Molecular Docking Studies of Chemical Constituents of *Adansonia digitata* targeting the DNMT1 Protein

Yusuf AJ[1*], Mohammed BS[2], Abdullahi MI[1], Adegboyega AE[3], Alhassan MA[1]

[1]*Department of Pharmaceutical and Medicinal Chemistry, Usmanu Danfodiyo University, Sokoto, Nigeria*

[2]*Department of Chemistry, Hayatt University College, Khartoum, Sudan*

[3]*Department of Biochemistry, College Of Health Sciences, University of Jos, Nigeria*

Introduction

- Cancer is the second leading cause of death globally (WHO, 2022).
- Cervical cancer is a common malignant tumor of the female reproductive system with high morbidity and mortality (Chen et al., 2016).
- Epidemiological studies have shown that the risk factors for cervical cancer include;
  - ✓High risk Human papillomavirus (HPV),
  - ✓HIV infection,
  - ✓Premature sexual age,
  - ✓Multiple sexual partners, and
  - ✓Smoking (Muñoz et al., 2003; Lu et al., 2016; Cao et al., 2019).

The most common symptoms of the disease (Figure 1) include, bleeding between periods, after sexual intercourse, and in post-menopausal women, discomfort during sexual intercourse, vaginal discharge with a strong odor and tinged with blood and pelvic pain (WHO, 2022).

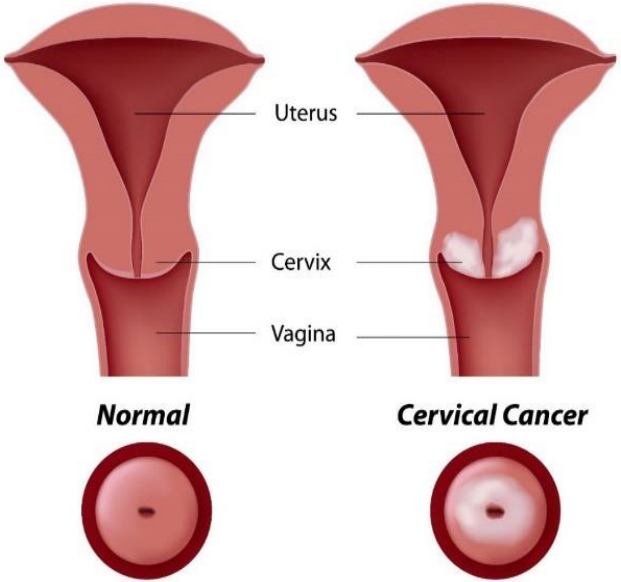


Figure 1. Symptoms of cervical cancer (Source: Team Dr Lal Path Labs)

Why Cervical cancer?

- Worldwide, cervical cancer is the fourth most frequent cancer in women with an estimated 604 000 new cases in 2020.
- Of the estimated 342,000 deaths from the disease in 2020, about 90 % of these occur in low- and middle-income countries (Sung et al., 2020).
- Women living with HIV are 6 times more likely to develop cervical cancer compared to women without HIV.
- In low-and middle-income countries, there is limited access to preventative measures (screening, vaccination, and treatment)
- and cervical cancer is often not identified until it has further advanced and symptoms develop (Lei et al., 2020).
- Although, there are many different approaches to cancer treatment, they are often painful due to adverse side effects and are sometimes ineffective due to increasing resistance to classical anti-cancer drugs or radiation therapy (WHO, 2022).

Justification of the Study

- Plant derived natural compounds are of major interest in cancer treatment due to their high bioavailability, safety, minimal side effects and, most importantly, cost effectiveness (Abdel-Rahman et al., 2018).
- *Adansonia digitata* L. belong to the Malvaceae family and it is commonly known as baobab (Rahul et al., 2015); the plant has been widely employed in traditional medicine to treat different ailments such as cancer, malaria, diarrhoea, dysentery, among others (Kamatou et al., 2011; Salim et al., 2012; Rahul et al., 2015).
- The anticancer effect of the seeds and fruit pulps *A. digitata* against Ehrlic Ascites Carcinoma was reported by Elsaid et al. (2020);
- The anticancer effects of the fruit against three human cancer cell lines including MCF-7, Hep-G2 and COLO-205 for breast, liver and colon cancers respectively was also reported by Kadam and Kondawar (2019).
- Anti-cervical cancer effect of the different parts of *A. digitata* extracts and characterization of their chemical constituents using GC-MS and LC-MS/QTOF was also reported (Suliman et al., 2022).

Aim and Objectives of the study

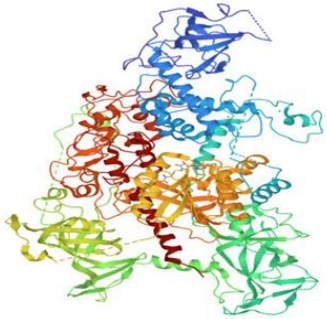
- The **aim** of this study was to conduct in-silico analysis including molecular docking and ADMET studies of the phytoconstituents of *A. digitata* against DNA methyltransferases 1 (DNMT1) through the following **objectives**;

- ✓ *To retrieve the crystal structure of **DNMT1 – PDB ID: 4WXX** from Protein Data Bank (PDB) repository and prepare it using the protein preparation wizard panel of Glide (Schrödinger Suite 2020-3).*
- ✓ *To retrieve the phytoconstituents of A. digitata from PubChem and prepare them for molecular docking using Lipprep module (Schrödinger Suite 2020-3).*
- ✓ *To conduct Protein-Ligand Docking using Glide tool of Schrödinger Maestro 12.5.*
- ✓ *To determine the ADME and Toxicity profile of the compounds using the SwissADME and ProTox-II online servers, respectively.*

Methodology

45 Phytoconstituents of *A. digitata*
(Ligands)

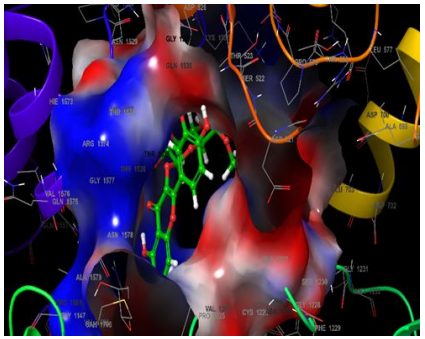
Lipprep module (Schrödinger Suite 2020-3)



Crystal structure of DNMT1
(Target)

Wizard Panel of Glide (Schrödinger Suite 2020-3)

Molecular Docking



Complexes

Glide tool of Schrödinger Maestro 12.5

ADMET

SwissADME
ProTox-II

Results and Discussion

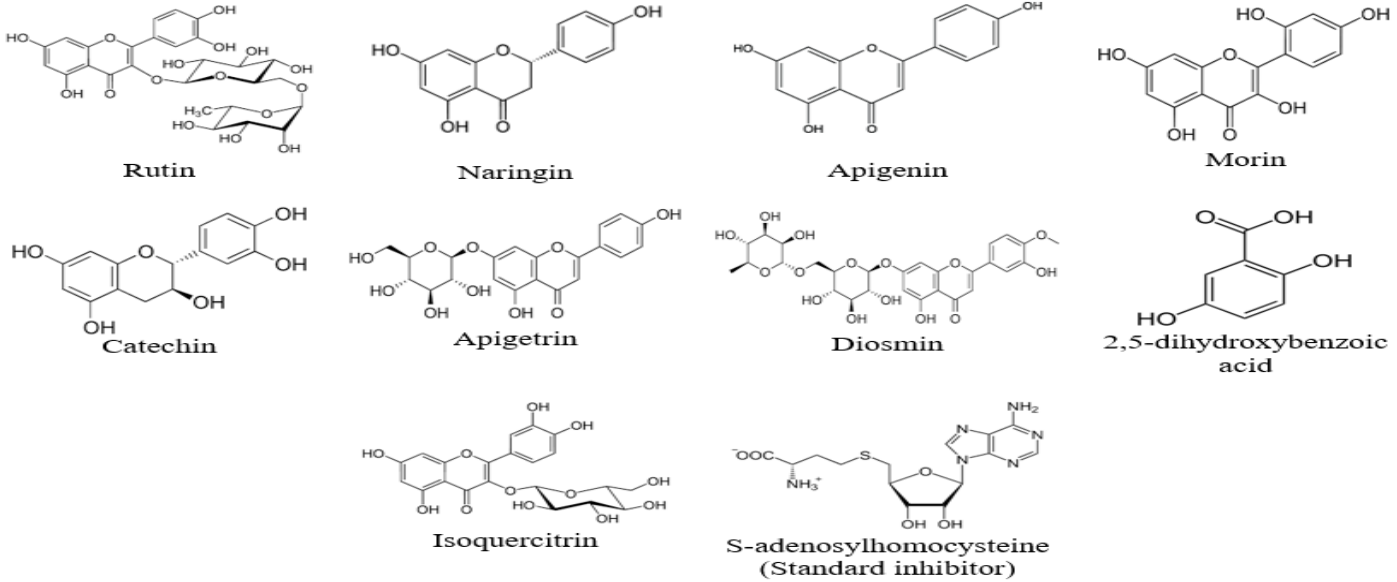


Figure 2. Chemical structures of top 9 compounds of *A. digitata* and the standard ligand

Molecular docking

Table 1. Docking scores of the top nine compounds of *A. digitata* against DNMT1

Compound ID	Compound Name	Docking score
5280805	Rutin	-7.006
442428	Naringin	-6.98
5280443	Apigenin	-6.882
5281670	Morin	-6.827
9064	Catechin	-6.67
5280704	Apigetrin	-6.284
5281613	Diosmin	-6.175
3469	2,5-dihydroxybenzoic acid	-6.11
348292394	Isoquercitrin	-5.943
439155	S-adenosylhomocysteine (Standard ligand)	-5.813

Biological interactions

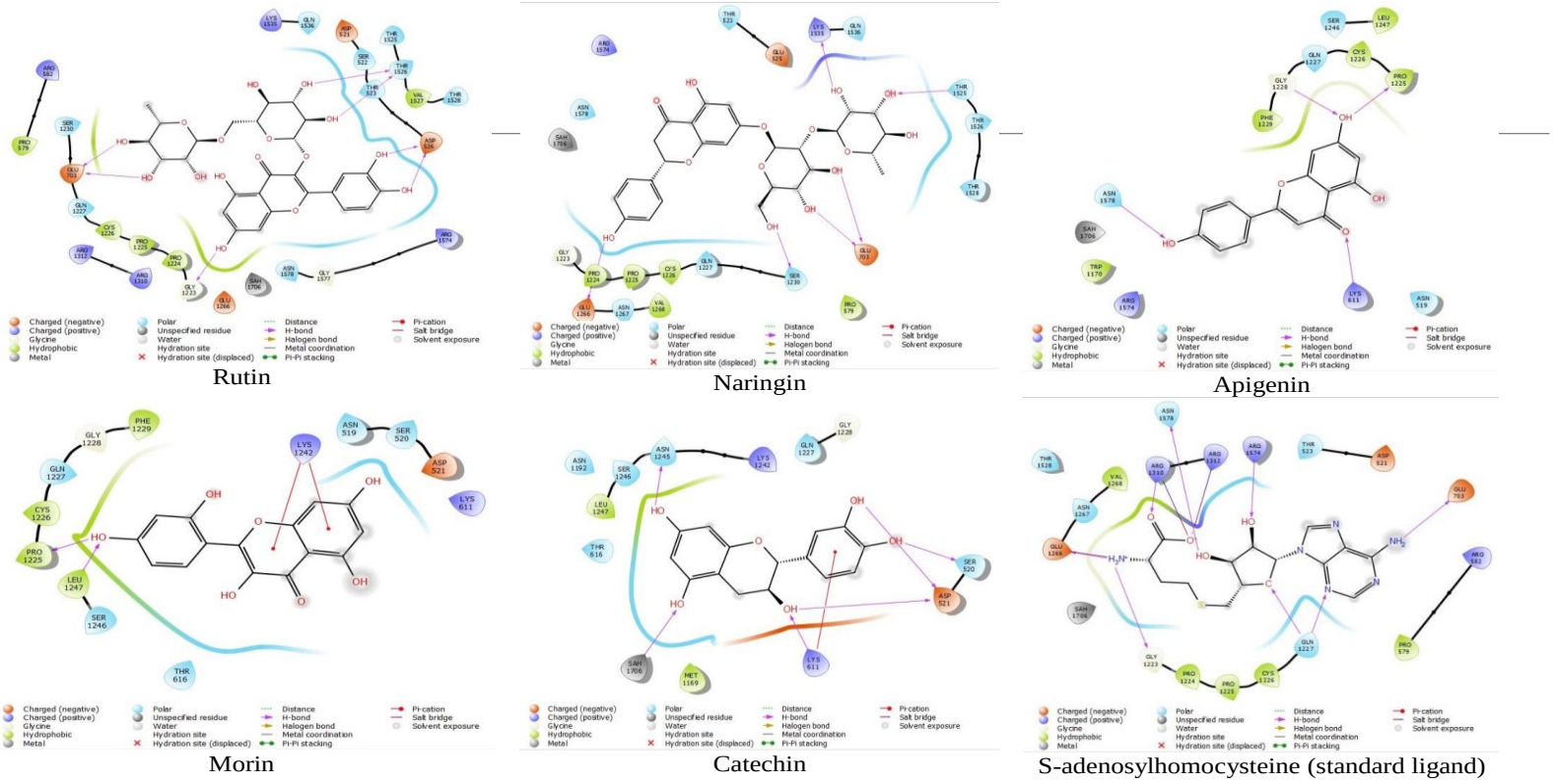


Figure 3. 2D view of the molecular interaction of rutin, naringin, apigenin, morin, catechin and standard ligand with DNMT1

Biological interactions

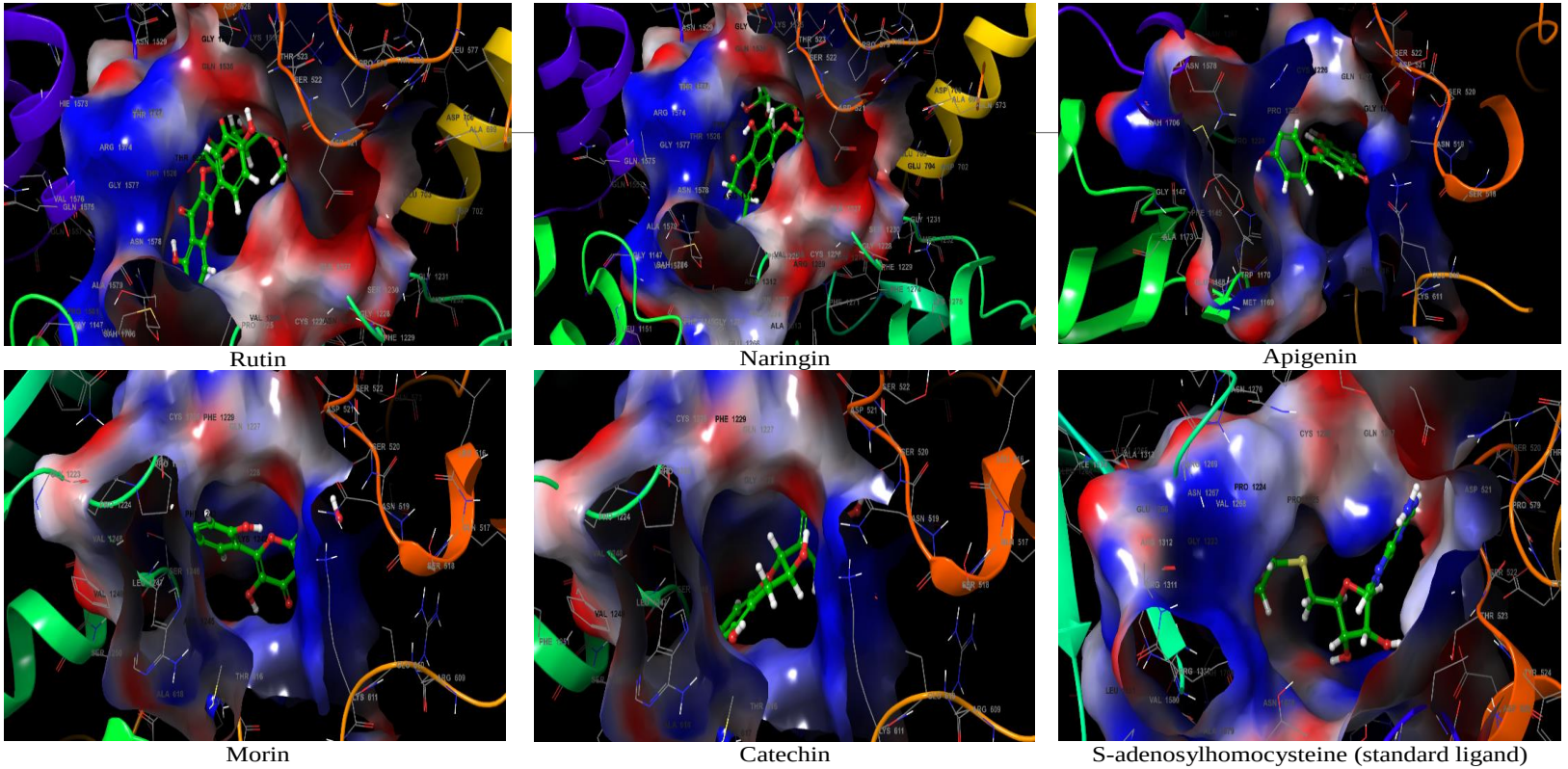


Figure 4. 3D view of the molecular interaction of rutin, naringin, apigenin, morin, catechin and standard ligand with DNMT1

Table 2. Molecular interactions of the top five compounds of *A. digitata* and standard ligand with DNMT1

Compound ID	Compound name	Interactions	
		H-Bond	Hydrophobic and Others
5280805	Rutin	THR1526, ASP526, GLY1223, GLU703	LYS1535, GLN1536, ASP521, SER522, THR1525, THR523, VAL1527, THR1528, ARG1574, GLY1577, ASN1578, SAH1706, GLU1266, PRO1225, CYS1226, GLN1227, SER1230, ARG1310, ARG1312, PRO579, ARG582, PRO1224
442428	Naringin	THR1525, GLU703, SER1230, GLU1266, LYS1535	THR1526, THR1528, PRO579, GLN1227, CYS1226, PRO1225, VAL1268, ASN1267, PRO1224, GLY1223, SAH1706, ASN1578, ARG1574, THR523, GLU525, GLN1536
5280443	Apigenin	LYS611, ASN1578, GLY1228, PRO1225	ASN519, ARG1574, TRP1170, SAH1706, PHE1229, GLN1227, SER1246, LEU1274, CYS1226
5281670	Morin	PRO1225, LEU1247	LYS611, ASP521, SER520, ASN519, LYS1242, THR616, SER1246, CYS1226, GLN1227, GLY1228, PHE1229
9064	Catechin	SER520, ASP521, LYS611, SAR1706, ASN1245	GLY1228, GLN227, LYS1242, SER1246, ASN1192, LEU1247, THR616, MET1169
439155	S-adenosylhomocysteine	GLU703, GLN1227, GLY1223, GLU1266, ARG1310, ASN578, ARG1312, ARG1574	ARG582, PRO579, CYS1226, PRO1225, PRO1224, SAH1766, ASN1267, THR1528, VAL1268, THR523, ASP521

Table 3. Drug likeness and pharmacokinetics prediction of the top 9 compounds of *A. digitata*

Parameters	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Drug likeness										
M.W (g/mol)	610.52	580.53	270.24	302.24	290.27	432.38	608.54	154.12	464.38	384.41
# H-bond acceptors	16	14	5	7	6	10	15	4	12	9
# H-bond donors	10	8	3	5	5	6	8	3	8	5
Molar refractivity	141.38	134.91	73.99	78.03	74.33	106.11	143.82	37.45	110.16	92.81
TPSA (A^2)	269.43	225.06	90.9	131.36	110.38	170.05	238.2	77.76	210.51	207.93
ESOL Log S	-3.3	-2.98	-3.94	-3.16	-2.22	-3.78	-3.51	-2.23	-3.04	0.19
Solubility class	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Highly soluble
Lipinski violations	3	3	0	0	0	1	3	0	2	1
Ghose violations	4	4	0	0	0	0	4	3	1	1
Veber violations	1	1	0	0	0	1	1	0	1	1
Egan violations	1	1	0	0	0	1	1	0	1	1
Muegge violations	4	3	0	0	0	2	4	1	3	2
Bioavailability score	0.17	0.17	0.55	0.55	0.55	0.55	0.17	0.56	0.17	0.55
Pharmacokinetics										
GI absorption	Low	Low	High	High	High	Low	Low	High	Low	Low
BBB permeant	No	No	No	No	No	No	No	No	No	No
P-gp substrate	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No
CYP1A2 inhibitor	No	No	Yes	Yes	No	No	No	No	No	No
CYP2C19 inhibitor	No	No	No	No	No	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No	No	No	No	No	No
CYP2D6 inhibitor	No	No	Yes	Yes	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	Yes	Yes	No	No	No	Yes	No	No
Log K_p (cm/s) (skin permeation)	-10.26	-10.15	-5.8	-7.05	-7.82	-7.65	-9.91	-6	-8.88	-11.13

Key: M1= Rutin; M2= Naringin; M3= Apigenin; M4= Morin; M5= Catechin; M6= Apigetrin; M7= Diosmin; M8= 2,5-dihydroxybenzoic acid; M9= Isoquercitrin; M10= S-adenosylhomocysteine

Table 4. Toxicity prediction output of test compounds of *A. digitata*

Target	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
LD_{50} (mg/kg)	5000	2300	2500	3919	10000	5000	5000	4500	5000	3320
Toxicity class	5	5	5	5	6	5	5	5	5	5
Hepatotoxicity	–	–	–	–	–	–	–	–	–	–
Carcinogenicity	–	–	–	–	–	–	–	–	–	–
Immunotoxicity	+	+	–	+	–	–	+	–	+	–
Mutagenicity	–	–	–	–	–	+	–	–	–	–
Cytotoxicity	–	–	–	–	–	–	–	–	–	–

Key: M1= Rutin; M2= Naringin; M3= Apigenin; M4= Morin; M5= Catechin; M6= Apigetrin; M7= Diosmin; M8= 2,5-dihydroxybenzoic acid; M9= Isoquercitrin; M10= S-adenosylhomocysteine

Conclusion

- In conclusion, 45 bioactive constituents of *A. digitata* were screened for their inhibitory effect against DNMT1 protein, out of which 9 including Rutin, naringin, apigenin, morin, catechin, Apigetrin, Diosmin, 2,5-dihydroxybenzoic acid, and isoquercitrin exhibited higher binding affinity than the standard ligand S-adenosylhomocysteine by interacting with clinically important amino acid residues.

- The constituents also exhibited good ADMET properties with Apigenin, morin, catechin being the best and none of the compounds have shown propensity for hepatoxicity, carcinogenicity and cytotoxicity.

- Hence, the phytochemical constituents of *A. digitata* could be studied further for development as effective therapeutic agents against cervical cancer

Some references

World Health Organization, WHO. Cervical Cancer. WHO Fact Sheets; [Retrieved on 13/09/2022] Available online at https://www.who.int/health-topics/cervical-cancer#tab=tab_1

Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin. 2016; 66:115–132.

Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, Snijders PJ, Meijer CJ International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003; 348:518–527.

Lu D, Sundström K, Sparén P, Fall K, Sjölander A, Dillner J, Helm NY, Adami HO, Valdimarsdóttir U, Fang F. Bereavement is associated with an increased risk of HPV infection and cervical cancer: an epidemiological study in Sweden. Cancer Res. 2016; 76:643–651.

Cao J, Dong J, Wang Y, Chen Y. The expressions of DNA methyltransferase 1 (DNMT1) and cyclin A1 (CCNA1) in cervical carcinogenesis. Int J Clin Exp Pathol. 2019 Jan 1;12(1):40-49. PMID: 31933719; PMCID: PMC6943998.

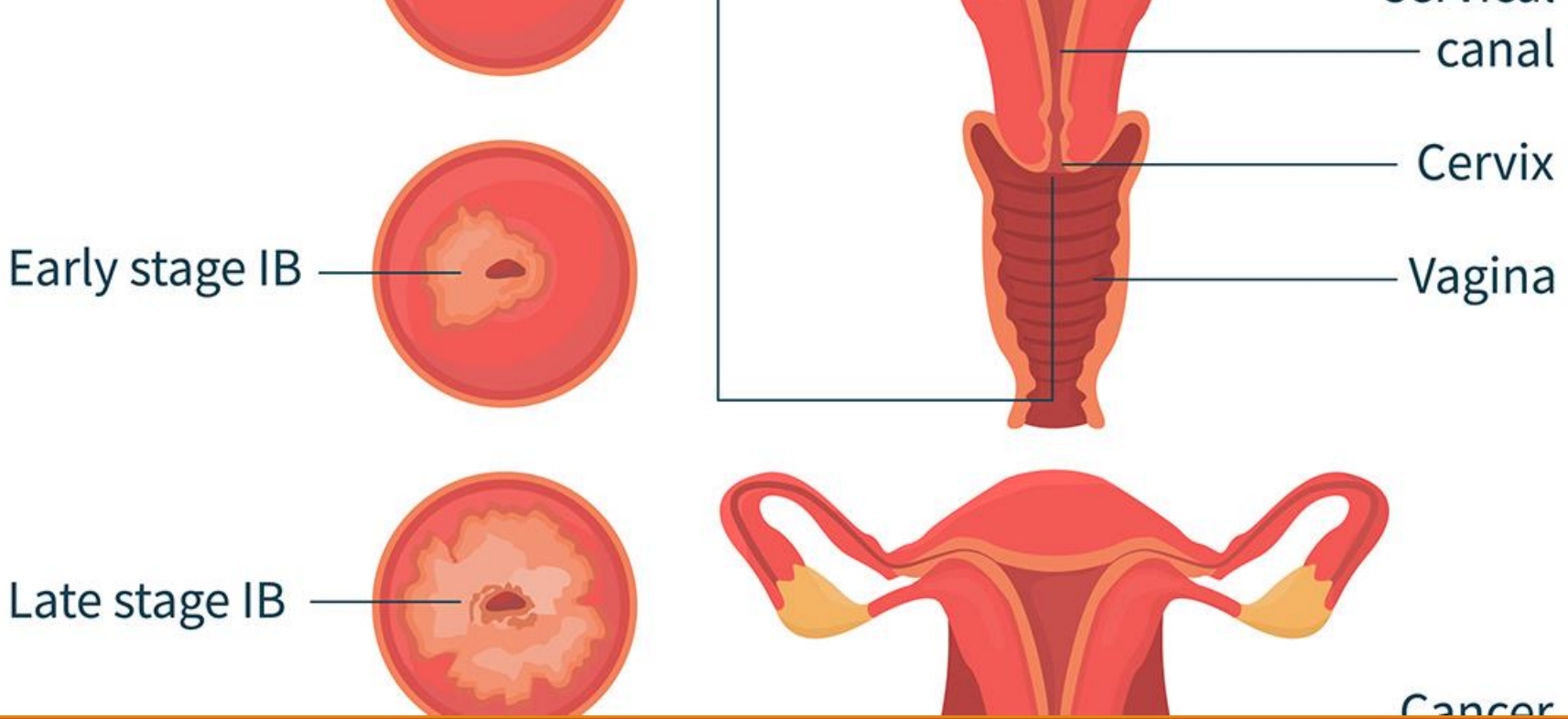
Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021:71:209–49. doi:10.3322/caac.21660.

Stelzle D, Tanaka LF, Lee KK, et al. Estimates of the global burden of cervical cancer associated with HIV. Lancet Glob Health 2020; published online Nov 16. DOI: S2214-109X(20)30459-9.

Johnson TO, Adegboyega AE, Ojo OA, Yusuf AJ, Iwaloye O, Ugwah-Oguejiofor CJ, Asomadu RO, Chukwuma IF, Ejembi SA, Ugwuja EI, Alotaibi SS, Albogami SM, Batiha GE, Rajab BS, Conte-Junior CA. A Computational Approach to Elucidate the Interactions of Chemicals From *Artemisia annua* Targeted Toward SARS-CoV-2 Main Protease Inhibition for COVID-19 Treatment. Front Med (Lausanne). 2022 Jun 15;9:907583. doi: 10.3389/fmed.2022.907583. PMID: 35783612; PMCID: PMC9240657.

Acknowledgement & Supports

We acknowledged the efforts of the staff of Jaris Computational Biology Center, Jos for providing the softwares for molecular docking studies.



THANK YOU FOR LISTENING

6th International Electronic Conference on Medicinal Chemistry
1-30 November 2020
sciforum.net/conference/ECMC2020
sponsored by pharmaceuticals

Identification of novel compounds from *Neocarya macrophylla* against toxins from *Naja nigricollis* using computational approach

Amina Jega Yusuf[1]*, Musa Ismail Abdullahi[2], and Aliyu Muhammad Musa[2]

[1] Department of Pharmaceutical & Medicinal Chemistry, Usmanu Danfodiyo University, Sokoto, Nigeria
[2] Department of Pharmaceutical & Medicinal Chemistry, Ahmadu Bello University, Zaria, Nigeria

* Corresponding author: amina.yusuf@udusok.edu.ng

Carbohydrate Research 509 (2021) 108436

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Biochemical evaluation and molecular docking assessment of glucosamines from *Neocarya macrophylla* fruits against *Naja nigricollis* venom

Amina Yusuf Jega [a,*], Musa Ismail Abdullahi [a], Aliyu M. Musa [b], Haruna A. Kaita [b], Vuyisa Mzozoyana [c], Adegboyega Abayomi Emmanuel [d]

[a] *Department of Pharmaceutical and Medicinal Chemistry, Usmanu Danfodiyo University, Sokoto, Nigeria*
[b] *Department of Pharmaceutical and Medicinal Chemistry, Ahmadu Bello University, Zaria, Nigeria*
[c] *School of Chemistry and Physics, University of KwaZulu-Natal, Westville, Durban, South Africa*
[d] *Department of Biochemistry, Faculty of Basic Medical Sciences, College of Health Sciences, University of Jos, Nigeria*

Turk J Pharm Sci 2022;19(2):202-212
DOI: 10.4274/tjps.galenos.2021.57527

ORIGINAL ARTICLE

Potential Inhibitors of SARS-CoV-2 from *Neocarya macrophylla* (Sabine) Prance ex F. White: Chemoinformatic and Molecular Modeling Studies for Three Key Targets

Amina Jega YUSUF[1]*, Musa Ismail ABDULLAHI[1], Aliyu Muhammad MUSA[2], Hassan ABUBAKAR[3], Abubakar Muhammad AMALI[4], Asma'u Hamza NASIR[2]

[1]Usmanu Danfodiyo University, Department of Pharmaceutical and Medicinal Chemistry, Sokoto, Nigeria
[2]Ahmadu Bello University, Department of Pharmaceutical and Medicinal Chemistry, Zaria, Nigeria
[3]Sokoto State University, Department of Chemistry, Sokoto, Nigeria
[4]Usmanu Danfodiyo University, Department of Pharmacology and Toxicology, Sokoto, Nigeria

frontiers | Frontiers in Medicine

ORIGINAL RESEARCH
published: 15 June 2022
doi: 10.3389/fmed.2022.907583

A Computational Approach to Elucidate the Interactions of Chemicals From *Artemisia annua* Targeted Toward SARS-CoV-2 Main Protease Inhibition for COVID-19 Treatment

Titilayo Omolara Johnson[1,2], Abayomi Emmanuel Adegboyega[1,2], Oluwafemi Adeleke Ojo[3], Amina Jega Yusuf[4], Opeyemi Iwaloye[5], Chinenye Jane Ugwah-Oguejiofor[6], Rita Onyekachukwu Asomadu[7], Ifeoma Felicia Chukwuma[7], Stephen Adakole Ejembi[1], Emmanuel Ike Ugwuja[8], Saqer S. Alotaibi[9], Sarah M. Albogami[9], Gaber El-Saber Batiha[10], Bodour S. Rajab[11] and Carlos Adam Conte-Junior[12]*

[1] Department of Biochemistry, Faculty of Basic Medical Sciences, University of Jos, Jos, Nigeria, [2] Jaris Computational Biology Centre, Jos, Nigeria, [3] Phytomedicine, Molecular Toxicology, and Computational Biochemistry Research Group, Department of Biochemistry, Bowen University, Iwo, Nigeria, [4] Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences Usmanu Danfodiyo University, Sokoto, Nigeria, [5] Bioinformatics and Molecular Biology Unit, Department of Biochemistry, Federal University of Technology, Akure, Nigeria, [6] Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria, [7] Department of Biochemistry, Faculty of Biological Sciences, University of Nigeria, Nsukka, Nigeria, [8] Department of Biochemistry, Faculty of Science, Ebonyi State University, Abakaliki, Nigeria, [9] Department of Biotechnology, College of Science, Taif University, Taif, Saudi Arabia, [10] Department of Pharmacology and Therapeutics, Faculty of Veterinary Medicine, Damanhour University, Damanhour, Egypt, [11] Laboratory Medicine Department, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, Saudi Arabia, [12] Technological Development Support Laboratory (LADETEC), Center for Food Analysis (NAL), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil

OPEN ACCESS

Edited by:
Qin An,
Salk Institute for Biological Studies, United States

Reviewed by:
Weinan Zhou,
University of Illinois at Urbana-Champaign, United States
Ziyi Zhao,
University of California, San Francisco, United States
Fei Gao,
Stanford University, United States

***Correspondence:**
Titilayo Omolara Johnson
titijohnson2004@yahoo.com

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 September 2022 doi:10.20944/preprints202209.0218.v1

Article

Potential Inhibitors of EGFR Tyrosine Kinase from *Scutellaria baicalensis*: A Cheminformatics and Molecular Docking Studies

Amina J. Yusuf[1,*], Abayomi E. Adegboyega [2,3,*], Abdulbasit H. Yakubu [4], Grace I. Johnson[3,5], Rita O. Asomadu[6], Mary N. Adeduro[7], Ifeoma F. Chukwuma[8], Chinenye J. Ugwah-Oguejiofor[9], Olayinka S. Okoh[10,11], Afrah F. Alkhuriji[12], Wafa Abdullah I. Al-Megrin[13], Michel De Waard[14,15,16], Gaber El-Saber Batiha[17] and Titilayo O. Johnson[3,18*]