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Letter to Editor

Can Curcumin be Used as an Anti-HIV Therapeutic Option?

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Dear Editor;

Curcumin is an herbal polyphenol compound which can be extracted from Curcuma longa L. plant in Asian countries. According to the literatures it has several medical advantages including anti-oxidant, anti-inflammatory and anti-coagulant properties and insulin like and lipid hemostasis [1-2].

Based on the previous researches, Curcumin has been shown to have efficient effects during clinical trials or in vitro experimental studies against cancer, arthritis, cardiovascular, nervous syndromes, bowel disease, diabetes, kidney maladies, and infectious disease particularly Human immunodefciency virus (HIV), cyto-megalovirus (CMV), hepatitis C virus (HCV), Helicobacter pylori, Salmonella Typhimurium, Vibrio vulnificus, Neisseria gonorrhea and, Trypanosoma cruzi without toxicity effects. Therefore, Curcumin has FDA (Food and Drug Administration) approval; because of its safety on human cell lines and efficacy in several disorders [2-4].

HIV is considered as one of the major global health concerns; According to WHO reports in 2017, it is estimated 1,800,000 HIV infected cases throughout the worldwide. [5]. Highly Active Antiretroviral Therapy (HAART) is only available strategy for control of AIDS which include six different classes of Nucleoside reverse transcriptase (NRTIs), Non-nucleoside reverse transcriptase (NNRTIs), Integrase inhibitor, Protease inhibitors (PIs), CCR5 inhibitor and viral fusion inhibitor which is recommended as one of the NNRTIs plus two NRTIs worldwide. Although, HAART has reduced global burden of AIDS, but it has several limitations for example toxic effects, low-bioavailability of NRTIs, restriction of NRTIs in tuberculosis infected individuals or drug resistant strains [6].

In conclusion, it is necessary to introduce novel therapeutic option against HIV in combination with classically HAARTs to gain more successive treatment in HIV/AIDS patients [4,7]. In this study, we reviewed recent papers reporting sufficient outcomes of Curcumin as novel anti-HIV-1 drug candidates; In addition, there are in sillico evidence for appropriate binding affinity of Curcumin to active sites of HIV-drug targets such as Protease, Integrase, Reverse-transcriptase, gp41 and CCR5 surface molecule using Molegro virtual Docker (MVD) via Evolutionary algorithms (EA) for the first time in present study.

The HIV-1 Protease (PR) is responsible for processing the viral poly-protein and its function is necessary for production of new viral particles [1]. Several studies have shown that Curcumin can inhibit HIV-1/HIV-2 Protease activities; Sui et al., found that Curcumin inhibits HIV-1 PR and HIV-2 PR with IC50 of 100µM and 250µM respectively [7]. Vajragupta et al. has been conducted docking analysis about binding efficacy of Curcumin into Protease; in this study it was shown that Curcumin is capable of binding to HIV PR and interacts with various residue

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consisting residues Asp25, Asp29, Asp30, Gly27', Asp29', and Asp30' [1]. In our study, it was observed that Curcumin can bind to active site of HIV-1 PR with suitable binding energy; also it can block S3/S3´ drug pocket. Its structure is well fitted in active site and interacted with two catalytic residues including Asp25 and Asp29 (Table 1).

The HIV-1 Integrase is coded by pol which is responsible for insertion of HIV genome into the host DNA [1]. Curcumin can also have considerable effect as anti-integrase inhibitors according to molecular docking and in vitro studies [1,8]. Curcumin can interact with active site of integrase throughout its two phenyl ring; experimental studies suggested that Curcumin inhibits HIV-1 Integrase with IC 40µM concentration; Furthermore, Curcumin analogues has great efficacy in prohibition integrase activity with IC50 lower than 10µM [1,3]. Vajragupta et al., have found that Curcumin can interact with Asp64, Asp116 and close to Mg2+ cofactor [1]. It has been shown that Curcumin can bind to active site of HIV-1 Integrase (Table 1).

The HIV-1 Reverse transcriptase (RT) plays an important role in HIV pathogenesis via conversion of viral RNA to double strand DNA. There are two classes of NRTIs and NNRTIs in HAART strategy for blocking

Table 1. Docking results of Curcumin and HIV molecular targets with root-mean-square deviation tolerance (RMSD) of ≤2.0 Å

Receptor/PDB accession number	Moldeock energy	H-bound score	Interaction with residues	Cartesian chart
Protease (2BPX)	-130.31	-6.51	Gly48 Ile 47 Arg8 Asp25 Ala28 Asp29	13.06 23.54 5.76
Integrase (3WNE)	-138.18	-3.71	Gln95 Glu96 Ala98 Tyr99 Leu102 Ala129 Trp132 Tyr174 Lys173	-8.94 4.66 15.82
Reverse-transcriptase (3V4I)	-135.05	-6.97	Lys219 Lys65 Arg72 Asp113 Phe116 Ala114 Lys219 Tyr115	-9.67 25.71 33.50
CCR5 chemokine receptor (2OT5)	-146.26	-6.07	Phe79 Asp76 Cys290 Asn293 His289 Leu72 Phe112 Ile116 Trp248 Tyr244	185.89 111.41 22.77
gp41 surface molecule (3GWO)	-109.49	-3.48	Asn42 Trp43 Phe44 Ser39 Leu40	8.14 -3.91 6.75

HIV-1 RT activities [6]. But available HIV-1 RT inhibitors have several restrictions such as high cost, toxicity, low bio-availability and interaction with other drugs particularly Rifampin in TB patients [6,9]. According to our docking analysis, Curcumin has the ability to bind to polymerase domain of HIV-1 RT; It has appropriate binding energy and H-bound capacity for interaction with polymerase residues of HIV-1 RT (Table 1). There are no experimental results for Curcumin inhibitory effects on HIV-RT.

The gp41 is an important surface glycoprotein of HIV which is necessary for fusion of viral particles to CD4+ T cells membrane.

Therefore, it is considered as new selective target for HIV drug development [10]. This study was the first document of molecular docking analysis of Curcumin against gp41 of HIV. According to our report, Curcumin has potential capacity to inhibit gp41 envelope protein during molecular Docking analysis (Figure 1). Given that docking our results, Curcumin can interact with aromatic groups of Trp43 and Phe44 of gp41 which is located in active sites via its two phenyl rings (Table 1).

The CCR5 (C-C chemokine receptor type 5) surface molecule on the surface of white blood cells specially CD4+ T cells which plays a key role in entry of HIV particle into the host cells. Consequently, CCR5/CXCR4 is considered as a reliable target for treatment of HIV [10]. Nowadays, there is one FDA approved anti-HIV drug (Maraviroc) for treatment of HIV/AIDS [6]. Talwar et al., have shown inhibitory effects of Curcumin in entry of HIV-1 into HeLa-based P4-CCR5 cells [11].

According to our analysis, Curcumin has potential ability to interact with active site of CCR5 (Figure 1). Curcumin has hydrophobic nature; thus, it can interact with several residues of active site of CCR5 molecule (Table 1).

However, Curcumin has anti-inflammatory effects including reduction of induce nitric oxide (iNOS), alternation in AMPK and mTOR signaling pathway, dysregulation of NF_kB, TNF-α, IL-1, IL-6, COX-2 and JAK-STAT3 transcription factors; In addition, it has been shown that Curcumin can reduce the expression of HIV proteins including Tat and gp120 [3,12-14]. It suggested that clinical trials of Curcumin have successful results in HIV infected patients [1,3-4].

Although, Curcumin has major restriction such as low water solubility and low-bioavailability capacity; however, the novel Curcumin analogues such as alkali analogues has better pharmaceutical features and anti-HIV activity [14].

In summary, Curcumin has the capacity as a novel candidate as anti-HIV compound.

According to clinical trials, experimental and molecular docking evaluation its remarkable novel anti-HIV compound; Consequently, It is suggested that Curcumin plus conventional HAART drugs has novel appropriate candidates for treatment of HIV/AIDS.

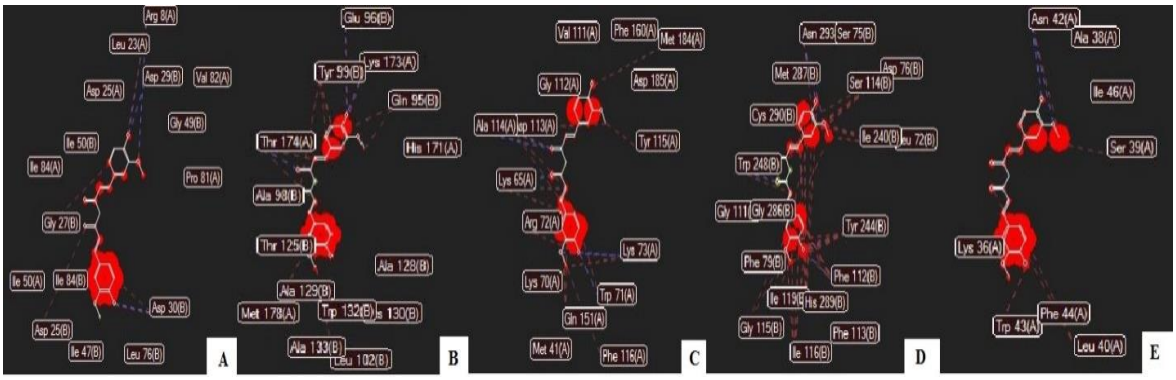

Fig. 1. Interaction of Curcumin with active sites of HIV-1 Protease, Integrase, Reverse transcriptase, gp41 and CCR5 surface molecule from A to E respectively.

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