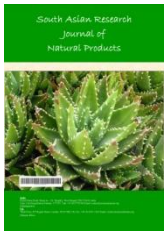

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Anticolorectal Cancer Properties of Some Flavonoids and Terpenoids from African Propolis via Molecular Docking

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Propolis, a resinous material produced by bees from plant exudates, has long been reported to be used in traditional herbal medicine and is widely consumed as a health aid and immune system booster. The colorectal cancer which is a world health emergency has renewed interest in propolis products worldwide. Fortunately, various aspects of the Poly adenosine diphosphate ribose polymerases (PARPs) mechanism are potential targets for propolis compounds. The treatment of Colerectal cancer (CRC) has been focused on the tumor site and stage of the disease using chemotherapy or radiotherapy, surgery, hormonal therapy, immunotherapy etc. Although apoptosis is being used in preventing damaged cells from developing out but due to secondary mutations in apoptosis-regulating gene, it can distort this order. This work aimed at evaluating the anticancer potential of some flavonoids and terpenoids from African propolis which can inhibit the protein of PARPs therefore preventing the growth of the cancer cell. From the result β- amyrin and naringin showed the best binding affinity and fit at -11.9 kcal/mol and -11.7 kcal/mol respectively which were better than standard drugs Irinotecan -11.2 kcal/mol and Doxorubicin -9.1 kcal/mol with the ligand at -11.2 kcal/mol. Other compounds also showed very high binding affinity of more than -9.0 kcal/mol suggesting the propolis compounds as potential anticancer compounds.

Keywords: Molecular docking; anticolorectal cancer; propolis; poly (ADP-ribose) polymerases (PARPs); flavonoids.

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1. INTRODUCTION

Cancer is a genetic disease that is said to be multifactorial and also one of the diseases caused by uncontrolled proliferation of abnormal cells in the body [1]. In comparison with other diseases cancer is complex in nature and therefore has many potential molecular targets for therapeutics development [2]. Cancer has remained a global health challenge as there are over 200 types of cancer, majority of them were named after the tissue they found to be infected for the first time like colorectal cancer, breast cancer, skin cancer, lung cancer, bone cancer etc. Cancer has been reported as one of the significant causes of death in the 21st century [3]. In 2015, World Health Organization (WHO) reported cancer as the second leading causes of death in people below 70 years of age in 91 different countries. Bray et al 2018 reported a global increase of 18.1 million new cancer cases and 9.6 million cancer related deaths [4]. The prevalence rate of colorectal cancer (CRC) is recorded as the third highest of all cancers in the world. By 2035 the cases are estimated to reach over 2.4 lakhs [5-6]. The treatment of CRC focuses on the tumor site and stage of the disease using chemotherapy or radiotherapy, surgery, hormonal therapy, immunotherapy etc. [7]. Apoptosis is used in preventing damaged cells from developing out but sometimes due to secondary mutations in apoptosis-regulating gene, it can distort this order [8]. Therefore natural products which can serve as an alternative have been the bedrock of modern therapeutic medicine as most of the drugs have their source from natural products, either as dietary supplement or synthetic analogues [9]. Most of the flavonoids and other phytochemicals found in nature are reported to trigger endoplasmic reticulum stress that may induce tissue damage through apoptosis and necrosis [10-11]. Also, modifications of some bioactive compounds have been implored to improve bioavailability, specificity and therapeutic effectiveness as well as other variety features that include implementation of potential chemotherapeutic agents [12-14]. Propolis is one of the natural products obtained from bees. It has been acclaimed and reported as a medicinal product. It is a complex resinous product having compositions of phytochemicals which can change depending on collection site, botanical origin, climatic condition, trees around and extraction methods. Propolis has been used ethnomedically in ancient times as a remedy for variety of diseases and recently interest has been renewed in reinvestigating the drug potentials. It is also reported to have antitumor and anticancer properties [15]. Flavonoids that are commonly found in propolis have highest antioxidant, antitumor, cytotoxic and chemopreventive properties [16]. Some of the flavonoids that are isolated from African propolis include Acacetin-Algeria, Quercetin-Algeria, Pinocembrin-Algeria and Egypt, Naringenin-Algeria, Chrysin-Algeria and Egypt, Apigenin-Algeria, Kaempferol-Algeria, Macarangin-Kenya and Nigeria, Liquiritigen-Nigeria, Narangin etc. [17]. Enzymes are biocatalysts and because of their remarkable properties, they are extensively used in medical diagnosis. They are preferred markers in various disease states such as myocardial infarction, cancer and neurodegenerative disorder, jaundice etc. they provide insight into the disease process by diagnosis, prognosis and assessment of response therapy, [18].

Poly (ADP-ribose) polymerases (PARPs) which are enzymes, activates DNA repair mechanisms upon stress and cytotoxin-induced DNA damage and inhibition of PARP activity. This is a leading mechanism in cancer drug therapy [19]. PARP-1 function as a DNA damage sensor and a signalling molecule. When it binds with DNA, the activated PARP cleaves NAD (+) into nicotinamide and ADP-ribose and polymerizes the ADP-ribose to nuclear acceptor proteins like histones, PARP and transcription factors contribute to inflammatory signal transduction processes. Activation of PARP has been connected in the pathogenesis of stroke and other diseases. Inhibition of PARP by pharmacological agents has proved useful for the therapy of cancer [20]. Colorectal cancer is common in both men and women. In terms of morbidity it is the third most common cancer while in terms of mortality it is rated second. About 10% cases of cancer in the world is colorectal cancer and drugs like cetuximab, Deracizumab and camptosar have been used in the management of colorectal cancer but their effects vary from patient to patient, and these drugs cause some side effects on the patients. Therefore the search for natural alternative remains sacrosanct [21]. Molecular docking is a vital tool which is used in computer aided drug design. It is one of the natural solutions towards this problem. The present study has focused on the use of phytochemical compounds (Flavonoids and Terpenoids) from African Propolis in docking on a protein from PARP to know whether it can inhibit its action and also to

identify the active site, binding affinity, ligand protein interaction and compare to the result of the docking of standard cancer drugs and co-crystallized ligand.

2. MATERIALS AND METHODS

2.1 Protein Receptors and Ligand Retrieval and Preparations

The list of some flavonoids and terpenoids from African propolis with proven anti-cancer properties were retrieved from literature [17]. Three dimensional (3D) structures of the drugs, flavonoid and terpenoid compounds were retrieved from PubChem web server in simple document format (SDF). They were optimized using Open babel in Python Prescription (version 0.8) which converted the ligands energetically to the most stable structures using Merk Molecular Force Field 94 (MMFF94). Similarly, the 3D X-ray crystallographic structure of the Poly (ADP-ribose) polymerases (PARPs) was retrieved from the RCSB protein data bank (PDB) (https://www.rcsb.org/) with ID 1UK0. The proteins were then prepared for docking and minimized using the relevant tools in Discovery studio.

2.2 Molecular Docking

Prior to molecular docking analysis, proteins were pre-processed using Discovery Studio 2020. This step includes the removal of any hetero-groups, other chains and water molecules. The active site of the protein was identified using Discovery studio. Furthermore, the preparation of ligands and receptors in the PDBQT file format were carried out in the AutoDock tool. Open babel in pyrx (version) was deployed for the optimization of our selected ligands. This converts ligands, compounds and drugs into most stable structures energetically. The molecular docking was carried out using AutoDock Vina to understand the interaction between receptors and ligands. A rigid-flexible docking was performed after setting a grid box surrounding the binding sites of the receptors at exhaustiveness = 8, center x = 5.62, center y = -0.97, center z = 32.52, size x = 20.61, size y = 23.59, size z = 23.74.

3. RESULTS AND DISCUSSION

The result of the molecular docking of some flavonoids, terpenoids, drugs and the co-crystallized ligand on the protein of PARP is shown below in the Table 1.

Fig. 1 shows the structure of 1UK0 protein which is crystal structure of catalytic domain of human poly (ADP-ribose) polymerase with a novel inhibitor which was crystallized with X-RAY diffraction with a resolution of 3.00Å deposited by Kinoshita.

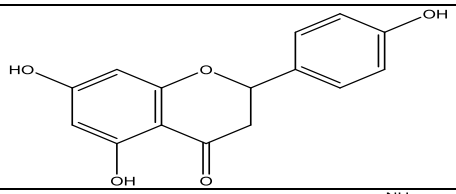
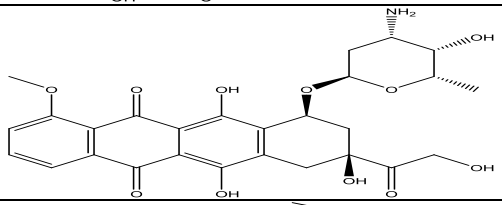
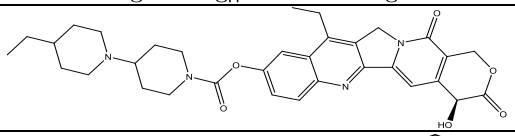
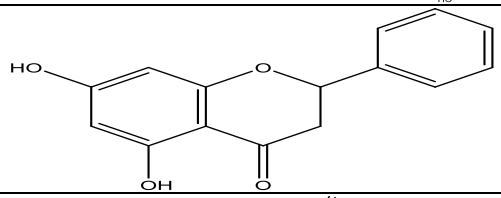
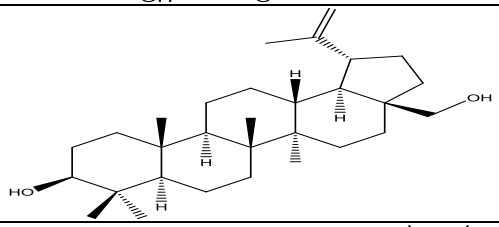
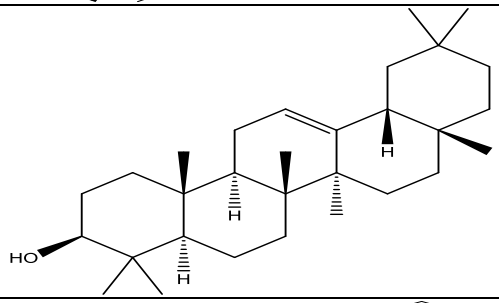
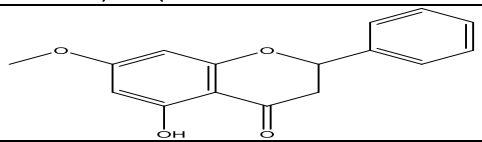
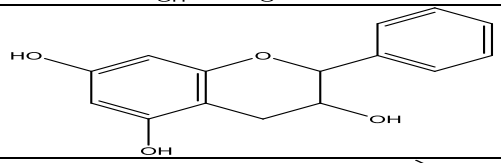
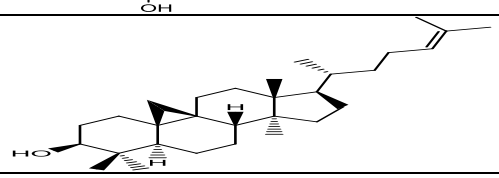
3.1 Docking Results

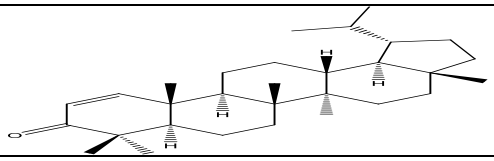
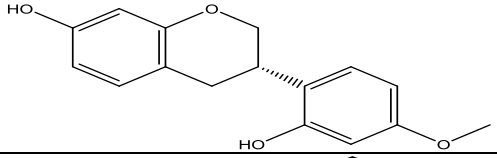
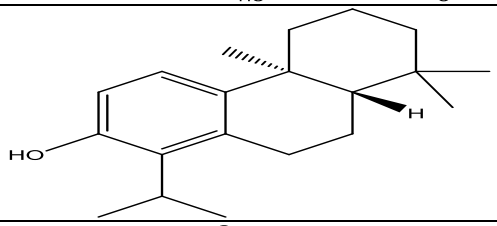
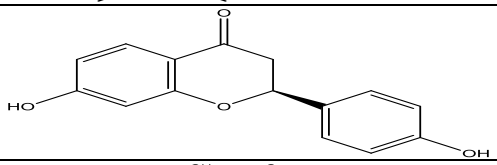
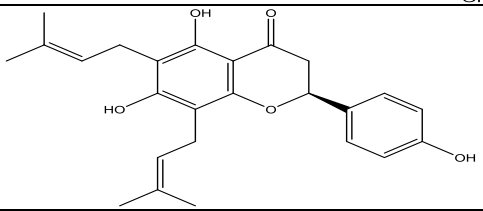
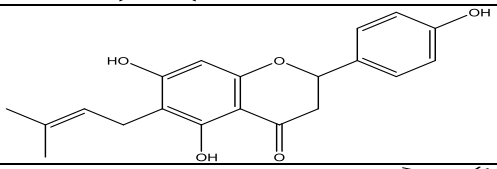
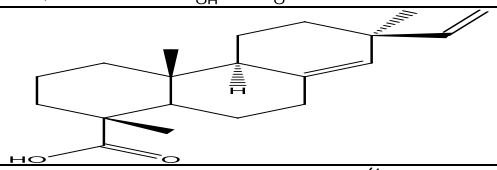
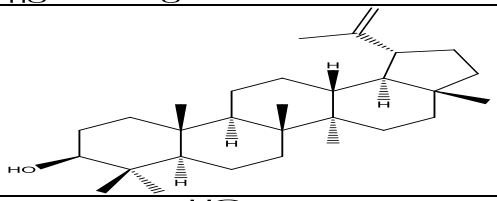
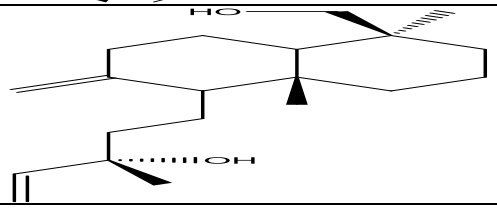
Irinotecan is an antineoplastic enzyme inhibitor primarily used in the treatment of colorectal cancer. It is a derivative of camptothecin that inhibits the action of topoisomerase I. Irinotecan prevents religation of the DNA strand by binding to topoisomerase I-DNA complex, and causes double-strand DNA breakage and cell death. It is a derivative of camptothecin. Irinotecan was approved for the treatment of advanced pancreatic cancer in October, 2015 (irinotecan liposome injection, trade name Onivyde) [22].

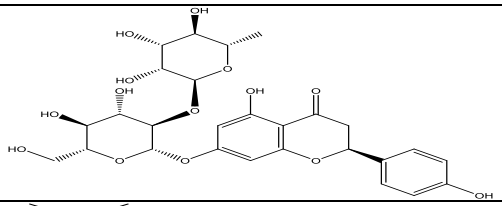
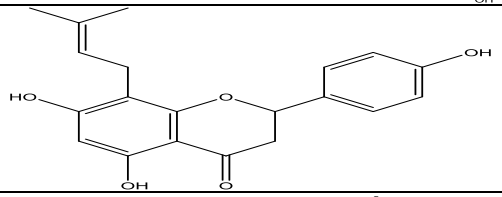
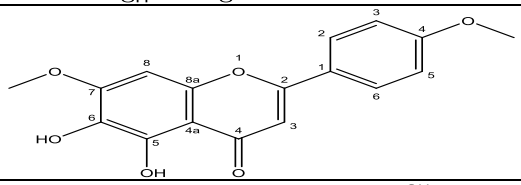
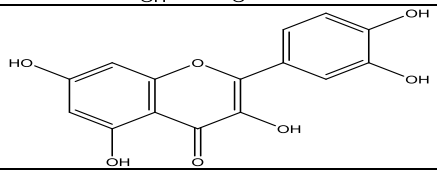
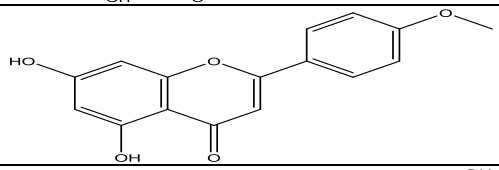
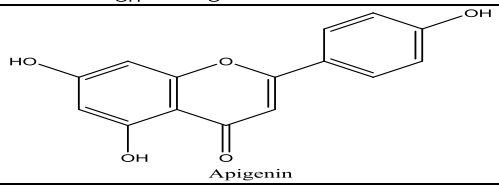
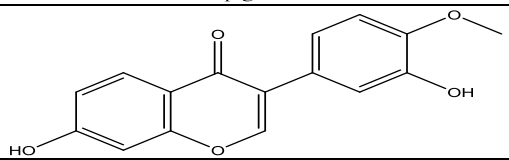
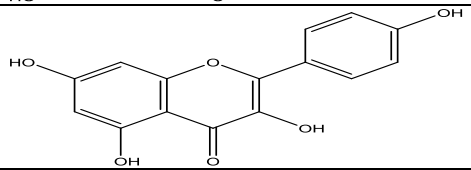
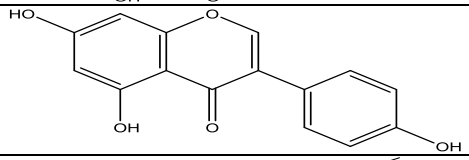
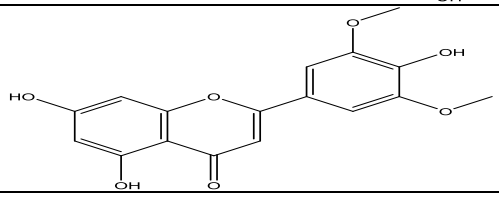
Picture of prepared protein **Picture of Raw protein**

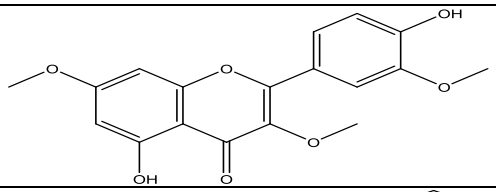
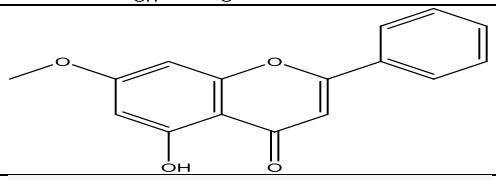
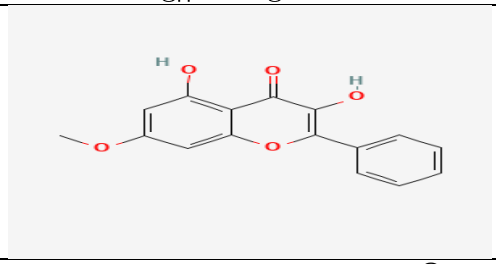
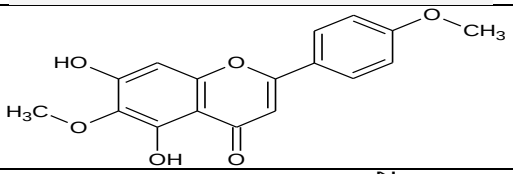
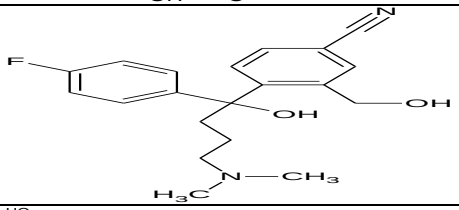
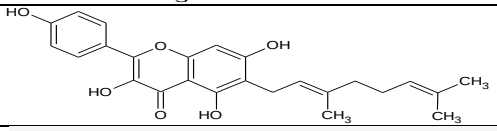
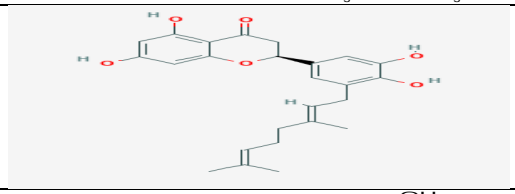
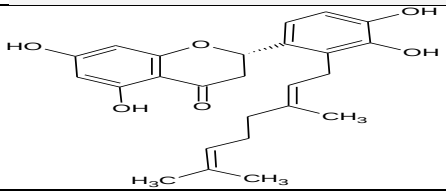
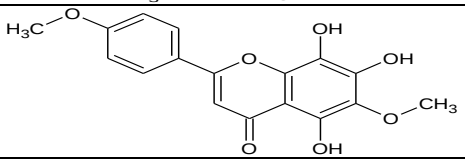
Fig. 1. pictures of protein of PARP

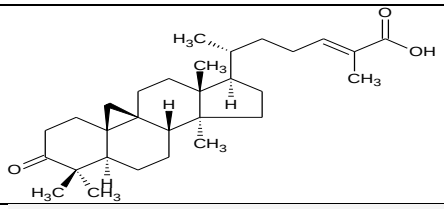
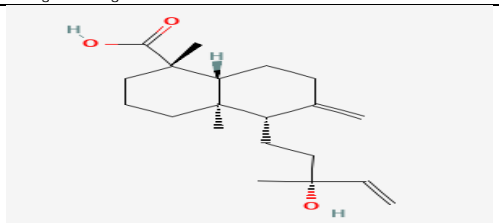
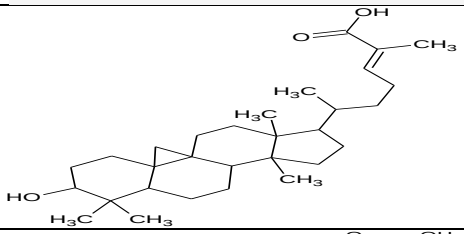
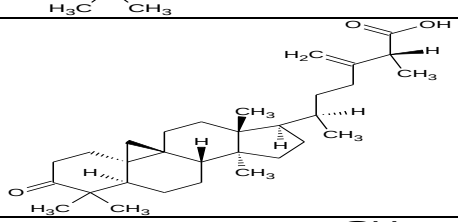
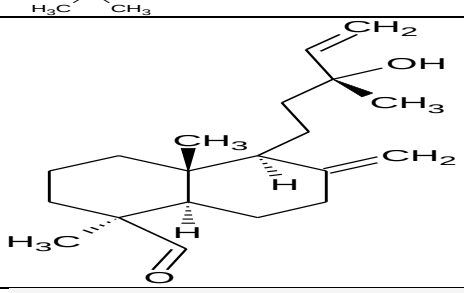
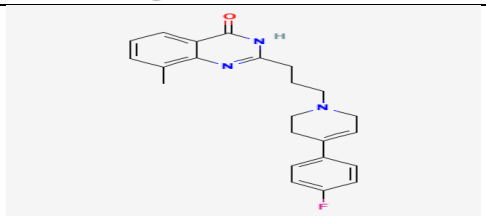
Table 1. The molecular docking result of the compounds, ligand and drugs

Name	Pub CID	Structure	Binding affinity
Naringenin	932		-9.2
Drug(Doxorubicin)	31703		-9.1
Drug(Irinotecan)	60838		-11.2
Pinocembrin	68071		-8.9
Betulin	72326		-9.7
β-Amyrin	73145		-11.9
Pinostrobin	73201		-8.8
Pinobanksin	73202		-8.9
Cycloartenol	92110		-11

Name	Pub CID	Structure	Binding affinity
Lupenone	92158		-10.4
Vestitol	92503		-8.8
Totarol	92783		-10.2
Liquiritigenin	114829		-9.3
Lonchocarpol A	124035		-10.7
6-prenylnaringenin	155094		-9.9
Pimaric acid	220338		-8.9
Lupeol	259846		-10
Torulosol	349315		-7.7

Name	Pub CID	Structure	Binding affinity
Naringin	442428		-11.7
8-prenylnaringenin	480764		-9.6
Ladanein	3084066		-9.4
Quercetin	5280343		-9.5
Acacetin	5280442		-9.1
Apigenin	5280443	 Apigenin	-9
Calycosin	5280448		-9.4
Kaempferol	5280863		-9
Genistein	5280961		-9.4
Chrysin	5281607		-8.9

Name	Pub CID	Structure	Binding affinity
Pachypodol	5281677		-8.7
Tectrochrysin	5281954		-8.9
Izalpinin	5318691		-8.7
Pectolinarigenin	5320438		-9.1
Citadiol	7472055		-8.3
Macarangin	10047854		-10.3
Isonymphaeol B	10070991		-11
Nymphaeol B	10387631		-10.2
Pilosin	12085264		-9.2

Name	Pub CID	Structure	Binding affinity
Mangiferonic acid	14034474		-11.1
Cupressic acid	44584269		-8.7
Mangiferolic acid	45270099		-11
Ambonic acid	101286242		-11.2
Torulosal	101306776		-8.1
Co-Ligand 2-{3-[4-(4-fluorophenyl)-3,6-dihydro-1(2h)-pyridinyl]propyl}-8-methyl-4(3h)-quinazolinone	135460986		-11.6

Doxorubicin is a chemotherapy drug and is a treatment for many different types of cancer. Doxorubicin is also known as Adriamycin. It slows or stops the growth of cancer cells by blocking an enzyme called topo isomerase 2. Cancer cells need this enzyme to divide and grow [23]. The binding energy of some compounds isolated from the African propolis is shown in the Table 1. The compounds obtained were flavonoids and terpenoids but other groups of phytochemicals like saponin, alkaloid and tannins were not analyzed because flavonoids and some terpenoids have been reported to have antioxidant and anticancer properties. The binding affinity score showed that all the compounds have high activity against the cancer protein and some of the compounds have activities higher than that of the control drugs and cocrystallized ligand. The control drug Irinotecan had -11.2 binding activity while Doxorubicin had binding affinity of -9.1. The co-crystallized ligand had binding affinity of -11.6, while most of the

compounds have binding activities of -9 and beyond. The most active compound was β-amyrin with binding energy of -11.9 followed by naringin -11.7, ambonic acid -11.2, mangiferonic and mangiferolic acids with binding affinity of -11.1 and -11 respectively. Isonympeol B and cycloartenol have -11 which were all higher than the drug Doxorubicin -9.1. Other compounds were also higher with negative binding energy higher than -9 which showed that most of the compounds have very high activities over the cancer disease. The protein- ligand interaction of the compounds with higher activities and that of the cocrystallized ligand and drugs are shown in Fig. 2.

3.2 Protein- Ligand Interaction

The Figs. 2(a-j) show the interaction of all the cocrystallized ligand, drugs and some phytocompounds that have higher activity with the protein.

From the drug and protein interaction shown above there was number of highest conventional hydrogen bond interaction in this interaction than any other compounds as hydrogen bond interaction was at ASP 105, ARG 217, MET 229 and TYR 235 while Carbon hydrogen bond interaction at TYR 49, GLN 98, VAL 101, LEU 108, ASP 109, LEU 216, ILE 218, ALA 219, GLY 227, ILE 234 and ASN 245. There were other interactions with weak bonds of van der waals, pi-anion and pi-alkyl.

The β - amyrin and protein interaction are shown below there was a conventional hydrogen bond interaction of ASP 105, while Van der waals interaction at GLN 98, GLU 102, ASN 106, LEU 108, ASP 109, HIS 201, SER 203, ASN 207, LEU 216, TYR 228, TYR 246. There were other interactions with weak bonds of van der waals, pi-anion and pi-alkyl.

From the result there was a conventional Hydrogen bond with the amino acid of ASP 105, ARG 217, SER 203, ALA 219.

From the result there was binding interaction of conventional hydrogen bond at SER 203, GLY 227, GLU 102 and other bond interaction which include carbon hydrogen bond, van der waal, Pi-akyl, and others at same binding site and amino acid. Showing that the bond of interaction was stronger for doxorubicin than some other compounds.

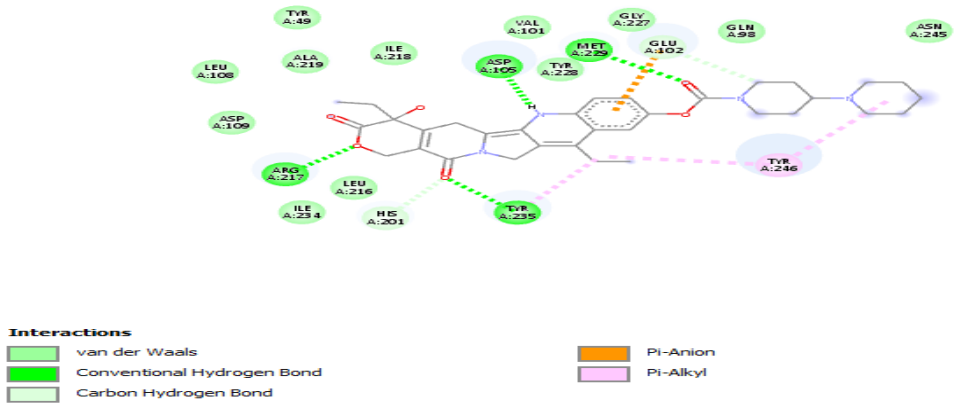


Fig. 2a. the interaction of the drug Irinotecan with the protein

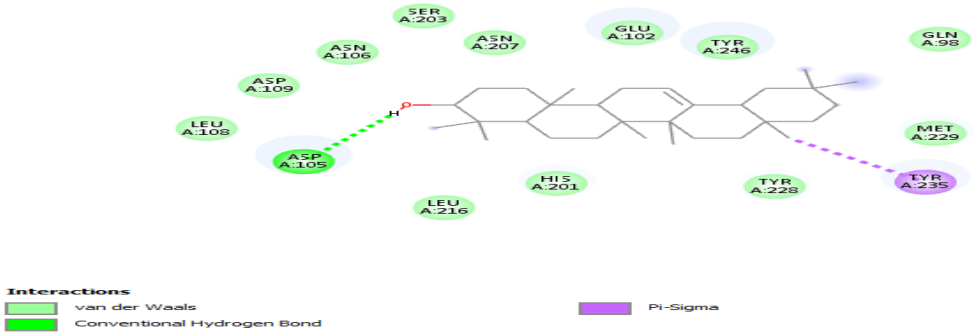


Fig. 2b. interaction of the protein with β-Amyrin

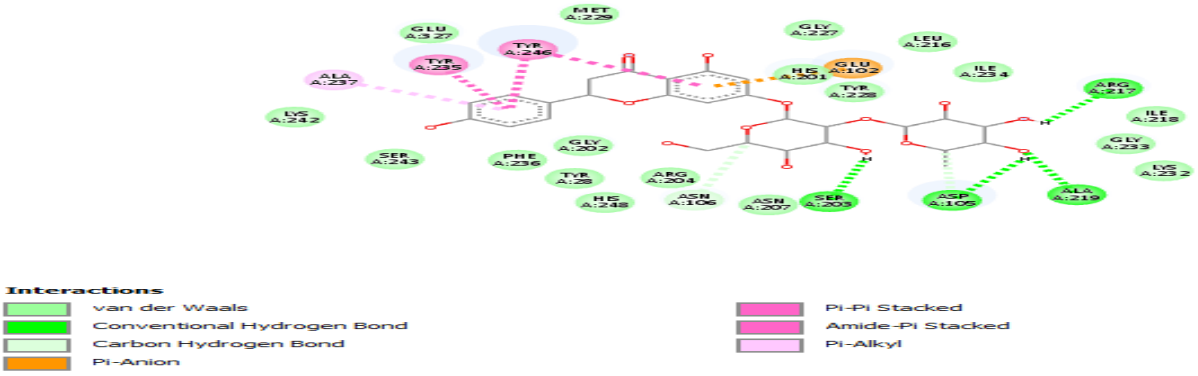


Fig. 2c. Interaction of the protein with naringin

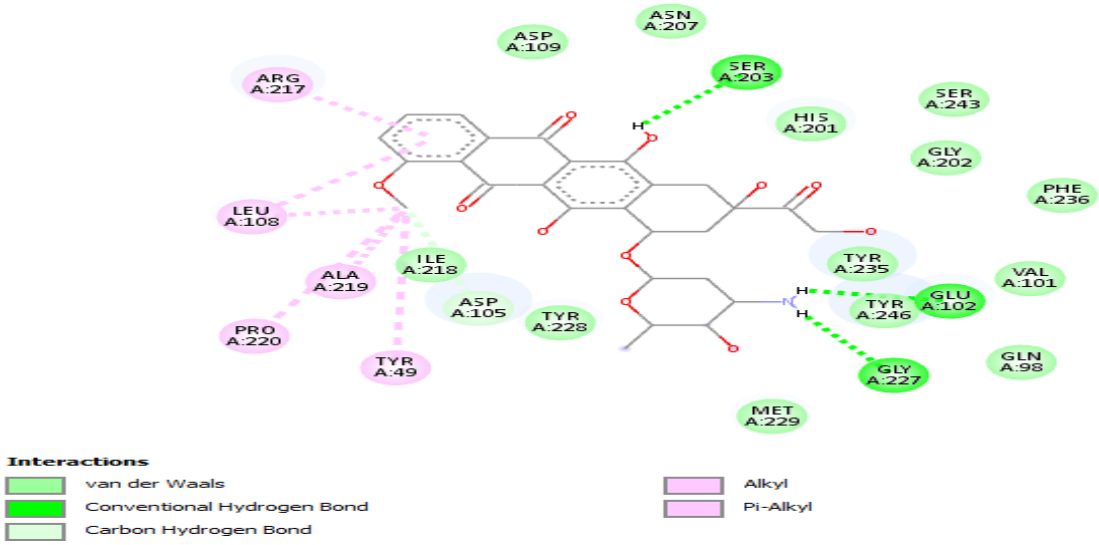


Fig. 2d. Interaction of the protein with doxorubicin

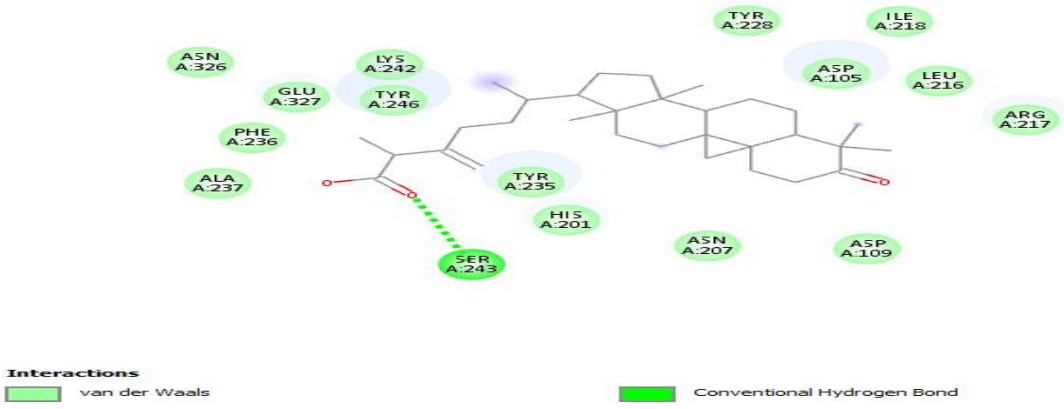


Fig. 2e. Protein interaction with ambonic acid

From the result and interaction it showed that the compounds from propolis bind very well with the protein and also fit perfectly to the protein binding cavity. Most of the compounds have good binding affinity of more than -9 kcal/mol and the amino acids at the binding site from the cocrystalline ligand, were also the amino acids that were also binded by the compounds and drugs thereby showing that the docking was at the binding site.

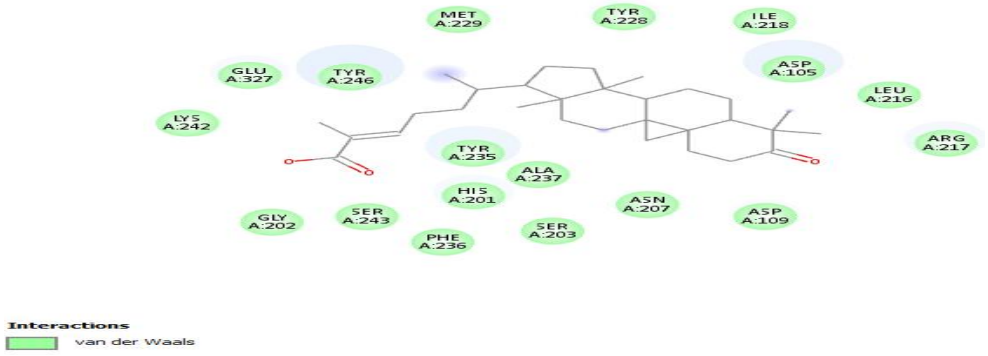


Fig. 2f. Interaction with mangiferonic acid

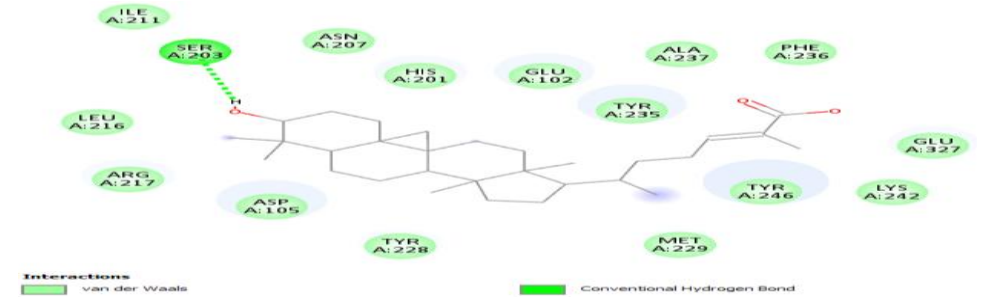


Fig. 2g. Interaction with mangniferolic acid

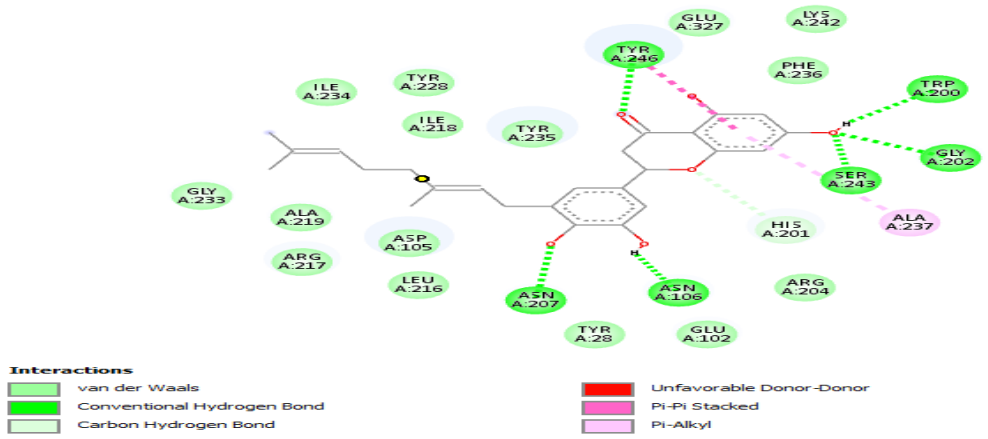


Fig. 2h. Interaction with isonympeol A

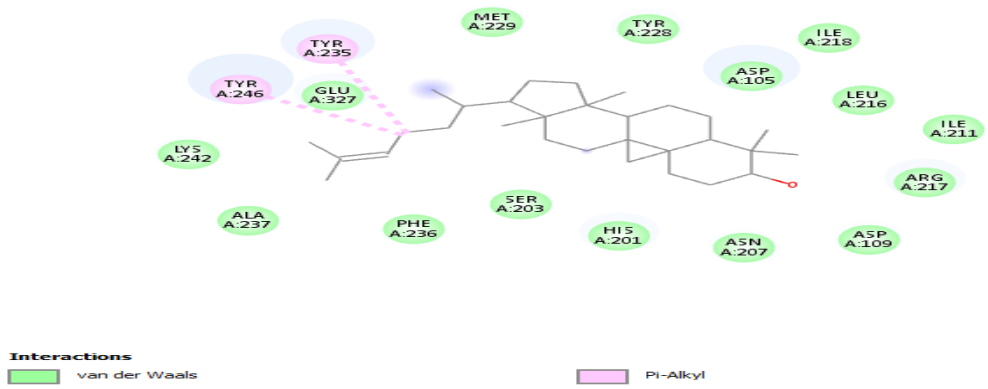


Fig. 2i. interaction with cycloartenol

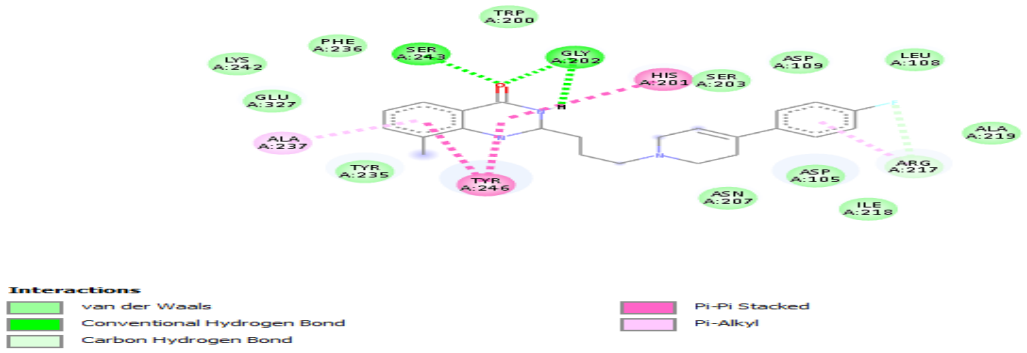


Fig. 2j. Co-crystallizied ligand interaction with the protein

4. CONCLUSION

African Propolis compounds have showed potential in treatment of colorectal cancer by binding with the protein of PARPs at the active site and having high (-) binding affinity in comparison with standard drugs used in the treatment and management of colorectal cancer though some of the compounds have a limited hydrogen bond and have more weaker bonds in it interactions in comparison with the standard drugs. Propolis compounds like cylcoartenol, Isonympeol A, Ambonic acid and naringin have good binding affinity with strong bond which stop the replication of the cancer cell.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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