Virtual Potential of Some Curcumin Derivatives as Inhibitors to Influenza: A Hemagglutinin and Neuraminidase

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Abstract
Influenza is known as a contagious, acute respiratory illness caused by influenza viruses. And it can cause mild to severe illness, furthermore, it may predispose to exacerbation of underlying disease or development of secondary bacterial infections. Additionally, the resistance of the antiviral drugs is recently spreaded. And new antiviral drugs are still needed to treat influenza epidemics and pandemics. There are several natural compounds have antiviral activity, one of these compounds was curcumin. Several studies demonstrated the curcumin as directly effective upon viral infection. This effect was observed in " H1N1 as well as H6N1 " subtypes. So that in current study a 58-curcumin derivatives potential to be inhibitors to influenza receptors were analyzed. The " Hemagglutinin " (HA) and " neuraminidase " (NA). This done by modelling and molecular docking of curcumin compounds against the active site of these receptors. Moreover, the results were showed that curcumin compounds with the best docking score (Perfluoro curcumin, N-(4-Fluoropheny-lpyrazole) Curcumin, Curcumin glucuronide, Curcumin-difluorinated (CDF) and Curcumin glucuronide) were blocked the viral active sites of most strains. And these agents had an acceptable " Lipinski rule of five " properties. In conclusions, this study led to conclude that the chosen curcumin compound (Perfluoro curcumin, N-(4-Fluoropheny-lpyrazole) Curcumin, Curcumin glucuronide, Curcumin-difluorinated (CDF) and Curcumin glucuronide) may have the best studied properties and suggest them to future studies in combination to traditional antiviral agent, both in-vivo and in-vitro. The current data supply basic information for further wet lab experiments in order to develop more Curcumin derivatives to reach the best therapeutic values.

1. Introduction

Influenza is a contagious, acute respiratory illness caused by influenza viruses, usually influenza A or B subtypes. Additionally, the Influenza virus causes from mild to severe diseases.
On the other hand, immunization is the best intervention to prevent influenza virus infection [1]. And the importance of influenza treatment is to relief symptoms, such as (high fever, headache, sneezing, cough, runny nose, etc.), to reduce morbidity and prevent complications. And because a wide range of complications can be caused by influenza virus infection of the upper respiratory tract and lower respiratory tract such as (Pneumonia, bronchitis, sinus infections and ear infections) [2].
Furthermore, the turmeric has a long history of use inflammatory conditions. And the C. longa plant which is it derived from, is a member of Zingiberaceae. In addition, the active constituent of turmeric responsible for its yellow color is the curcumin [3]. And turmeric mainly comprises group of three curcuminoids, the first one is diferuloylmethane, the second is demethoxycurcumin, and the third is bisdemethoxycurcumin, also sugars, proteins, resins, and volatile oils [4]. Furthermore, in ancient medicine, numerous therapeutic procedures used turmeric for sevweral diseases. And extensive research within the last half century has showed that the most of these pharmacological activities related with turmeric are due to active ingredient curcumin. And it has been reported that these effects are mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes [5]. On the other hand, curcumins compounds as a plant derivative have a broad antiviral activity against different viruses [6].

2. Materials and Methods

Influenza Virus Receptors

Neuraminidase (11 molecules) and hemagglutinin (18 molecules) three-dimensional structure are derived from " Protein Data Bank " with PDB IDs shown in tables 1 and 2. The Neuraminidase active site centers are " R118, E119, and I222 " , in addition, the center of selected hemagglutinin active site are " Y98, W153, H183, and L194 " .

Table (1): Neuraminidase molecules.

" Neuraminidase type	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11
PDB ID	2hu4	1ivf	4hzv	2htw	3sal	1v0z	4qn7	2htu	1f8b	4gdi	4mc7 "

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Table (2): Hemagglutinin molecules.															
" Hemagglutinin type		H1	H2	H3	H4	H5	H6	H7	H9	H10	H13	H14	H15	H16	H17	H18
PDB ID	4edb	2wrd	3ztj	5xl2	5e2y	5t0b	4lkh	1jsh	4xq5	4kpq	3eyj	5tg8	4f23	4i78	4k3x "	

Curcumins Compounds

Many Curcumin compounds (58 molecules) were used in current study in order to inhibit influenza virus. These chemical compounds listed in table 3.

Table 3: Curcumins chemical compounds [26].		
IUPAC Name	Chemical Formula	No
(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione	Curcumin	1
" (2S,3S,4S,5R,6S)-3,4,5-trihydroxy-6-[4-[(1E,6E)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dienyl]-2-methoxyphenoxy] oxane-2-carboxylic acid "	Curcumin glucuronide	2
(1E,6E)-1,7-bis(4-hydroxyphenyl) hepta-1,6-diene-3,5-dione	Bisdemethoxycurcumin	3
" [4-[(1E,6E)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dienyl]-2-methoxyphenyl] hydrogen sulfate "	Curcumin sulfate	4
[4-[(1E,6E)-7-(4-acetyloxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dienyl]-2-methoxyphenyl] acetate	Curcumin bisacetate	5
" 1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	Curcuma longa L	6
" (4Z)-4-[(2Z)-2-[5-[(E)-2-(4-hydroxy-3-methoxyphenyl) ethenyl]-1,2-dihydropyrazol-3-ylidene] ethylidene]-2-methoxycyclohexa-2,5-dien-1-one "	Curcumin pyrazole	7
" 3,4,5-trihydroxy-6-[4-[7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dienyl]-2-methoxyphenoxy] oxane-2-carboxylic acid "	Curcumin beta-D-glucuronide	8
" (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-4-[(4-hydroxy-3-methoxyphenyl) methylidene] hepta-1,6-diene-3,5-dione "	4-(4-hydroxy-3-methoxybenzylidene) curcumin	9
[2-methoxy-4-[(1E,6E)-7-[3-methoxy-4-(thiophene-2-carbonyloxy) phenyl]-3,5-dioxohepta-1,6-dienyl] phenyl] thiophene-2-carboxylate	Di-O-(2-Thienoyl) curcumin	10
" (1E,4Z,6E)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-[3-methoxy-4-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]oxyphenyl]hepta-1,4,6-trien-3-one "	Curcumin monoglucoside	11
1,7-bis(4-hydroxy-3-methoxyphenyl) heptane-3,5-dione	Tetrahydro-curcumin	12
" (1E,6E)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	Demethyl Curcumin	13
" 1-(3,4-dihydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	OR223598	14
" (1E,6E)-1,7-bis(3,4-dihydroxyphenyl) hepta-1,6-diene-3,5-dione "	Didemethyl Curcumin	15
1,7-bis(3,4-dihydroxyphenyl) hepta-1,6-diene-3,5-dione	1,7-bis(3,4-dihydroxyphenyl) hepta-1,6-diene-3,5-dione	16
" (1E,4Z,6E)-7-[4-(3-fluoranylpropoxy)-3-methoxyphenyl]-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl) hepta-1,4,6-trien-3-one "	[18FP]-curcumin	17
" (4E)-4-[(2Z)-2-[5-[(E)-2-(4-hydroxy-3-methoxyphenyl) ethenyl]-1,2-dihydropyrazol-3-ylidene] ethylidene]-2-methoxycyclohexa-2,5-dien-1-one "	Curcumin pyrazole	18
" Methyl (2S,3S,4S,5R,6S)-3,4,5-triacetyloxy-6-[4-[(1E,6E)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dienyl]-2-methoxyphenoxy] oxane-2-carboxylate "	Curcumin |A-D-Glucuronide Triacetate Methyl Ester	19
" 1,5-bis(2-fluorophenyl) penta-1,4-dien-3-one "	AC1N69I4	20
" (1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,4,6-trien-3-one	CURCUMIN PE	21
" (1E,6E)-4-[(3,4-difluorophenyl) methylidene]-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	Curcumin-difluorinated (CDF)	22
" (3S,6S)-3,4,5-trihydroxy-6-[4-[(1E,6E)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dienyl]-2-methoxyphenoxy] oxane-2-carboxylic acid "	Curcumin beta-D-glucuronide	23
" (1Z,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	Cis-Curcumin	24
" (1E,6E)-1,7-bis(3-methoxy-4-prop-2-enoxyphenyl) hepta-1,6-diene-3,5-dione "	Allyl-curcumin	25
" (1E,6E)-1-(4-hydroxy-3-methoxyphenyl)-7-[4-hydroxy-3-[[(3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] methoxy] phenyl] hepta-1,6-diene-3,5-dione	glucosyl-curcumin	26
" (1E,6E)-1,2,4,4,6,7-hexafluoro-1,7-bis[2,3,6-trifluoro-4-hydroxy-5-(trifluoromethoxy) phenyl] hepta-1,6-diene-3,5-dione "	Perfluoro Curcumin	27
" (1E,6E)-1-[3-(difluoromethoxy)-4-hydroxyphenyl]-7-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	Di-fluoro curcumin	28
(E,1Z)-4-(4-hydroxy-3-methoxyphenyl)-1-[7-(4-hydroxy-3-methoxyphenyl)-1,2,3,4-tetrahydro-1,4-diazepin-5-ylidene] but-3-en-2-one	Curcumin ED	29
(1E,6E)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl) hepta-1,6-diene-3,5-dione	O-demethyl-demethoxy-curcumin	30

1,7-bis(4-hydroxyphenyl) heptane-3,5-dione	Tetrahydrobisdemethoxycurcumin	31
" [4-[7-(4-acetyloxy-3-methoxyphenyl)-3,5-dioxoheptyl]-2-methoxyphenyl] acetate	Tetrahydro-curcumin diacetate	32
4-[2-[3-[2-(4-hydroxy-3-methoxyphenyl) ethyl]-1,2-oxazol-5-yl] ethyl]-2-methoxyphenol	Tetrahydro-curcumin isoxazole	33
" 5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl) heptan-3-one "	Hexahydro-curcumin	34
" (1E,6E)-1-(4-hydroxy-3-methoxyphenyl)-7-(3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	Curcumin 2	35
" 1,7-bis(4-hydroxy-3-methoxyphenyl) heptane-3,5-diol "	Octahydro-curcumin	36
" (3S,5S)-1,7-bis(4-hydroxy-3-methoxyphenyl) heptane-3,5-diol "	Octahydro-curcumin	37
" (3S,7S)-3,7-diamino-5-[2-hydroxy-5-[(1E,6E)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dienyl] phenoxy]-2,8-dimethylnonane-4,6-dione "	di-valinoyl curcumin	38
" (1E,6E)-1-[3-[1,3-bis(2-hydroxyphenyl)-1,3-dioxopropan-2-yl] oxy-4-hydroxyphenyl]-7-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	Disalicyloyl Curcumin	39
" (3R,5S)-1,7-bis(4-hydroxy-3-methoxyphenyl) heptane-3,5-diol "	Meso-Octahydro-curcumin	40
" [4-[(1E,6E)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dienyl]-2-methoxyphenyl] (2S)-2-amino-3-methylbutanoate "	Monovalinoyl curcumin	41
" (E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hept-1-ene-3,5-dione "	Dihydrocurcumin	42
" (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	[13C]-Curcumin	43
" (1E,6E)-1-(4-hydroxy-3-methoxyphenyl)-7-(3-methoxy-4-methylphenyl) hepta-1,6-diene-3,5-dione "	SCHEMBL2622435	44
" [[(1E,2Z,6E)-7-(4-hydroxy-3-methoxyphenyl)-1-(3-methoxy-4-oxocyclohexa-2,5-dien-1-ylidene)-5-oxohepta-2,6-dien-3-yl] amino] urea "	Curcumin semicarbazone	45
" [4-[(1E,6E)-7-(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dienyl]-2-methoxyphenyl] 2-aminoacetate "	Monoglycinoyl curcumin	46
" (1E,6E)-4-benzylidene-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	4-benzylidene curcumin	47
" (1E,6E)-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl) hepta-1,6-diene-3,5-dione "	Demethoxycurcumin	48
" (2S)-2-[[(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-3,5-dioxohepta-1,6-dien-4-yl] amino]-5-[[(2R)-1-(carboxymethylamino)-1-oxo-3-sulfanylpropan-2-yl] amino]-5-oxopentanoic acid "	monoglutathionyl-curcumin	49
" (1E)-1-(4-hydroxy-3-methoxyphenyl)-4-[(E)-3-(4-hydroxy-3-methoxyphenyl) prop-2-enoyl]-6-methylhepta-1,6-diene-3,5-dione "	mono-methacryloyl-curcumin	50
" [4-[(1E,6E)-7-(4-heptanoyloxy-3-propoxyphenyl)-3,5-dioxohepta-1,6-dienyl]-2-methoxyphenyl] heptanoate "	di-O-heptanoylethyl curcumin	51
" (1E,6E)-1-[4-hydroxy-3-(hydroxymethyl) phenyl]-7-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	US9187406, Curcumin	52
" (1E,6E)-1,7-bis[4-(2-hydroxyethoxy)-3-methoxyphenyl] hepta-1,6-diene-3,5-dio "	Di-O-(2-hydroxyethyl) curcumin	53
" (1E,6E)-1-[4-(2-hydroxyethoxy)-3-methoxyphenyl]-7-(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione "	Mono-O-(2-hydroxyethyl) curcumin	54
" (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-4-[(4-hydroxyphenyl) methylidene] hepta-1,6-diene-3,5-dione "	4-(4-hydroxybenzylidene) curcumin	55
" (4E)-4-[(2Z)-2-[2-(4-fluorophenyl)-3-[(E)-2-(4-hydroxy-3-methoxyphenyl) ethenyl]-1H-pyrazol-5-ylidene] ethylidene]-2-methoxycyclohexa-2,5-dien-1-one "	N-(4-Fluorophenylpyrazole) Curcumin	56
" (4E)-4-[(2Z)-2-[3-[(E)-2-(4-hydroxy-3-methoxyphenyl) ethenyl]-2-(3-nitrophenyl)-1H-pyrazol-5-ylidene] ethylidene]-2-methoxycyclohexa-2,5-dien-1-one "	N-(3-Nitrophenylpyrazole) Curcumin	57
" (4E)-4-[(2Z)-2-[3-[(E)-2-(4-hydroxy-3-methoxyphenyl) ethenyl]-2-(4-methoxyphenyl)-1H-pyrazol-5-ylidene] ethylidene]-2-methoxycyclohexa-2,5-dien-1-one "	N-(4-Methoxyphenylpyrazole) Curcumin	58

Programs

Several programs, both online and standalone are used. Including: MCUL {1-click docking} [7], Protein data bank (PDB) [8], [9].

Strategy of Potential Inhibitors

Selecting all of 58 studied curcumin compounds, then molecular docking done. Through " MCULE " server, by " 1-click docking " tool against " hemagglutinin and neuraminidase " active sites. Additionally, docking score less than -7, give thought to stable attachment of curcumin to corresponding active sites.

3. Results

Curcumin compounds, 58 compounds at the current study, are examined using MCUL docking to neuraminidase and hemagglutinin. Molecular docking of studied curcumin to neuraminidase and hemagglutinin strains are detailed in tables 4 and 5, with score stronger

than -7.

Table (4): " Molecular docking of curcumin to hemagglutinin strains from 1 to 18 " .																
positives No.	H18	H17	H16	H15	H14	H13	H10	H9	H7	H6	H5	H4	H3	H2	H1	Curcumin Compounds
13	-	+	+	+	+	+		-	+	+	+	+	+	+	+	Perfluoro Curcumin
9	-	-	+	-	+	-	+	-	+	-	+	+	+	+	+	N-(4-Fluorophenyl-pyrazole) Curcumin
9	-	-	+	-	+	-	+	+	-	-	+	+	+	+	+	N-(3-Nitrophenylpyrazole) Curcumin
6	-	-	+	+	+	-	-	-	-	-	+	+	+	-	-	Curcumin-difluorinated (CDF)
6	-	-	-	+	-	-	-	+	-	-	+	+	+	+	-	4-benzylidene curcumin
6	-	-	+	-	+	-	+	-	-	-	+	+	+	-	-	N-(4-Methoxyphenylpyrazole) Curcumin
5	-	-	+	+	-	-	-	+	-	-	+	+	-	-	-	Curcuminpyrazole
5	-	-	+	-	-	+	-	-	-	-	+	+	-	-	+	Curcumin ED
5	-	-	+	-	-	-	-	+	-	-	+	+	-	+	-	Curcuminsemicarbazone
3	-	-	+	-	+	-	-	-	-	-	-	-	+	-	-	4-(4-hydroxy-3-methoxy-benzylidene) curcumin
3	-	-	-	-	-	-	-	+	-	-	-	+	-	+	-	Curcuminmonoglucoside
3	-	-	+	-	-	-	-	-	-	-	+	-	-	+	-	4-(4-hydroxy-benzylidene) curcumin
2	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	Curcuminpyrazole
1	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	Didemethyl-Curcumin
1	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	CURCUMIN PE
1	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	glucosyl-curcumin
1	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	Tetrahydrocurcuminisoxazole
1	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	Disalicyloyl Curcumin
1	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	mono-methacryloyl-curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Curcumin glucuronide
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Bisdemethoxycurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Curcumin sulfate
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Curcuminbis-acetate
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Curcuma longa L
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Curcumin beta-D-glucuronide
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Di-O-(2-Thienoyl) curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Tetrahydrocurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	DemethylCurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	OR223598
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1,7-bis(3,4-dihydroxyphenyl) hepta-1,6-diene-3,5-dione
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	[18FP]-curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Curcumin |A-D-Glucuronide Triacetate Methyl Ester
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	AC1N69I4
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Curcumin beta-D-glucuronide
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Cis-Curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Allyl-curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Di-fluorocurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	O-demethyldemethoxycurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Tetrahydrobisdemethoxycurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Tetrahydrocurcumindiacetate
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Hexahydrocurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Curcumin 2
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Octahydrocurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Octahydrocurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	di-valinoyl curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Meso-Octahydrocurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Monovalinoylcurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Dihydrocurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	[13C]-Curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	SCHEMBL2622435
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Monoglycinoylcucumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Demethoxycurcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	monoglutathionyl-curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	di-O-heptanoylethyl curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	US9187406, Curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Di-O-(2-hydroxyethyl) curcumin
0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Mono-O-(2-hydroxyethyl) curcumin

Table (5): " Molecular docking of curcumin to neuramindase strains. "												
Positive s No.	N11	N10	N9	N8	N7	N6	N5	N4	N3	N2	N1	Curcumin
8	+	-	-	+	+	+	+	+	+	-	+	Perfluoro Curcumin
7	+	-	-	+	+	+	+	+	+	-	-	N-(4-Fluorophenylpyrazole) Curcumin
7	+	-	+		+	+	+	+	-	-	+	N-(3-Nitrophenylpyrazole) Curcumin
6	-	+	-	-	+	+	-	+	+	-	+	Curcumin-difluorinated (CDF)
6	+	-	+	+	+	-	+	-	+	-	-	4-benzylidene curcumin
6	+	-	+	-	+	+	+	+	-	-	-	N-(4-Methoxyphenylpyrazole) Curcumin
5	-	-	+		+	-	+	+	+	-	-	Curcuminpyrazole
5	+	-	-	-	+	+	-	+	-	-	+	Curcumin ED
5	-	-	-	+	+	+	+	-	-	-	+	Curcuminsemicarbazone
5	+	-	-	-	+	+	-	+	-	-	+	4-(4-hydroxy-3-methoxybenzylidene) curcumin
5	+	-	-	-	+	+		+	-	-	+	Curcuminmonoglucoside
5	+	-	+	-	-	+	+	+	-	-	-	4-(4-hydroxybenzylidene) curcumin
5	+	-	-	-	+	+	+	+	-	-	-	Curcuminpyrazole
5	+	-	-	-	+	+	-	+	+	-	-	DidemethylCurcumin
4	-	-	-	-	+	+	+	+	-	-	-	CURCUMIN PE
4	+	-	-	-	+	+	-	+	-	-	-	glucosyl-curcumin
4	+	-	-	-	+	+	-	+	-	-	-	Tetrahydro-curcuminisoxazole
4	-	-	-	-	+	+	+	+	-	-	-	Disalicyloyl Curcumin
4	+	-	-	-	+	+	-	+	-	-	-	mono-methacryloyl-curcumin
4	+	-	-	-	+	+	-	+	-	-	-	Curcumin
3	-	-	-	-	+	+	-	+	-	-	-	Curcumin glucuronide
3	+	-	-	-	-	-	-	+	+	-	-	Bisdemethoxycurcumin
3	-	-	-	-	+	+	-	-	-	-	+	Curcumin sulfate
3	-	-	-	+	+	-	-	-	+	-	-	Curcuminbis-acetate
3	-	-	-	-	+	+	-	+	-	-	-	Curcuma longa L
3	+	-	-	-	-	-	+	+	-	-	-	Curcumin beta-D-glucuronide
2	-	-	-	-	+	-	-	-	-	-	+	Di-O-(2-Thienoyl) curcumin
2	-	-	-	-	+	+	-	-	-	-	-	Tetrahydrocurcumin
2	-	-	-	-	+	+	-	-	-	-	-	DemethylCurcumin
2	-	-	-	-	-	-	+	-	+	-	-	OR223598
2	-	-	-	-	-	-	+	-	+	-	-	1,7-bis(3,4-dihydroxyphenyl) hepta-1,6-diene-3,5-dione
2	-	-	-	-	+	+	-	-	-	-	-	[18FP]-curcumin
2	-	-	-	-	+	-	-	+	-	-	-	Curcumin |A-D-Glucuronide Triacetate Methyl Ester
2	-	-	-	+	-	+	-	-	-	-	-	AC1N69I4
2	-	-	-	-	+	+	-	-	-	-	-	Curcumin beta-D-glucuronide
2	-	-	-	-	+	-	-	-	-	-	+	Cis-Curcumin
2	-	-	-	-	-	+	+	-	-	-	-	Allyl-curcumin
2	-	-	-	-	+	-	-	+	-	-	-	Di-fluorocurcumin
2	-	-	-	-	+	+	-	-	-	-	-	O-demethyldemethoxy-curcumin
1	-	-	-	-	+	-	-	-	-	-	-	Tetrahydrobisdemethoxy-curcumin
1	-	-	-	-		-	-	+	-	-	-	Tetrahydro-curcumindiacetate
1	-	-	-	-	-	+	-	-	-	-	-	Hexahydrocurcumin
1	-	-	-	-	-	+	-	-	-	-	-	Curcumin 2
1	-	-	-	-	-	-	-	-	-	-	+	Octahydrocurcumin
1	-	-	+	-	-	-	-	-	-	-	-	Octahydrocurcumin
1	-	-	+	-	-	-	-	-	-	-	-	di-valinoyl curcumin
1	-	-	-	-	-	-	-	-	-	-	+	Meso-Octahydrocurcumin
1	-	-	-	-	-	+	-	-	-	-	-	Monovalinoylcurcumin
0	-	-	-	-	-	-	-	-	-	-	-	Dihydrocurcumin
0	-	-	-	-	-	-	-	-	-	-	-	[13C]-Curcumin
0	-	-	-	-	-	-	-	-	-	-	-	SCHEMBL2622435
0	-	-	-	-	-	-	-	-	-	-	-	Monoglycinoylcucumin
0	-	-	-	-	-	-	-	-	-	-	-	Demethoxycurcumin
0	-	-	-	-	-	-	-	-	-	-	-	monoglutathionyl-curcumin
0	-	-	-	-	-	-	-	-	-	-	-	di-O-heptanoylethyl curcumin
0	-	-	-	-	-	-	-	-	-	-	-	US9187406, Curcumin
0	-	-	-	-	-	-	-	-	-	-	-	Di-O-(2-hydroxyethyl) curcumin
0	-	-	-	-	-	-	-	-	-	-	-	Mono-O-(2-hydroxyethyl) curcumin

able (6): Lipinski rule of curcumin compounds properties with best docking score to hemagglutinin and Neuraminidase.						
Normal values	Neuraminidase			Hemagglutinin		Property
	Curcumin-difluorinated (CDF)	Curcumin glucuronide	Perfluoro Curcumin	N-(4-Fluoropheny-lpyrazole) Curcumin	Perfluoro Curcumin	
Less than 500	492.4655	544.5023	692062	458.4793	692062	mass
Less than 5	5.3416	0.9353	7.4185	4.4863	7.4185	logP
Less than 10	6	12	6	6	6	H-bond acceptors
Less than 5	2	5	2	2	2	H-bond donors
Less than 10	9	11	10	6	10	Rotatable bonds
0	1	2	2	0	2	RO5 violations
0	5	5	5	5	5	RO3 violations

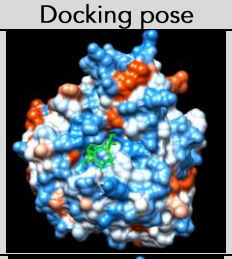
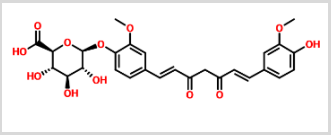
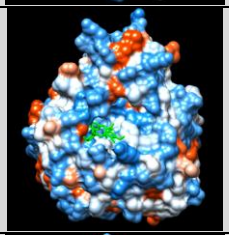
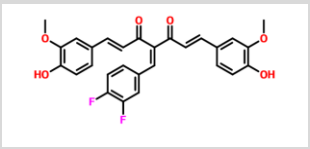
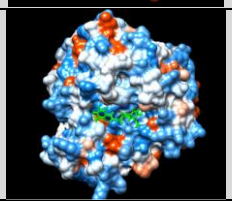
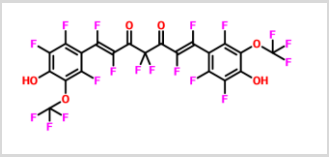
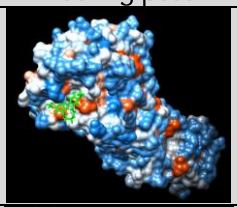
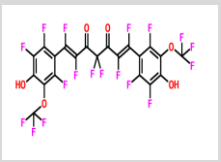
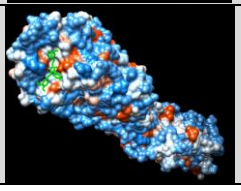
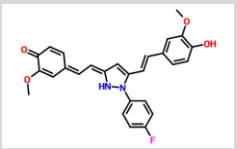
Table (7): structure and curcumin docking with wide spectrum against neuraminidase attachment.		
Docking pose	Structure	Curcumin
		Curcumin glucuronide
		Curcumin-difluorinated (CDF)
		PerfluoroCurcumin

Table (8): structure and curcumin docking with wide spectrum against hemagglutinin attachment.		
Docking pose	Structure	Curcumin
		Perfluoro Curcumin
		N-(4-Fluorophenyl-pyrazole)Curcumin

4. Discussion

Influenza is a viral infectious illness, it causes approximately millions of deaths worldwide through pandemic episodes [10]. In addition, the influenza a viruses infect a wide range of avian and mammalian hosts, unlike other influenza viruses. Additionally, the influenza a virus's envelope had two surface glycoproteins, the " hemagglutinin (HA) and neuraminidase (NA) ". And influenza viruses are categorized into antigenic 18 HA and 12 NA subtypes [11]. Furthermore, the primary defense against influenza a pandemic, is the vaccinations. Either inactivated or live-attenuated virus [12]. Additionally, traditional influenza medications are targeted the M2 ion channel, which considered

amantadine target. In addition to neuraminidase, which is the target of zanamivir and oseltamivir. On the other hand, resistance to those drugs is spread widely. And new antivirals are still needed to treat influenza, epidemics and pandemics [13]. On the other hand, previous studies combined with extensive molecular and virology research needed to provide chances to invent several new therapeutic agents [14].

On the other hand, there are natural products provide rich resource of new antiviral drugs, curcumin is one of these products which have potency to inhibit the influenza receptor, hemagglutinin (HA) and neuraminidase. In addition, several studies are showed curcumin as a direct effective on virus that inhibited haemagglutinin. And this effect observed in " H1N1 as well as H6N1 " subtypes, and viruses did not develop resistance to curcumin effect [15.].

On the other hand, the current study was adapted the combinatorial chemistry to examine the effect of curcumine on influenza viruses instead of conventional method. The combinatorial chemistry is a technique by which large number of different but structurally similar molecules are produced rapidly with low risk of failure done by computer software, then these products submitted for pharmacological assay [16].

Additionally, the results were showed that best curcumin compounds bind and cover the active sites of most strain of hemagglutinin (HA) and neuraminidase (NA), the best binding and covering occurs by Perfluoro Curcumin, N-(4-Fluorophenylpyrazole) Curcumin, Curcumin glucuronide, Curcumin-difluorinated (CDF). So that, these compounds are observed to have the most acceptable values of Lipinski rule of five properties, and deviation is slight.

Additionally, perfluoro Curcumin exhibits the strongest affinity to 13 out of 15 tested strain of hemagglutinin including " H1, H2, H3, H4, H5, H6, H7, H10, H13, H14, H15, H16 and H17 " and to 8 out of 11 tested strain of neuraminidase including (N1, N3, N4, N5, N6, N7, N8 and N11). The structure of Perfluoro curcumin is wealthy with flourien functional groups that enhanced the binding of curcumin with the active site of neuroamindase molecules.

In addition, N-(4-Fluorophenylpyrazole) Curcumin have strong affinity to 9 out of 15 tested strain of hemagglutinin, their structure also contain flourien functional group in addition to amine group. Both of Curcumin glucuronide and Curcumin-difluorinated (CDF) have potent binding to 7 out of 11 strain of neuraminidase.

Perfluoro curcumin and Curcumin glucuronide were have large mass more than the normal values of Lipinski rules, also logP for Perfluoro curcumin and Curcumin-difluorinated (CDF) more than the normal values of Lipinski rules, In future may be modify the structure of them to use these compounds in treat influenza.

On the other hand, the information about toxicity are limited for these experiment compounds (Perfluoro curcumin, N-(4-Fluoropheny-lpyrazole) Curcumin, Curcumin glucuronide, Curcumin-difluorinated (CDF) and Curcumin glucuronide) and internet sources are limited about the previously used of these compounds in the treatment of influenza.

This study led to conclude that the chosen curcumin compound (Perfluoro curcumin, N-(4-Fluoropheny-lpyrazole) Curcumin, Curcumin glucuronide, Curcumin-difluorinated (CDF) and Curcumin glucuronide) may have the best studied properties and suggest them to future studies in combination to traditional antiviral agent , both in-vivo and in-vitro.

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