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Research Article

An *in silico* ADME/T and molecular docking studies of phytochemicals derived from *Holigarna caustica* (Dennst.) for the management of pain

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Abstract

In traditional medicine, *Holigarna caustica*, also known as "Borola" or "Katebel" in Bangladesh, is used to cure tumors, malignancies, skin disorders, obesity, inflammation, eye irritation, and arthritis. The purpose of this study was to identify the bioactive phytochemicals in this plant that are responsible for the analgesic effect using computational models such as in silico ADME/T and molecular docking studies. Glide of Schrödinger Maestro (version 10.1) was used to perform the molecular docking investigation, whereas SwissADME was employed to determine the pharmacokinetic properties of this plant. Our computational analysis suggested that a total of eighteen phytocompounds may be responsible for the plant's analgesic effects, all of which were proven to be safe during the ADME/T study and should be investigated further in experimental models.

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1.1 Introduction

Humans used plants to cure many diseases in the past, but the trend has shifted, and the usage of lab-produced medication has expanded significantly [1]. Because of their structural diversity, low toxicity, accessible availability, and diverse mode of action, scientists have been more oriented toward the research of prospective medications from plant sources during the past few decades [2]. *Holigarna caustica* (Dennst.) Oken is a member of the Anacardiaceae family. It is locally known as "Borola" or "Katebel" in Bangladeshi and is more often known in English as the black varnish tree. This plant is native to Bangladesh's Chittagong, Cox's Bazar, and Chittagong Hill Tract regions [3]. Hemorrhoids, tumors, malignancies, skin problems, obesity, inflammation, eye irritation, and arthritis are all illnesses that the herb is used to cure in traditional medicine [4]. The preliminary phytochemical studyrevealed that the plant contains alkaloids, carbohydrates, flavonoids, proteins, terpenoids, cardiac glycosides, saponins, sterols, steroids, coumarins and fixed oils and also a GC-MS analysis of this plant reported that it contains fourty phytocompounds. It's also been used as an antiseptic for cuts and wounds, and a chloroform extract of this plant has been proven to have antibacterial and

cytotoxic properties. Furthermore, earlier research on this plant has revealed that it has antinociceptive, anti-inflammatory, and nematicidal characteristics [5]. However, the plant has proven analgesic activity though there hasn't been any evidence or report demonstrating which phytocompounds of this plant were responsible for that activity [6]. With this in mind, the goal of the current study was to look into it using computational models namely ADME/T and molecular docking studies.

2. Materials and methods

2.1. Selection of compounds for *in silico* study

Thirty-six phytocompounds have been selected for this study (as shown in Table 1). All compounds were chosen as major compounds based on their availability in the literature [4], and the chemical structures of the compounds were retrieved from the PubChem compound library.

Table 1. Pharmacokinetic properties (ADME) of the identified compounds in MEHC

Compounds	Lipinski rules					Lipinski's Rule violations
	MW	HBA	HBD	Log P	MR	
	< 500	< 10	≤ 5	≤ 5	40-130	≤ 1
Santalol, *E*-cis,epi-β-	220.35	1	1	3.86	69.94	0
β-D-Glucopyranoside, methyl	194.18	6	4	-1.64	40.47	0
6-Hydroxy-4,4,7α-trimethyl-5,6,7,7a tetrahydrobenzofuran-2(4H)-one	196.24	3	1	1.53	52.51	0
1-(7-Hydroxy-1,6,6-trimethyl-10-oxatricyclo [5.2.1.0(2,4)] dec-9-yl) ethanone	238.32	3	1	2.07	65.33	0
Neophytadiene	278.52	0	0	7.07	97.31	1
2-Pentadecanone, 6,10,14-trimethyl-	268.48	1	0	5.66	88.84	1
3,7,11,15-Tetramethyl-2-hexadecen-1-ol	296.53	1	1	6.22	98.94	1
Hexadecanoic acid, methyl ester	270.45	2	0	5.54	85.12	1
n-Hexadecanoic acid	256.42	2	1	5.20	80.80	1
2(3H)-Furanone, dihydro-5-(2-octenyl)-, (*Z*)-	196.29	2	0	3.19	58.49	0
9,12-Octadecadienoic acid (*Z, Z*)-, methyl ester	294.47	2	0	5.69	91.78	1
9-Octadecenoic acid, methyl ester, (*E*)-	296.49	2	0	5.95	94.26	1
Phytol	296.53	1	1	6.22	98.94	1
Methyl stearate	298.50	2	0	6.24	94.73	1
9,12-Octadecadienoic acid (*Z, Z*)-	280.45	2	1	5.45	89.46	1
9-Octadecenoic acid, (*E*)-	282.46	2	1	5.71	89.94	1
Octadecanoic acid	284.48	2	1	5.93	90.41	1
3-Tridecylphenol	276.46	1	1	6.17	91.11	1
9-Octadecenamide, (*Z*)-	281.48	1	1	5.32	91.07	1
(*Z*)-3-(pentadec-8-en-1-yl) phenol	302.49	1	1	6.39	100.25	1
Phenol, 3-pentadecyl-	304.51	1	1	6.89	100.73	1

(*Continued on next page*)

Table 1. (*Continued*)

Compounds	Lipinski rules					Lipinski's Rule violations
	MW	HBA	HBD	Log P	MR	
	< 500	≤ 1	≤ 5	≤ 5	40-130	≤ 1
Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester	330.50	4	2	4.72	97.06	0
Bis(2-ethylhexyl) phthalate	390.56	4	0	6.17	116.30	1
(*Z*)-3-(Heptadec-10-en-1-yl) phenol	330.55	1	1	7.15	109.87	1
3-((4*Z*,7*Z*)-Heptadeca-4,7-dien-1-yl) phenol	328.53	1	1	6.84	109.39	1
Squalene	410.72	0	0	9.38	143.48	2
α-Tocospiro A	462.70	4	1	6.37	139.58	1
β-Sitosterol acetate	456.74	2	0	7.63	142.97	2
γ-Tocopherol	416.68	2	1	7.83	134.31	1
Stigmasta-5,22-dien-3-ol, acetate, (3β,22*Z*)-	454.73	2	0	7.38	142.49	2
Cholesta-4,6-dien-3-ol, (3β)-	384.64	1	1	6.51	123.14	1
Stigmast-5-en-3-ol, oleate	679.15	2	0	12.96	290.40	3
α-Tocopherol	430.71	2	1	8.27	139.27	1
Campesterol	400.68	1	1	6.90	128.42	1
Stigmasterol	412.69	1	1	6.96	132.75	1
γ-Sitosterol	414.17	1	1	7.19	133.23	1

MR: Molar refract`

2.2. *In silico* ADME/T study

Lipinski's rule of five was used to examine the pharmacokinetic features of all key identified compounds. According to Lipinski, a molecule can exhibit drug-like behavior if it meets at least one of the following criteria: (i) molecular weight of less than 500; (ii) H-bond donors of 5; (iii) H-bond acceptors of 10; (iv) Lipophilicity of 5; and (v) molar refractivity of 40 to 130. The ADME characteristics of all substances were evaluated using the web application Swiss ADME. Compounds that follow the Lipinski rule are thought to be good drug candidates [7].

2.3. *In silico* Molecular docking study

2.3.1. Preparation of Ligands

The structures of thirty-six major representative compounds were retrieved from the PubChem database, as described above. The ligands were prepared using the LigPrep tool in Maestro 2015, neutralized using Epik at pH 7.0±2.0, and minimized using the force field OPLS_2005.

2.3.2. Preparation of enzymes or Receptors

3D crystal structures of the enzymes used for the test have been downloaded from the Protein Data Bank RCSB PDB [8]: cyclooxygenase 1 (PDB ID: 2YOE) [9], cyclooxygenase 2 (PDB ID: 6COX) enzymes [10], kappa receptor (PDB ID: 4DJH) [11], and mu receptor (PDB ID: 5C1M) [12]. The Protein Preparation Wizard in Schrödinger Maestro 10.1 was used to prepare and refine the crystal structure, including assigning charges, bond orders, hydrogens to heavy atoms, and converting selenomethionines and selenocysteines into methionines and cysteines, respectively, before removing all water molecules. Minimization was accomplished using the force field OPLS_2005 to set the maximum heavy atom RMSD to 0.30 Å.

2.3.3. Receptor grid generation and glide standard precision ligand docking

Glide Schrödinger Maestro v10 was used to generate receptor grids and conduct molecular docking

experiments. A grid was generated for each enzyme using the OPLS_2005 force field and default values of van der Waals scaling factor 1.00 and charge cut-off value 0.25. In addition, for receptor docking, a cubic box with specific dimensions centered on the centroid of the active site residues was created, with the size of the box set to 14 Å × 14 Å × 14 Å. The docking tests were conducted using Glide's standard precision (SP) scoring function, and only the best scoring pose with docking score for each ligand was recorded [13–15].

3. Results and Discussion

3.1. ADME/T study

Screening the pharmacokinetic properties of the chemical compounds is the most crucial step during the drug development process, more specifically during the exploratory phase. In this stage, a drug has been gone through the most rigorous process which saves a lot of money and mostly the number of repetitions of the experimental study. Lipinski's stated that a drug or compound could be a good candidate for pre-clinical trial if it follows the given rules such as molecular weight less than 500 amu, hydrogen bond acceptor sites less than 10, hydrogen bond donor sites less than or equal to 5, lipophilicity value (LogP) less than or equal to 5, and molar refractivity between 40 to 130. The present study demonstrated that all the compounds have followed Lipinski's rule of five except four compounds namely Squalene, β-Sitosterol acetate, Stigmasta-5,22-dien-3-ol, acetate, (3β,22Z)-, Stigmast-5-en-3-ol, oleate which indicates that the remaining 32 compounds are safe from the druggable point of view.

3.2 Molecular docking study

In this study, four key proteins (COX-1, PDB: 2YOE; COX-2, PDB: 6COX; kappa receptor, PDB ID: 4DJH; mu receptor, PDB ID: 5C1M) were used to investigate the possible mechanism of action of *H. causitica* plant's potential anti-nociceptive activity, which was previously reported in anexperimental study. In this study, 32 main *H. causitica* compounds were docked against all enzymes and receptors, with the results of molecular docking displayed in Table 2 and ligand compound binding interactions illustrated in Tables 3-4 and Figure 1.

Table 2. Docking score of the identified compounds in MEHC against cyclooxygenase 1 (PDB ID: 2YOE), cyclooxygenase 2 (PDB ID: 6COX) enzymes, kappa receptor (PDB ID: 4DJH), and mu receptor (PDB ID: 5C1M) for anti-nociceptive activity

Compounds	Com. No.	Docking Score (kcal/mol)			
		2OYE	4DJH	5C1M	6COX
Santalol, *E*-cis,epi-β-	C1	-6.222	-5.991	-4.587	-6.715
β-D-Glucopyranoside, methyl	C2	-5.672	-5.399	-5.855	-6.598
6-Hydroxy-4,4,7α-trimethyl-5,6,7,7a tetrahydrobenzofuran-2(4H)-one	C3	-6.783	-6.627	-5.795	-6.767
1-(7-Hydroxy-1,6,6-trimethyl-10-oxatricyclo [5.2.1.0(2,4)] dec-9-yl) ethanone	C4	-6.022	-7.468	-5.431	-6.361
Neophytadiene	C5	-2.448	-1.941	-1.262	-2.098
2-Pentadecanone, 6,10,14-trimethyl-	C6	-3.14	-2.333	-2.439	-2.569
3,7,11,15-Tetramethyl-2-hexadecen-1-ol	C7	-2.941	-1.478	-2.499	-3.761
Hexadecanoic acid, methyl ester	C8	-0.957	-1.332	-0.245	-0.76
n-Hexadecanoic acid	C9	-1.663	-0.897	-0.708	0.182
2(3H)-Furanone, dihydro-5-(2-octenyl)-, (*Z*)-	C10	-6.007	-4.676	-4.281	-5.841
9,12-Octadecadienoic acid (*Z, Z*) -, methyl ester	C11	-3.112	-2.00	-1.912	-1.952
9-Octadecenoic acid, methyl ester, (*E*)-	C12	-2.711	-0.989	-1.749	-1.189

(*Continued on next page*)

Table 2. (*Continued*)

Compounds	Com. No.	Docking Score (kcal/mol)			
		2OYE	4DJH	5C1M	6COX
Phytol	C13	-3.295	-2.288	-2.612	-3.452
Methyl stearate	C14	-1.956	-1.483	-1.393	-0.078
9,12-Octadecadienoic acid (*Z, Z)* -	C15	-2.229	-0.66	-2.285	-2.099
9-Octadecenoic acid, (*E*)-	C16	-2.107	-1.459	-1.224	-3.127
Stearic acid	C17	-2.026	-0.406	-0.972	-2.694
3-Tridecylphenol	C18	-3.829	-2.807	-2.417	-4.135
9-Octadecenamide, (*Z*)-	C19	-3.695	-2.501	-1.891	-1.748
(*Z*)-3-(pentadec-8-en-1-yl) phenol	C20	-7.465	-6.689	-5.527	-5.08
Phenol, 3-pentadecyl-	C21	-6.989	-6.28	-5.125	-5.471
Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester	C22	-5.385	-4.042	-4.57	-3.941
Bis(2-ethylhexyl) phthalate	C23	-6.919	-5.974	-5.343	-
(*Z)*-3-(Heptadec-10-en-1-yl) phenol	C24	-7.387	-5.084	-5.15	-6.49
3-((*4Z,7Z*)-Heptadeca-4,7-dien-1-yl) phenol	C25	-6.517	-5.99	-5.728	-6.78
α-Tocospiro A	C26	-	-5.175	-4.722	-
γ-Tocopherol	C27	-	-6.618	-5.933	-
Cholesta-4,6-dien-3-ol, (3β)-	C28	-	-5.667	-6.756	-
α-Tocopherol	C29	-5.462	-5.26	-5.59	-
Campesterol	C30	-	-4.186	-6.448	-
Stigmasterol	C31	-	-5.196	-6.756	-
γ-Sitosterol	C32	-	-5.516	-7.069	-

Com. No.: Compound number

Table 3. Binding interactions of the selected eighteen compounds with cyclooxygenase 1 (PDB ID: 2YOE) and cyclooxygenase 2 (PDB ID: 6COX) enzymes for anti-nociceptive activity, respectively

Compounds	COX-1 (PDB ID: 2YOE)		COX-2 (PDB ID: 6COX)	
	Hydrogen bond interactions	Hydrophobic interactions	Hydrogen bond interactions	Hydrophobic interactions
Santalol, *E*-cis,epi-β-	Ser530	Val349 (3), Ala527 (2), Leu352, Ile523, Met522, Tyr355 (3), Trp387	His90, Leu352 (2)	Val349 (3), Leu352 (3), Ala527 (2), Val523 (2), His90, Tyr355, Trp387, Phe518
β-D-Glucopyranoside, methyl	Ser530 (2), Met522, Tyr355	-	Tyr385, Met522, Ser530 (2), Gly526	-
6-Hydroxy-4,4,7α-trimethyl-5,6,7,7a tetrahydrobenzofuran-2(4H)-one	Ser530 (2), Tyr355	Val349, Leu359, Val116, Val349 (2), Leu531, Leu352, Tyr355	Met522, Ala527, Ser530	Leu352 (2), Val523, Val349

(*Continued on next page*)

Table 3. (*Continued*)

Compounds	COX-1 (PDB ID: 2YOE)		COX-2 (PDB ID: 6COX)	
	Hydrogen bond interactions	**Hydrophobic interactions**	**Hydrogen bond interactions**	**Hydrophobic interactions**
1-(7-Hydroxy-1,6,6-trimethyl-10-oxatricyclo [5.2.1.0(2,4)] dec-9-yl) ethanone	-	Val349 (4), Ala527 (2), Ile523, Phe518	Ala527 (2), Ser530 (2)	Val523 (2), Ala527, Leu352 (2), Val349 (2), Tyr355, Phe518 (2)
2(3H)-Furanone, dihydro-5-(2-octenyl)-, (*Z*)-	Ser530, Ala527, Ile523	Ala527, Phe518	Arg120	Val349, Val523, Met522, Tyr355, Trp387, Phe518
9-Octadecenamide, (*Z*)-	Glu524	Leu384, Phe381, Tyr385, Trp387	His90, Gln192 (2), Leu352	Tyr115
(*Z*)-3-(pentadec-8-en-1-yl) phenol	-	Tyr385, Gly526, Ala527 (2), Ile523, His90, His513, Leu352	-	Leu123, Leu352
Phenol, 3-pentadecyl-	-	Tyr385, Trp387 (2), Ile523	Ser119	Leu384, Phe381, Tyr385, Trp387 (2), Val89
Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester	Ser530, Ile523, Met522	Leu92, Leu93, Trp100	Lys83 (3), Arg120, Tyr122, Ser471, Glu524 (2), Phe470	Ala527
Bis(2-ethylhexyl) phthalate	Arg120 (2)	Tyr355, Ala527, Leu115, Val349, Leu531, Ile89, Leu92, Leu93, Leu352, Trp100, Phe518	-	-
(*Z*)-3-(Heptadec-10-en-1-yl) phenol	Tyr385	Tyr385, Gly526, Ala527, Leu115, Val119	Tyr385	Trp387, Pro86, Gly526, Ala527, Val89
3-((*4Z,7Z*)-Heptadeca-4,7-dien-1-yl) phenol	-	Leu384, Met522, Trp387 (2), Leu115, Val119	-	Gly526, Ala527, Arg120, Leu352
α-Tocospiro A	-	-	-	-
γ-Tocopherol	-	-	-	-
Cholesta-4,6-dien-3-ol, (3β)-	-	-	-	-
α-Tocopherol	-	Val116 (2), Ala527 (4), Ile89, Val349 (2), Leu531, Ile523, Leu352, Leu115 (2), Val119 (2), Tyr355, Phe518	-	-

(*Continued on next page*)

Table 3. (*Continued*)

Compounds	COX-1 (PDB ID: 2YOE)		COX-2 (PDB ID: 6COX)	
	Hydrogen bond interactions	**Hydrophobic interactions**	**Hydrogen bond interactions**	**Hydrophobic interactions**
Campesterol	-	-	-	-
Stigmasterol	-	-	-	-
γ-Sitosterol	-	-	-	-

Table 4. Binding interactions of the selected eighteen compounds with kappa receptor (PDB ID: 4DJH) and mu receptor (PDB ID: 5C1M) for anti-nociceptive activity, respectively

Compounds	kappa receptor (PDB ID: 4DJH)		mu receptor (PDB ID: 5C1M)	
	Hydrogen bond interactions	**Hydrophobic interactions**	**Hydrogen bond interactions**	**Hydrophobic interactions**
Santalol, *E*-cis,epi-β-	-	Tyr313 (2), Ala317, Ile62 (2), Val65, Val69, Tyr66, Tyr119 (2)	Asp147, His54	Ile144 (2), Cys217, Val143, His54 (2), Trp133, Tyr148
β-D-Glucopyranoside, methyl	Tyr312, Asp138 (3), Gln115 (2), Tyr320, Thr111	-	Asp147 (3), Asn127	-
6-Hydroxy-4,4,7α-trimethyl-5,6,7,7a tetrahydrobenzofuran-2(4H)-one	Tyr66, Ser116	Ala317, Ile316, Met112, Ile62, Tyr66, Tyr320	Asp147	Met151, Ile296 (2), Ile322, Val236, Trp293, Tyr326
1-(7-Hydroxy-1,6,6-trimethyl-10-oxatricyclo [5.2.1.0(2,4)] dec-9-yl) ethanone	Ser116	Ala317 (3), Ile62 (2), Tyr66, Tyr119 (2), Tyr313	Asp147, Tyr326	Val236, Val300, Met151, Ile296 (3), Ile322, Met151, His54, Tyr148, Tyr326 (2)
2(3H)-Furanone, dihydro-5-(2-octenyl)-, (*Z*)-	Tyr312, Asp138	Met142, Ile290, Tyr320	Trp318, His319, Gln124	Trp293, Tyr326
9-Octadecenamide, (*Z*)-	Tyr312, Asp138	Val134, Trp124	His319, Ser55, Asn127, His319	Leu219, His54, Phe221
(*Z*)-3-(pentadec-8-en-1-yl) phenol	Tyr139	Val134, Val230, Ile294	Asp147, Ile144	Leu232, Lys233, His54
Phenol, 3-pentadecyl-	Tyr139	Val118, Trp124, Val230, Ile294	Ser53	His54, Val143, Ile144, Leu219, Lys233
Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester	Ile208 (2), Cys210, Glu209	Ile208, Met142, Ile290, Ile294, His291	Trp318, Asn127 (2), His54, Ser55 (2)	Leu219, His54
Bis(2-ethylhexyl) phthalate	Asp138 (2)	Trp287, Tyr320, Met142, Ile290 (2), Ile294 (2), Val108, Val134, Leu135, Cys210, Trp124, His291, Ile316	-	Met151, Ile296, Ile322 (2), His54, Tyr148, Trp293, His319, Tyr326, Lys233, Val300

(*Continued on next page*)

Table 4. (*Continued*)

Compounds	kappa receptor (PDB ID: 4DJH)		mu receptor (PDB ID: 5C1M)	
	Hydrogen bond interactions	**Hydrophobic interactions**	**Hydrogen bond interactions**	**Hydrophobic interactions**
(*Z*)-3-(Heptadec-10-en-1-yl) phenol	Gln115	Leu135, Tyr139, Val134	Tyr326	His319, Met151
3-((*4Z,7Z*)-Heptadeca-4,7-dien-1-yl) phenol	Tyr139	Val118, Cys210, Trp124, Val230, Ile290, Ile294	Asp147, Ile144	His54 (2), Leu219, Phe221, Ile144
α-Tocospiro A	Ser211, Tyr219, Lys227, Tyr312	Leu135 (2), Ile294, Val134, Val108 (2), Ile290, Trp124, Trp287 (4), Tyr312, Tyr320	-	Val300 (2), Ile296 (2), Ile322 (2), Met151 (2), Val143, Ile144, Cys217, His54, Trp133 (2), Tyr148, Trp293, Trp318, Tyr326
γ-Tocopherol	Lys227	His291, Met142 (3), Ile294 (4), Ile290, Val230, Val118, Trp124 (2), Tyr139, Trp287 (2), His291, Val230	Ser53, Lys233	Val236 (2), Val300 (3), Met151, Ile144, Ile322, His54 (2), Tyr148, Trp318 (4), His319 (2)
Cholesta-4,6-dien-3-ol, (3β)-	-	Tyr320, Val118, Cys210, Ile316 (2), Ile290, Trp124, Trp287 (2), Tyr320 (2)	His297	Ile322 (2), Ile296, Val300, Met151, Val143 (2), Ile144 (2), Cys217, His54, Trp133, Tyr148
α-Tocopherol	Asn122	Val118 (3), Cys210, Met142, Ile290, Ile294, Trp287, Tyr312, Tyr320	Asn127, Ser55	Ile144, Val236, Val300 (2), Cys217, Ile322 (2), His54 (3), Trp133, Trp293, Trp318, Tyr326
Campesterol	-	Trp287, Ile294 (2), Ile316, Ile290, ile316 (2), Val108, Trp287 (3), Tyr312, Tyr320 (2)	Lys233, His297	Ile296, Val300 (3), Val236 (2), Ile296, Ile322, Ile144 (2), Val143, Cys217, His54 (3), Trp133 (3), Tyr148, His297
Stigmasterol	-	Ile62, Ala317, Ile316, Met112, Tyr66, Tyr119, Tyr313, Tyr320	Lys233, His297	His297 (2), Ile296 (2), Val300 (3), Val236 (2), Met151, Ile322, Val143 (2), Ile144 (2), Cys217, His54 (3), Trp133 (2), Tyr148
γ-Sitosterol	-	Val118, Cys210, Val134, Trp124	Asn127, Gln124	Ile322 (3), Met151, Lys233, Val236 (2), Val300 (2), His54 (2), Tyr148 (2), His297, Trp318 (2)

In the case of the COX-1 enzyme, twenty-six compounds have shown the docking scores among all compounds in which thirteen compounds have given the highest scores namely C1, C2, C3, C4, C10, C19, C20, C21, C22, C23, C24, C25, C27. The amino acid residues through which all the compounds interact with the respective enzymes are mainly two types such as hydrogen bond and hydrophobic interactions. The most common amino acid residue for hydrogen bond interactions is Ser530, Ser530, Met522, Tyr355, and

Ile523, and hydrophobic interactions are Val349, Ala527, Leu352, Ile523, Met522, Tyr355, Trp387, Val116, Leu531, Phe518, Leu384, Tyr385, Trp100, Ile89, Leu92, Leu93, Val119. Oppositely, for COX-2 enzyme, twenty-four compounds have been docked among all compounds in which eleven compounds have given the highest scores namely C1, C2, C3, C4, C10, C19, C20, C21, C22, C24, C25. The most common amino acid residue for hydrogen bond interactions are His90, Leu352, Tyr385, Met522, Ser530, Ala527, and hydrophobic interactions are Val349, Leu352, Ala527, Val523, Tyr355, Trp387, Phe518, Val523, and Val89.

Furthermore, for the kappa receptor, thirty-two compounds have been docked with the kappa receptor of which nineteen compounds have given the highest scores viz. C1, C2, C3, C4, C10, C19, C20, C21, C22, C23, C24, C25, C26, C27, C28, C29, C30, C31, C32 (Table 2). The most common amino acid residue for hydrogen bond interactions are Tyr312, Asp138, Ser1-16, Tyr312, Asp138, Tyr139, Lys227, and hydrophobic interactions are Tyr313, Ala317, Ile62, Tyr66, Tyr119, Ile316, Met112, Tyr320, Met142, Ile290, Val134, Trp124, Val230, Ile294, Val118, His291, Trp287, Ile294, Val108, Leu135, Cys210, Tyr139, Trp287, Tyr312, and Tyr320. Besides, for mu receptor, twenty-four compounds have been docked among all compounds in which nineteen compounds have given the highest scores i.e., C1, C2, C3, C4, C10, C19, C20, C21, C22, C23, C24, C25, C26, C27, C28, C29, C30, C31, C32 (Table 2). The most common amino acid residue for hydrogen bond interactions is Asp147, His54, Asn127, Tyr326, Trp318, His319, Gln124, Ile144, Lys233, His297, and hydrophobic interactions are Ile144, Cys217, Val143, His54, Trp133, Tyr148, Met151, Ile296, Ile322, Val236, Trp293, Tyr326, Val300, Leu219, Phe221, His319, Val236, Trp318, and His297. From the molecular docking analysis, it can be inferred that in total eighteen phytocompounds (C1, C2, C3, C4, C10, C19, C20, C21, C22, C23, C24, C25, C27. C28, C29, C30, C31, C32) might in some way be accountable for the analgesic effects of the plant by establishing several molecular interactions with target proteins.

4. Conclusions

In summary, the present study demonstrated that the eighteen phytocompounds (C1, C2, C3, C4, C10, C19, C20, C21, C22, C23, C24, C25, C27. C28, C29, C30, C31, C32) may be responsible for the plant's analgesic properties which were found safe during ADME/T study. As a result, it is obvious that those chemicals could be a promising source for the development of new analgesics, and they deserve additional research to determine their exact molecular mechanism of action in the experimental study.

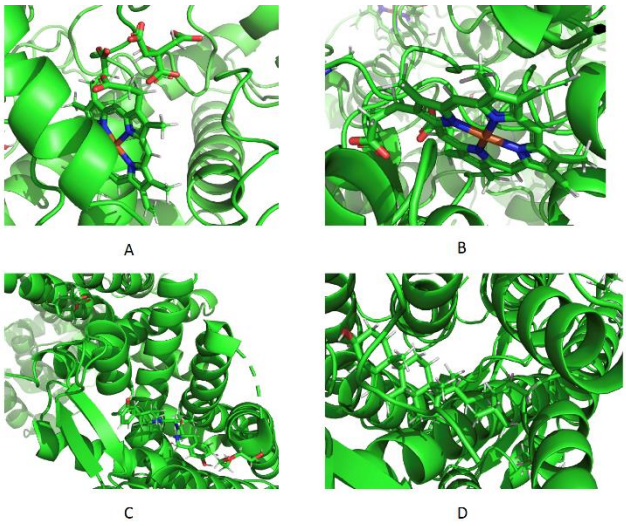

Figure 1. Best ranked pose of (A) (*Z*)-3-(pentadec-8-en-1-yl) phenol in the binding pocket of cyclooxygenase 1 (PDB ID: 2YOE), Best ranked pose of (B) 3-((*4Z,7Z*) Heptadeca-4,7-dien-1-yl)phenol in the binding pocket of cyclooxygenase 2 (PDB ID: 6COX) enzymes, Best ranked pose of (C) 1-(7-Hydroxy-1,6,6-trimethyl-10-oxatricyclo[5.2.1.0(2,4)]dec-9-yl)ethanone in the binding pocket of kappa receptor (PDB ID: 4DJH), and Best ranked pose of (D) γ-Sitosterol in the binding pocket of mu receptor (PDB ID: 5C1M) for anti-nociceptive activity.

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6. Author's contributions

MA, MNUC and TE. conceived and designed the experiments. MNUC, TE, RA, and MHUC performed the computational study, analyzed the data and wrote the final manuscript. MA supervised this study.

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8. Conflicts of Interest

The authors declare that they have no conflict of interest

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