 https://doi.org/10.51972/tfsd.848202

Extracts of *Mesua ferrea Linn* as the Natural Inhibitors of COVID-19 Main Protease: A Computational Quest

Aisha Saddiqa[1]*, Osman Çakmak[2], Muhammad Usman[3], Salih Ökten[4]

[1]Department of Chemistry, Government College Women University, Sialkot, Pakistan
[2]Department of Gastronomy, Faculty of Arts and Design, İstanbul Rumeli University, Silivri, İstanbul, Turkey
[3]Department of Chemistry, Lahore Garrison University, Lahore, Pakistan
[4]Department of Maths and Science Education, Division of Science Education, Faculty of Education, Kırıkkale University, Yahşihan, Kırıkkale, Turkey

ABSTRACT:
Purpose: The coronavirus, known as severe acute respiratory syndrome (SARS-CoV-2), is accountable for the global epidemic disease COVID-19. The effective treatment of this disease is still unknown and there is an emergent need to use all resources to find the effective medication. The use of off-label natural medicinal compounds may be effective remedy for this scourge. For this reason, it was aimed to investigate the theoretical effect of *Mesua ferrea Linn*, an Asian medicinal plant, against COVID-19 disease.
Material and Methods: In silico studies, molecular docking was performed using AutoDock Tools (ADT) version 1.5.6 package, and the coupling processes were performed using AutoDock 4.2 package.
Results: Towards the investigation of effective inhibitor of 3CL protease, we studied the *in silico* interaction of the selected compounds of *Mesua ferrea Linn*. The studied compounds have shown significant inhibition properties. The timber extracts, Mesuabixanthone-B (ΔG_{bind} = -15.51 kcal/mol) and Mesuferrol-B (ΔG_{bind} = -14.32 kcal/mol) have the exciting impact on 6LU7.
Conclusion: The *in silico* prediction of toxicities of the extracts are promising. The further lab research is necessary to identify their drug candidate capabilites against COVID-19 infections.
Keywords: *Coronavirus, Mesua ferrea Linn, molecular docking, autodock, 6LU7*

COVID-19 Ana Proteazının Doğal Inhibitörleri Olarak *Mesua ferrea Linn*'in Özleri: Hesaplamalı Bir Araştırma

ÖZET:
Amaç: Şiddetli akut solunum sendromu (SARS-CoV-2) olarak bilinen koronavirüs, küresel salgın COVID-19 hastalığından sorumludur. Bu hastalığın etkili tedavisi hala bilinmemektedir ve etkili ilacı bulmak için tüm kaynakların kullanılmasına acil bir ihtiyaç vardır. Başka bir hastalık tedavisinde kullanılan doğal tıbbi bileşikler bu hastalık için etkili bir çare olabilir. Bu sebeple bir Asya tıbbi bitkisi olan *Mesua ferrea Linn* COVID-19 hastalığına karşı teorik olarak etkisinin araştırılması amaçlanmıştır.
Gereç ve Yöntem: In siliko çalışmalarda, moleküler yerleştirme, AutoDock Tools (ADT) sürüm 1.5.6 paketi kullanılarak birleştirme işlemleri ise AutoDock 4.2 paketi kullanılarak gerçekleştirildi.
Bulgular: 3CL proteazın etkili inhibitörünün araştırması için, *Mesua ferrea Linn*'in seçilen bileşiklerinin *in siliko* etkileşimini inceledik. İncelenen bileşikler, etkili inhibisyon özellikleri göstermiştir. Ağaç özleri, Mesuabixanthone-B (ΔG_{bind} = -15.51 kcal/mol) ve Mesuferrol-B (ΔG_{bind} = -14.32 kcal/mol), 6LU7'da heyecan verici etkiye sahiptirler.
Sonuç: Ekstrelerin toksisitelerinin in silico tahmini ümit vericidir. Bunların COVID-19 enfeksiyonlarına ilaç adayı kapasitelerinin belirlenmesi için daha fazla laboratuvar araştırması gereklidir.
Anahtar Kelimeler: *Koronavirüs, Mesua ferrea Linn, moleküler yerleştirme, autodock, 6LU7*

*Corresponding author: Aisha Saddiqa, email: aashe06@gmail.com, aisha.saddiqa@gcwus.edu.pk

INTRODUCTION

Among viruses, the coronavirus has gained much significance. A number of coronaviruses has been identified during the last decade. They are the potent infectants with diverse range of hosts from mammals to birds (Peiris et al., 2003; Masters, 2006). COVID-19, a novel coronavirus has been first reported from Wuhan in China and associated with rapid inter-human transmission, leading to various infections symptoms such as pneumonia, cough, weakness and digestive tract problems. Upon the exhaustive examination, it was observed that the COVID-19 mainly consist of three essential proteins: PLpro, 3CL and spike proteins (Zhang et al., 2020). The 3CLpro main protease (PDB: 6LU7) is responsible for regulating vital functions in the virus body (Anand et al., 2003; Jin et al., 2020). The most important function which makes this protein an ideal target for the medicinal chemists is replication process and by inhibiting these proteins with the help of innocuous natural products can reduce the severity of infection (Bacha et al, 2004). Mesua ferrea Linn (Ceylon iron wood) belongs to family Clusiaceae, is a rich source of secondary metabolites and is blessed with diverse medicinal properties e.g. antioxidant, antimicrobial, antiviral, antitumor and immunomodulatory (Teh et al., 2012; Asif et al., 2016). This evergreen plant is found abundantly in the Asian countries. Traditionally, the various parts of this plant is use for treatment of various diseases. A number of medicinal compounds have been isolated from the seed oil with significant antispasmodic, antibacterial and hypotensive activity (Verotta et al., 2004; Adewale et al., 2011; Chanda et al., 2013). Additionally, the seed oil is beneficial for the soothing the itch (Jalalpure et al., 2011). The ornamental flowers exhibit various medicinal assets including an antidote for the venomous snake bite. Furthermore, the paste of flower, butter and sugar is traditionally recommended for the treatment of bleeding piles and burning of feet. Leaves extracts are beneficial for cough, stomach disorders and the treatment of scorpion prickle (Neligan, Hauser, & Sander, 2012). The use of medicinal herbs is an ancient method for the treatment of infectious diseases (Hsu et al., 2008; Asadbeigi et al., 2014; Lin, Hsu, & Lin, 2014; Chaachouay et al., 2019).

MATERIAL and METHODS

Purpose and Type of the Study

The specific remedy for COVID-19 is still unidentified. Therefore, several ethnophamacological attempts have been made for the treatment of the viral infection (Aktas et al., 2020; Cetiner et al., 2020; Gedikli et al., 2021). In order to find the most suitable molecule for the treatment of COVID-19, herein, we demonstrated the computational interaction between the *Linn* extracts and Mpro. A clever experimentalist can get direction from the current study in order to find the suitable natural product for the treatment of COVID-19 infections.

Data Collection Tools (3D structure of the ligands and receptor)

The crystal structure of the $3CL^{pro}/M^{pro}$ COVID-19 (PDB ID: 6LU7) was downloaded from the Protein Data Bank (PDB) (Berman et al., 2000). The small molecules of *Mesua ferrea Linn* are selected from literature (Table 1) (Chahar, 2013; Sharma et al., 2017) and all 3D structures of the ligands except Mesuabixanthone-A and -B, were obtained from PubChem Open Chemistry Database (Kim et al., 2019). The 3D structures of Mesuabixanthone-A and –B were obtain from ChemDraw professional 17.1.

Molecular Docking

The residues inside the active pocket of 6LU7 were determined by Biovia Discovery studio client 2020 (Systemes Dassault, 2016). The molecular docking was performed using AutoDock Tools (ADT) version 1.5.6 package and the coupling processes use the AutoDock 4.2 package which is assisted by AutoDock and MGL tools. The protein is set as rigid while the ligands as flexible. The global search was doing Lamarckian genetic algorithm (Goodsell et al., 1996; Morris et al., 1998; Morris et al., 2008; Huey et al., 2012; Ravindranath et al., 2015). The reported binding interaction of chloroquine and small molecules showed the standard interaction (Samant & Javle, 2020) with MET49. This evidence was kept under consideration while adjusting the grid box. The box size was adjusted at 60 x 60 x 60 Å with spacing 0.5 Å. The docking results were interpreted and pictured with the help of PyMOL Molecular Graphics System (Schrödinger LCC, 2020) and Biovia

Discovery studio client 2020 systemes (Systemes Dassault, 2016).

Toxicity Prediction

The cardiotoxicity and carcenoginicity were predicted from the webserver eMOLTox (Ji et al., 2018). while the software TEST (Martin, 2016) facilitated the mutagenicity forecast. The site of metabolism is calculated from the web server SOMP (Rudik et al., 2015). The SMILES strings of each compound was submitted to the web server. The SOM prediction results include a tested structure with numbered atoms and tables, which include the atoms and their ranks according to the probability to be attacked by each enzyme. The result was saved in the form of PDF files, which contain CYPs and UGT tables with the prediction results.

RESULTS and DISCUSSION

Keeping in view the tremendous medicinal applications of *Mesua ferrea Linn*, we selected some small molecules (flavonoids, coumarins, xanthones etc.) from the various parts of the tree and carried out Molecular Docking simulations in order to identify the suitable inhibitors against the coronavirus peptidase (PDB ID: 6LU7).

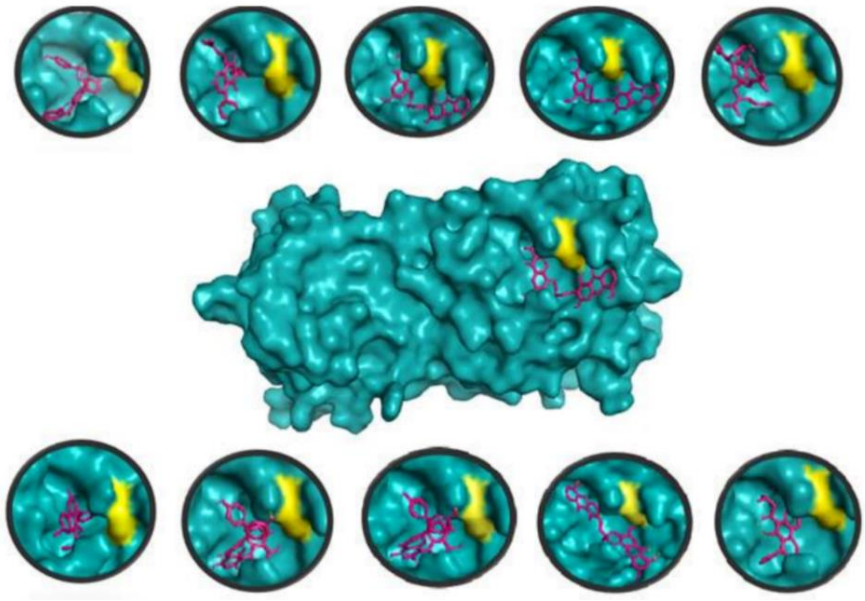

Figure 1. The surface presentation of 6LU7 peptidase receptor (blue) with ligands (pink sticks) in the binding pocket and residue MET 49 (yellow).

The molecular docking results, presented in Table 1, indicates that the compounds under investigation showed excellent inhibition activity (Figure 1). Mesuabixanthone-B, extracted from the stem (Taylor et al., 1993) of *Mesua ferrea linn*. has shown the most intense interaction with the target protein (6LU7). The binding energy of -15.51 kcal·mol^{-1} with inhibition constant of 0.0043 nM indicates that the compound under observation possess the excellent molecular affinity (Table 1, Figure 3). The two hydrogen bridges positioned on the residues THR 26 and GLY 143, formed the strongest interaction between the ligand and the protein. Another dimeric xanthone called Mesuabixanthone-A (Taylor et al., 1993) is a stem extract and exhibit attractive molecular affinity value -13.32 kcal·mol^{-1} and an inhibition constant 0.173 nM. The residues THR 24, THR 26, GLY 143, HIS 164 and ARG 188 form the intense hydrogen bond interaction with the ligand molecule (Figure 2).

The docking molecular affinity studies of Mesuaferrol-A and Mesuaferrol-B, found in the timber extract, revealed to exhibit the excellent inhibitory properties with binding energy of -13.91 and 14.32 kcal·mol^{-1} respectively. The value of their inhibition constants 0.063 nM and 0.032 nM respectively, strongly endorse that the both compounds are potential inhibitors. The amino acids THR 26, GLY 143, ASP187 and GLN 189 are involve in hydrogen link interaction.

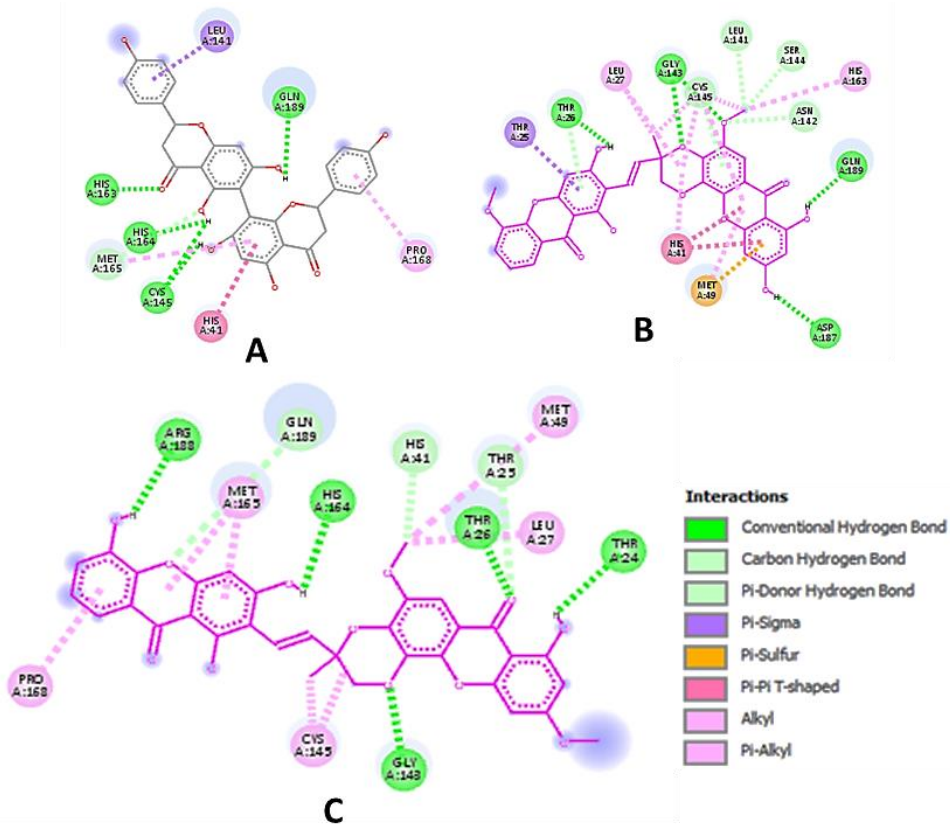

Figure 2. The interactions of selected ligands with active residues of 6LU7. **A**) Rusflavanone, **B**) Mesuaferrol-B, **C**) Mesuabixanthone-A

Table 1. Molecular affinity parameters of the ligands with 6LU7

Ligand (pubchem id)	Isolated from	ΔG_{bind} (kcal·mol^{-1})	*(IME, IE, TFE, UBS) (kcal·mol^{-1})	K_i (nM)	Amino acid interact via hydrogen bonds
Rhusflavanone 466314	Stamen, flower	-12.95	-15.63, -5.10, +2.68, -5.10	0.324	CYS 145, HIS 163, HIS 164, GLN 189
Mesuol 5277586	Seed oil	-11.91	-14.00, -2.64, +2.09, -2.64	1.85	HIS 164
Mesuaferrol-B 101995076	Stem bark	-14.32	-16.70, -2.76, +2.39, -2.76	0.032	THR 26, GLY 143, ASP187, GLN 189
Mesuaferrol-A 101995075	Stem bark	-13.91	-16.30, -3.19, +2.39, -3.19	0.063	THR 26, GLY 143, ASP187
Mesuagin 5319380	Flower, seed	-11.17	-12.36, -1.80, +1.19, -1.80	6.52	CYS 145, HIS 164
Mesuaferrone-B 90472563	Stamen, flower	-12.79	-15.47, -6.46, +2.68, -6.46	0.423	PHE 140, LEU141, GLY 143, SER 144, CYS 145, GLU 166, HIS 172
Mesuaferrone-A 101324837	Flower stamen	-12.79	-15.48, -6.47, +2.68, -6.47	0.418	PHE 140, LEU141, GLY 143, SER 144, CYS 145, GLU 166, HIS 172
Mesuabixanthone-B-	Stem bark	-15.51	-17.89, -2.91, +2.39, -2.91	0.0043	THR26, GLY 143
Mesuabixanthone-A-	Stem bark	-13.32	-15.70, -3.12, +2.39, -3.12	0.173	THR 24, THR 26, GLY 143, HIS 164, ARG 188
Mammeigin 5319255	Seeds and flowers	-11.20	-12.69, -2.19, +1.49, -2.19	6.17	GLY 143, GLU 166
Mesuanic acid 101277421	Stamen, flower	-10.70	-14.58, -4.87, +3.88, -4.87	14.26	-

*IME = intermolecular energy, IE = internal energy, TFE = tortional free energy, UBS = unbound system energy

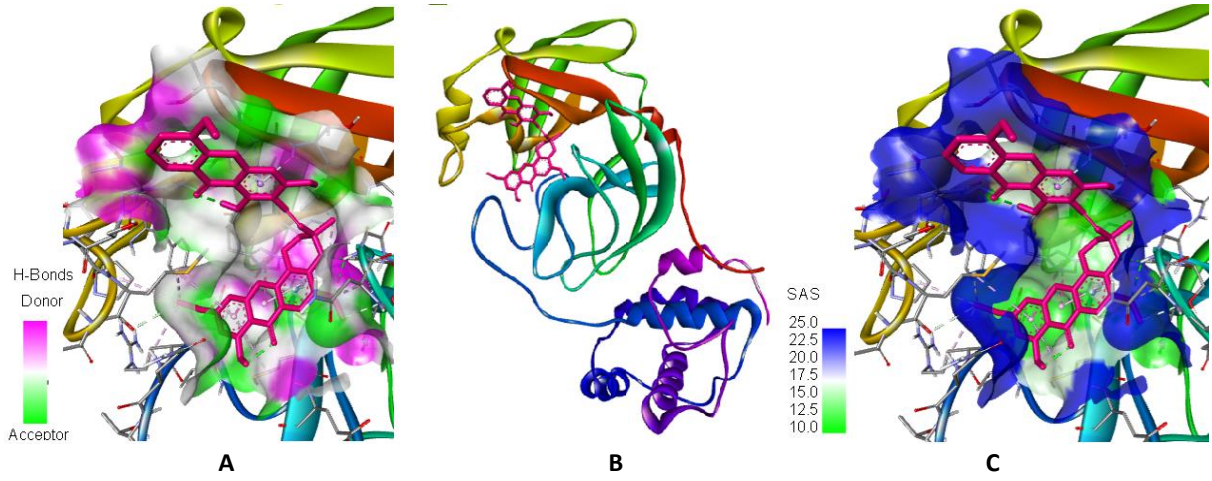

Figure 3. Different presentations of 6LU7 main protease with Mesuabixanthone-B (pink stick) **A)** hydrogen bond donor and acceptor surface on 6LU7 **B)** cartoon presentation of protein with the ligand **C)** solvent accessibility surface on the receptor

The stamen extracts, Rhusflavanone, Mesuaferrone-A, Mesuaferrone-B and Mesuanic acid unveiled the in silico binding energies as -12.95, -12.79, -12.79 and 10.70 kcal·mol^{-1} respectively with low values of inhibition constants (0.324, 0.418, 0.423 and 14.26 respectively). The molecular interaction of Mesuanic acid did not result in hydrogen bondings, unlike the other three stamen extracts where PHE 140, LEU141, GLY 143, SER 144, CYS 145, HIS 163, HIS 164, GLU 166, HIS 172 and GLN 189 are the prominent hydrogen bonding residues. Conversely, in Mesuanic acid, the residues HIS 41, MET165 and pro168, present a strong interaction in the active border of the target. Mesuol (Márquez et al., 2005), Mesuagin (Bhattacharyya et al., 1979; Wezeman et al., 2015) and Mammeigin were isolated from the seed extract. The docking results of these coupled compounds with the active site of 6LU7 showed the ΔG_{bind} and inhibition constants -11.91 kcal·mol^{-1} (K_i = 1.85 nM), -11.17 kcal·mol^{-1} (K_i = 6.52 nM) and -11.20 kcal·mol^{-1} (6.17 nM) respectively. The docking analysis of small molecules reflected typical interaction with MET49 residue (Samant et al., 2020) among our studied compounds, Mesuferrol (Zar et al., 2019), Mesuagin, Mesuabixanthone-A and Mammeigin showed interaction with MET49 but these interactions did not result in hydrogen bridge.

Next, the selected compounds are subjected to test for various toxicity assessment parameters (Table 2). Mutagenicity is the aptitude of a substance to stimulate mutations by interacting with DNA and to change its structure. A carcinogen is a type of mutagen that specifically causes cancer. Drug metabolism directly influence the drug effectiveness and toxicity. The metabolism reactions are classified into Phase I (oxidation, hydrolysis, reduction) and Phase II (conjugation). The Phase I enzymes includes Cytochromes P450 (CYP) (Lewis & Ito, 2008; Williams et al., 2004), which metabolize most drugs. Glucuronidation is the main reaction of Phase II, which is catalysed by UDP-glucuronosyltransferase (UGT) and serves as a clearance mechanism for drugs from many therapeutic classes (King et al., 2000). Site of metabolism prediction process identifies the location in a chemical structure, which is most likely to undergo metabolization, hence aiding with decision support in the drug optimization process. A positive result suggests liability of the site for metabolism while negative results point out the resistance of the moiety for undergoing metabolism. The inhibition of this CYP isoforms reduces the elimination and change in metabolic pathways of their substrates, which is the major cause of adverse drug-drug interactions.The toxicity assessment of the *Linn* extracts is displayed in Table 2 which clearly indicates that all compounds are non-carcinogenic and are susceptible to the metabolism. The negative or weak results in the mutagenicity and cardiotoxicity columns suggest that compounds are computationally predicted to be safe. Whereas

positive outcome provide computational evidence of the compound to be potential toxic. Overall, the study shows that compounds are likely to exhibit low probable toxicity risks.

The results obtained from AutoDock and toxicity calculation reflect that the candidates under investigation appeared to have the excellent potential to act as 6LU7 inhibitor. Nevertheless, further experimental studies are also required to investigate their potential medicinal use against COVID-19 main protease.

Table 2. Predicted toxicity parameters of *Mesua ferrea Linn*. Extracts

Entry	Toxicity			Site of metabolism
	Cardiotoxicity	Carcinogenicity	Mutagenicity	
Rhusflavanone	negative	negative	negative	U: 32, 40, 12, 20.
Mesuol	negative	negative	negative	B: 2, C: 16. U: 12, 29.
Mesuaferrol-B	weak	negative	positive	E: 2, 17. C: 2, 17. D: 2, 17.
Mesuaferrol-A	weak	negative	positive	E: 10. C: 10. D: 10. U: 31, 38, 15.
Mesuagin	negative	negative	negative	U: 1. F: 28.
Mesuaferrone-B	weak	negative	negative	U: 27, 40, 30, 6.
Mesuaferrone-A	weak	negative	negative	U: 6,7,21,23,19,16
Mesuabixanthone-B	weak	negative	positive	E: 43, 44, 8. D: 43, 44. U: 40
Mesuabixanthone-A	weak	negative	positive	D: 44. U: 36.
Mammeigin	negative	negative	negative	B: 30. C: 30. F: 30. U: 30.
Mesuanic acid	weak	negative	negative	U: 30, 37

B = CYP3A4, C = CYP2C19, D = CYP2C9, E = CYP2D6, U = UGT

CONCLUSION

The constituents of *Mesua ferrea Linn* has been chosen to study the interactions against SARS-CoV-2 Mpro (PDB 6LU7). The investigation provided interesting results. The values of binding energies, inhibition constants and toxicity predictions revealed that the observed small molecules are potential inhibitors of 6LU7. These theoretical results allow a direction for further studies in the mode *in vitro* and *in vivo*.

Conflict of interest

We certify that there is no actual or potential conflict of interest in relation to this article.

Author Contributions:

Aisha Saddiqa: Literature, docking, writing.

Osman Cakmak: Writing, editing, review.

Muhammad Usman: Software (Toxicity), literature survey.

Salih Okten: Writing, editing, corrections.

REFERENCES

Adewale, A. I., Mirghani, M. E. S., Muyibi, S. A., Daoud, J. I., Abimbola, M. M. (2011). Disinfection studies of Nahar (Mesua ferrea) seed kernel oil using pour plate method. African Journal of Biotechnology, 10(81), 18749-18754. https://doi.org/10.5897/AJB11.2747

Aktaş, A., Tüzün, B., Aslan, R., Sayin, K., Ataseven, H. (2020). New anti-viral drugs for the treatment of COVID-19 instead of favipiravir. Journal of Biomolecular Structure and Dynamics, (accepted manuscript), 1-11. https://doi.org/10.1080/07391102.2020.1806112

Aktaş, A., Tuzun, B., Taskin, K. A. H., Sayin, K., Ataseven, H. (2020). How do arbidol and its analogs inhibit the SARS-CoV-2? Bratisl. Med. J., 121(10), 705-711. https://doi.org/10.4149/BLL_2020_115

Anand, K., Ziebuhr, J., Wadhwani, P., Mesters, J. R., & Hilgenfeld, R. (2003). Coronavirus Main Proteinase (3CL pro) Structure : Basis for Design of Anti-SARS Drugs. Science, 300, 1763-1767. https://doi.org/10.1126/science.1085658

Asadbeigi, M., Mohammadi, T., Rafieian-Kopaei, M., Saki, K., Bahmani, M., & Delfan, M. (2014). Traditional effects of medicinal plants in the treatment of respiratory diseases and disorders: an ethnobotanical study in the Urmia. Asian Pacific Journal of Tropical Medicine, 7, S364-S368. https://doi.org/https://doi.org/10.1016/S1995-7645(14)60259-5

Asif, M., Shafaei, A., Jafari, S. F., Mohamed,S. K., Ezzat, M. O., Majid, A. S. A., Oon, C. E., Petersen,S. H., Kono,K., Majid, A. M. S. A. (2016). Isoledene from Mesua ferrea oleo-gum resin induces apoptosis in HCT 116 cells through ROS-mediated modulation of multiple proteins in the apoptotic pathways : A mechanistic study. Toxicology Letters, 257, 84-96. https://doi.org/10.1016/j.toxlet.2016.05.027

Bacha, U., Barrila, J., Velazquez-Campoy, A., Leavitt, S. A., & Freire, E. (2004). Identification of Novel Inhibitors of the SARS Coronavirus Main Protease 3CLpro.

Biochemistry, 43(17), 4906-4912. https://doi.org/10.1021/bi0361766

Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I.N., Bourne, P. E. (2000). The Protein Data Bank. Nucleic Acids Research, 28(1), 235-242. https://doi.org/10.1093/nar/28.1.235

Bhattacharyya, P., Chatterjee, D., Chakrabarti, A., Chakraborty, D. P. (1979). Synthesis of Mesuagin, A Plant antibiotic from Mesua ferrea. Indian J. Chem., 17, 111-112.

Cetiner, E., Sayin, K., Tuzun, B., & Ataseven, H. (2020). Could boron-containing compounds (BCCs) be effective against SARS-CoV-2 as anti-viral agent? Bratislava Medical Journal, 122(4), 263-269. https://doi.org/10.4149/BLL_2021_044

Chaachouay, N., Benkhnigue, O., Fadli, M., El Ibaoui, H., El Ayadi, R., & Zidane, L. (2019). Ethnobotanical and Ethnopharmacological Study of Medicinal and Aromatic Plants Used in the Treatment of Respiratory System Disorders in the Moroccan Rif. Ethnobotany Research and Applications, 18, 1-17. http://dx.doi.org/10.32859/era.18.22.1-17

Chahar, K. (2013). Mesua ferrea L.: A review of the medical evidence for its phytochemistry and pharmacological actions. African Journal of Pharmacy and Pharmacology, 7(6), 211219. https://doi.org/10.5897/ajpp12.895

Chanda, S., Rakholiya, K., & Parekh, J. (2013). Indian medicinal herb: Antimicrobial efficacy of Mesua ferrea L. seed extracted in different solvents against infection causing pathogenic strains. Journal of Acute Disease, 2(4), 277-281. https://doi.org/10.1016/S2221-6189(13)60143-2

Gedikli, M. A., Tuzun, B., Aktas, A., Sayin, K., & Ataseven, H. (2021). Are clarithromycin, azithromycin and their analogues effective in the treatment of COVID19? Bratislavske Lekarske Listy, 122(2), 101-110. https://doi.org/10.4149/bll_2021_015

Goodsell, D. S., Morris, G. M., & Olson, A. J. (1996). Automated Docking. Journal of Molecular Recognition, 9, 15. https://doi.org/10.1002/(SICI)1099-1352(199601)9:1%3C1::AID-JMR241%3E3.0.CO;2-6

Hsu, C. H., Hwang, K. C., Chao, C. L., Chang, S. G. N., Ho, M. S., Lin, J. G., Chang, H. H., Kao, S. T., Chen, Y. Mi., Chou, P. (2008). An evaluation of the additive effect of natural herbal medicine on SARS or SARS-like infectious diseases in 2003: A randomized, double-blind, and controlled pilot study. Evidence-Based Complementary and Alternative Medicine, 5(3), 355-362. https://doi.org/10.1093/ecam/nem035

Huey, R., Morris, G. M., & Forli, S. (2012). Using AutoDock 4 and AutoDock vina with AutoDocktools : a tutorial. Retrieved from http://autodock.scripps.edu/faqs-help/tutorial/using-autodock-4-with-autodocktools/2012_ADTtut.pdf

Jalalpure, S. S., Mandavkar, Y. D., Khalure, P. R., Shinde, G. S., Shelar, P. A., & Shah, A. S. (2011). Antiarthritic activity of various extracts of Mesua ferrea Linn seed. Journal of Ethnopharmacology, 138(3), 700-704. https://doi.org/https://doi.org/10.1016/j.jep.2011.09.042

Ji, C., Svensson, F., Zoufir, A., & Bender, A. (2018). eMolTox: prediction of molecular toxicity with confidence. Bioinformatics, 34(14), 2508-2509. https://doi.org/10.1093/bioinformatics/bty135

Jin, Z., Du, X., Xu, Y. et al. (2020). Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. Nature, 582(7811), 289-293. https://doi.org/10.1038/s41586-020-2223-y

Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., et al. (2019). PubChem 2019 update: Improved access to chemical data. Nucleic Acids Research, 47(D1), D1102-9. https://doi.org/10.1093/nar/gky1033

King, C. D., G. R. Rios, Green, M. D., Tephly, T. R. (2000). UDP-Glucuronosyltransferases. Current Drug Metabolism. 1(2), 143-161. https://doi.org/10.2174/1389200003339171

Lewis, D. F. V, & Ito, Y. (2008). Human cytochromes P450 in the metabolism of drugs: new molecular models of enzyme–substrate interactions. Expert Opinion on Drug Metabolism & Toxicology, 4(9), 1181-1186. https://doi.org/10.1517/17425255.4.9.1181

Lin, L.-T., Hsu, W.-C., & Lin, C.-C. (2014). Antiviral Natural Products and Herbal Medicines. Journal of Traditional and Complementary Medicine, 4(1), 24-35. https://doi.org/https://doi.org/10.4103/2225-4110.124335

Márquez, N., Sancho, R., Bedoya, L. M., Alcamí, J., López-Pérez, J. L., San Feliciano, A., et al. (2005). Mesuol, a natural occurring 4-phenylcoumarin, inhibits HIV-1 replication by targeting the NF-κB pathway. Antiviral Research, 66(2-3), 137-145. https://doi.org/10.1016/j.antiviral.2005.02.006

Martin, T. (2016). Toxicity Estimation Software Tool (TEST). Retrieved from https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=NRMRL&dirEntryId=326330#:~:text=Citation%3A,%2C%20Washington%2C%20DC%2C%202016

Masters, P. S. (2006). The Molecular Biology of Coronaviruses. Advances in Virus Research, 65(06), 193-292. https://doi.org/10.1016/S0065-3527(06)66005-3

Morris, G. M., Goodsell, D. S., Halliday, R. S., Huey, R., Hart, W. E., Belew, R. K., & Olson, A. J. (1998). Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. Journal of Computational Chemistry, 19(14), 1639-1662. https://doi.org/doi:10.1002/(SICI)1096-987X(19981115)19:14<1639::AID-JCC10>3.0.CO;2-B

Morris, G. M., Huey, R., & Olson, A. J. (2008). UNIT using AutoDock for ligand-receptor docking. In Current Protocols in Bioinformatics. https://doi.org/10.1002/0471250953.bi0814s24

Neligan, A., Hauser, W. A., & Sander, J. W. (2012). The epidemiology of the epilepsies. In W. H. T. Hermann Stefan (Ed.), Handbook of Clinical Neurology, 107, 113-133). https://doi.org/10.1016/B978-0-444-52898-

8.00006-9

Peiris, J. S. M., Lai, S. T., Poon, L. L. M., Guan, Y., Yam, L. Y. C., Lim, W., … Yuen, K. Y. (2003). Coronavirus as a possible cause of severe acute respiratory syndrome. The Lancet, 361(9366), 1319-1325. https://doi.org/10.1016/S0140-6736(03)13077-2

Ravindranath, P. A., Forli, S., Goodsell, D. S., Olson, A. J., & Sanner, M. F. (2015). AutoDockFR: Advances in Protein-Ligand Docking with Explicitly Specified Binding Site Flexibility. PLOS Computational Biology, 11(12), 1-28. https://doi.org/10.1371/journal.pcbi.1004586

Rudik, A., Dmitriev, A., Lagunin, A., Filimonov, D., & Poroikov, V. (2015). SOMP: web server for in silico prediction of sites of metabolism for drug-like compounds. Bioinformatics, 31(12), 2046-2048. https://doi.org/10.1093/bioinformatics/btv087

Samant, L. R., Javle, V. R. K. (2020). Comparative Docking analysis of rational drugs against COVID-19 Main Protease. https://doi.org/10.26434/chemrxiv.12136002

Schrödinger LCC. (2020). The PyMOL Molecular Graphics System, Version 2.4.

Sharma, A., Sharma, S., Parashar, B. (2017). Mesua ferrea linn:-A Review of the Indian Medical Herb. Systematic Reviews in Pharmacy, 8(1), 19-23. https://doi.org/10.5530/srp.2017.1.5

Systemes Dassault (2016). BIOVIA Discovery Studio. Dassault Syst Mes BIOVIA, Discovery Studio Modeling Environment, Release 2017. https://www.3ds.com/products-services/biovia/products/molecular-modeling-simulation/biovia-discovery-studio/

Taylor, P., Singh, S., Gray, A. I., Waterman, P. G. (1993). Mesuabixanthone-A and Mesuabixanthone-B : Novel Bis- Xanthones from the Stem Bark of Mesua ferrea (Guttiferae). 3(1), 53-58. https://doi.org/10.1080/10575639308043837

Teh, S. S., Ee, G. C. L., Mah, S. H., Lim, Y. M., & Rahmani, M. (2012). Mesua beccariana (Clusiaceae), a source of potential anti-cancer lead compounds in drug discovery. Molecules, 17(9), 10791-10800. https://doi.org/10.3390/molecules170910791

Verotta, L., Lovaglio, E., Vidari, G., Finzi, P. V., Neri, M. G., Raimondi, A. et al. (2004). 4-Alkyl- and 4-phenylcoumarins from Mesua ferrea as promising multidrug resistant antibacterials. Phytochemistry, 65(21), 2867-2879. https://doi.org/10.1016/j.phytochem.2004.07.001

Wezeman, T., Bräse, S., & Masters, K.-S. (2015). Xanthone dimers: A compound family which is both common and privileged. Natural Product Reports, 32(1), 6-28. https://doi.org/10.1039/c4np00050a

Williams, J. A., Hyland, R., Jones, B. C., Smith, D. A., Hurst, S., Goosen, T. C. et al. (2004). Drug-drug interactions for UDP-Glucuronosyltransferase substrates: A pharmacokinetic explanation for typically observed low exposure (AUC_i/AUC) ratios. Drug Metabolism and Disposition, 32(11), 1201-1208. https://doi.org/10.1124/dmd.104.000794

Zar, K., Myint, W., Kido, T., Kusakari, K., Devkota, H. P., Kawahara, T., & Watanabe, T. (2019). Rhusflavanone and mesuaferrone B: tyrosinase and elastase inhibitory biflavonoids extracted from the stamens of Mesua ferrea L . Natural Product Research, 0(0), 1-5. https://doi.org/10.1080/14786419.2019.1613395

Zhang, D. hai, Wu, K. lun, Zhang, X., Deng, S. qiong, Peng, B. (2020). In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. Journal of Integrative Medicine, 18(2), 152-158. https://doi.org/10.1016/j.joim.2020.02.005