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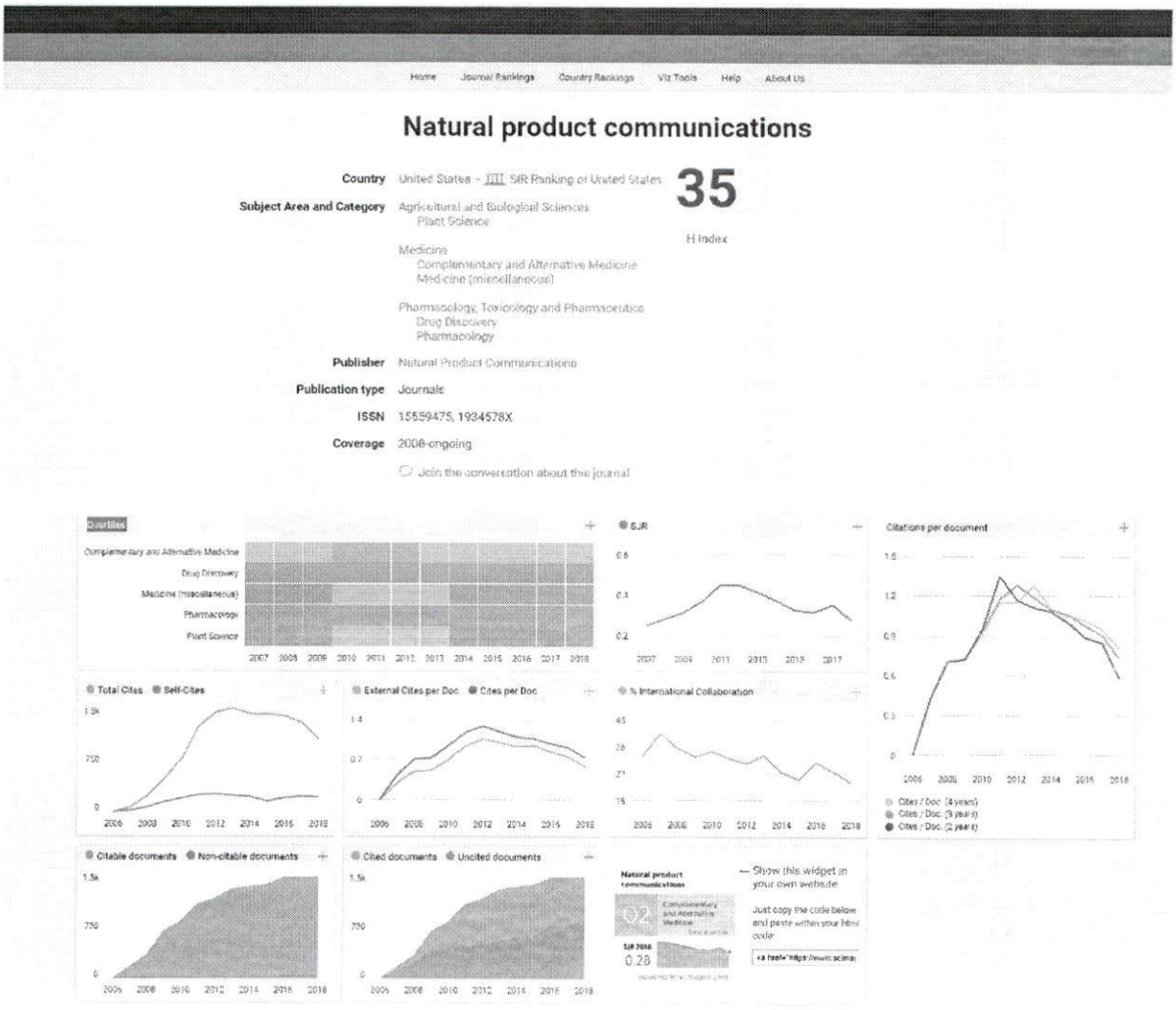
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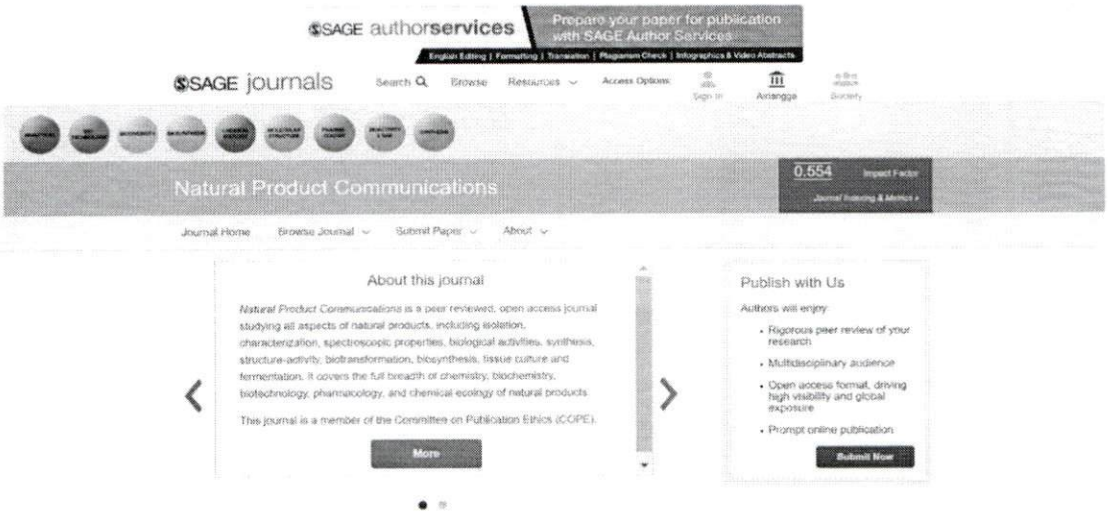
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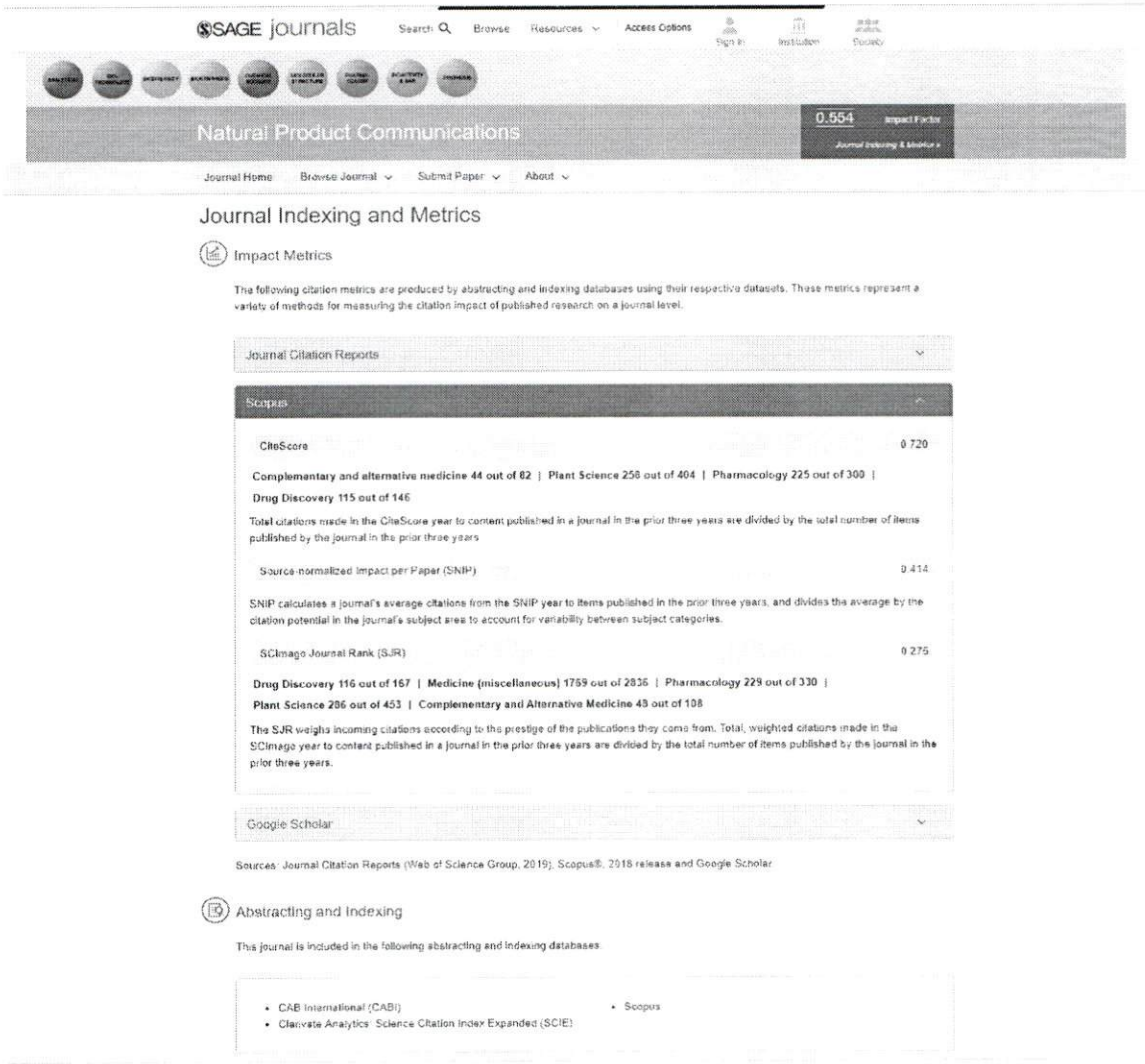
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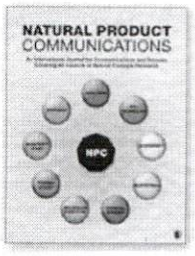


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# Antiviral Activities of *Curcuma* Genus against Hepatitis C Virus

**Tutik Sri Wahyuni[a,b*], Adita Ayu permatasari[b], Tri Widiandani[c], Achmad Fuad[a,b], Aty Widyawaruyanti[a,b], Chie Aoki-Utsubo[d] and Hak Hotta[e]**

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Hepatitis C virus (HCV) infection is one of the major public health problems in the world. Even though the new agents are shown to increase the sustained virology response, however, there are still many people who cannot access the therapy due to the high cost. Moreover, the emergence of resistance and side effects presented the necessity to develop alternative treatment agents for HCV infection. Plants of the genus of curcuma are popular among traditional medicines in the world, including Indonesia. They have been used for many herb remedies and reported to possess many biological activities. Several plants from the curcuma genus were known as treatment agents in liver disease and jaundice. Our current study determines antiviral activities of *Curcuma domestica*, *Curcuma xanthorrhiza*, and *Curcuma heyneana* against HCV and further examines the mechanism of actions. Antiviral activity was performed by *in vitro* culture cells using Huh 7.5it cells and treated with the mixture of extract and virus JFH1. The effects of extracts in HCV life cycle were determined by mode of action analysis to examine the action of substances in the entry or post entry steps. The results revealed that ethanol extract of *C. domestica*, *C. xanthorrhiza*, and *C. heyneana* showed strong anti-HCV activities with $IC_{50}$ values of 1.68 ± 0.05, 4.93 ± 0.42 and 5.49 ± 0.59 μg/mL, respectively without any cytotoxicity effect. Mode of action analysis demonstrated that of *C. domestica* and *C. heyneana* exhibit HCV in the entry step, while *C. xanthorrhiza* inhibit in the entry and post entry steps of HCV life cycle. Docking analysis to predict the interaction of curcumin, the main compound of curcuma genus, revealed a strong interaction between curcumin and 4GAG receptor, a protein involved in the entry step of HCV infection. Moreover, it was also reported to possess good interaction with 4EAW, an HCV NS5B, which plays an important role in HCV replication. These results suggested that *C. domestica, C. xanthorrhiza*, and *C. Heyneana* possessed strong inhibition against hepatitis C virus, therefore they may be good candidates for anti-HCV agents.

**Keywords:** Hepatitis C virus, *Curcuma domestica*, *Curcuma xanthorrhiza*, *Curcuma heyneana*, Curcumin, Docking analysis.

Hepatitis C virus (HCV) infection is still a big issue in the world. It is estimated that 71 million people suffer chronic HCV and approximately 400.000 people die each year due to cirrhosis and hepatocellular carcinoma [1]. Direct acting antivirals (DAAs) are currently used to cure HCV infection. Oral interferon (IFN) free regimen by combination of NS3/NS4A or NS5A inhibitor increased the sustained virology response (SVR). However, the emergence of antiviral drug resistance and the limited patients who can access drugs due to the high cost remain the necessities to find new effective anti-viral agents [2, 3].

Medicinal plants are potential resources to search for new drug candidates. They consist of various chemical substances possessing strong biological activities including anti-HCV activities. Secondary metabolites of plants, such as silymarin, epigallocatechin gallate, naringenin that belong to the flavonoid compounds, have been reported to inhibit HCV [4-6]. Our previous study reported anti-HCV activity of Indonesian medicinal plants and obtained active anti-HCV extract of *Toona sureni*, *Melicope latifolia*, *Melanolepis mutiglandulosa* and *Ficus fistulosa* with $IC_{50}$ value 3.5-15.0 μg/mL [7]. In another study we evaluated *Ruta angustifolia* leaves and further isolated anti-HCV compounds, chalepin, a coumarin compound and pseudane IX, an alkaloid compound which mediated a strong anti-HCV activity [8]. Exploration of natural sources to search for anti-HCV activity still remained a big chance.

*Curcuma domestica, Curcuma xanthorrhiza* and *Curcuma heyneana* belong to the *Zingiberaceae* family. Plants of the genus of curcuma are popular in many areas in the world for several kinds of diseases including their use in traditional herbs [9]. In Indonesia, it has been used for many ingredients of *Jamu*, the traditional medicine of Indonesia [10]. *C. domestica* or *C. longa*, also called turmeric have been used for infection, dermatologic diseases and depression in India and China. Recently, it also shows anti-oxidant, anti-inflammatory, anti-cancer and antibacterial activities [11-13]. *C. xanthorrhiza* is locally known as temulawak in Indonesia. The isolated compound from the fresh rhizome, xanthorrizol, possesses antimicrobial activities against pathogenic bacteria and fungi [14-16]. It has been reported to have hepatoprotective activities, reduced the fatty liver symptom and inhibit alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and protein content [10, 15]. *C. heyneana* contain oxycurcumenol epoxide, curcumenol and isocurcumenol that have cytotoxicity activity against T-acute lymphoblastic leukemia cells (CEM-SS) with $IC_{50}$ values of 11.9, 12.6 and 13.3 μg $mL^{-1}$, respectively [17]. Furthermore, its isolation compounds, heyneanone A, heyneanone C, 4,10-epizedoarondiol, procurcumenol, aerugidiol, zerumin A, and (E)-15,16-bisnorlabda-8,11-dien-13-one inhibited protein tyrosine phosphatase 1B (PTP1B) with $IC_{50}$ values of 42.5, 35.2, 35.1, 45.6, 35.7, 10.4, and 14.7 μM, respectively [18]. Since it has been reported to have many bioactivities, however, there is no report yet for anti-HCV activity.

This study examined anti-viral activities of *C. domestica, C. xanthorrhiza,* and *C. heyneana* against HCV. Anti-hepatitis C activity was performed by *in vitro* culture cells using Huh 7it and further determine the mode of action of extracts. The cytotoxic effect was accessed by MTT assay.

The results showed that *C. domestica, C. xanthorrhiza,* and *C heyneana* possess potential inhibition against hepatitis C virus without any cytotoxicity (Figure 1). *C. domestica* revealed the strongest anti-HCV activity among the tested extracts and showed a stronger activity than the positive control ribavirin (Table 1).

**Table 1:** Antiviral activity ($IC_{50}$) against HCV and cytotoxicity ($CC_{50}$) of *C. domestica, C. xanthorrhiza,* and *C heyneana.*

| Extract | $IC_{50}$ (µg/mL) | $CC_{50}$ (µg/mL) | SI |
|---|---|---|---|
| *C. domestica* | 1.68 ± 0.05 | >100 | >59.5 |
| *C. xanthorrhiza* | 4.93 ± 0.42 | >100 | >20.3 |
| *C. heyneana* | 5.49 ± 0.59 | >100 | >18.2 |
| Ribavirin (positive control) | 2.79 ± 0.3 | >50 | >10 |

The data represent means ± SEM of data from three independent experiments.

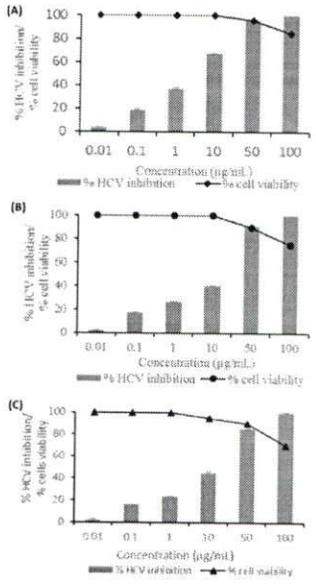



**Figure 1:** Dose dependent inhibition of extracts and their cytotoxicity. Various concentrations of extracts (A) *Curcuma domestica*, (B) *Curcuma xanthorrhiza*, (C) *Curcuma heyneana*, 100 to 0.01 µg/mL were inoculated to the Huh7it cells (MOI=0.1). After virus adsorption, the cells were cultured with the same concentrations of compounds for 46 hours. The culture supernatants were harvested and titrated for virus infectivity. Percent inhibitions of HCV infectivity by each compound are shown in Figure 1. In parallel, cytotoxicity of the compounds was measured by MTT-1 assay. All three extracts did not show any cytotoxicity effect.

Mode of action analysis was accessed to explore the effect of extracts in the entry or post entry steps of HCV life cycle which divided into: entry steps that include viral attachment and viral entry to the target cells, and post entry steps that include synthesis protein, replication of viral genome, assembly and release of viral particles [19, 20].

*C. domestica* and *C. heyneana* proved to possess stronger inhibition in the entry step with HCV inhibition higher than 70%, while in the post entry step was around 30% in the concentration of 50 µg/mL. On the other hand, *C. xanthorrhiza* showed a weaker effect in the entry step with 60% inhibition; however, in the post entry step mediated higher inhibition with percentage of HCV inhibition 53.6 ± 3.9% compared to *C. domestica* and *C heyneana.* Therefore *C. xanthorrhiza* might be conducted to act in the entry and post entry (Table 2).

**Table 2:** Mode of action of *C. domestica, C. xanthorrhiza,* and *C heyneana* extracts.

| Plant Extract | % HCV inhibition (50µg/mL) | | | Mode of action |
|---|---|---|---|---|
| | During +Post infection | During infection | Post infection | |
| *C. domestica* | 96.2 ±1.2 | 75.2 ± 2.1 | 34.9 ± 2.0 | Enty inhibition |
| *C. xanthorrhiza* | 90.8 ±0.8 | 60.8 ± 0.8 | 53.6 ± 3.9 | Enty, Post-entry inhibition |
| *C. heyneana* | 84.8 ±1.4 | 70.2 ± 1.5 | 30.5 ±1.4 | Enty inhibition |

Curcumin, a popular compound in the genus of curcuma, has been identified to have many therapeutic effects including antiviral against HIV, influenza, HPV, H5N1 and all HCV genotypes [10, 21-23]. Curcumin acts as anti-HCV activities by suppressing viral entry step [23] and replication [24].

Further examining to predict the mechanism-of-action of curcumin to the receptors, docking analysis was performed by Molegro Virtual Docking ver 5.5 program to determine the possible interaction of compounds with the protein target. We evaluated several proteins from Protein Data Base which reported to possess interaction with HCV (www.rcsb.org). We found that curcumin has a strong interaction with 4GAG, the protein involved in the entry step of HCV, neutralizing antibody AP33 in complex with E2 epitope [25, 26]. The rerank score of curcumin was -116.94 kcal/mol while the rerank score of ligand was -45 kcal/mol. The lower value of rerank indicated the stronger interaction of curcumin to the receptor. Hydrogen binding of curcumin with Thr 165 and Asp 167, and the steric van der walls between curcumin with Thr 165, Asp 167, His 164 and Val 163 contributed the binding interaction of 4GAG and curcumin (Figure 2). While, the standard ligand revealed hydrogen binding to His 164 and Asp 167, and steric van der walls to Asp 167. The interaction was clearly described in 3D profile (Figure 3).

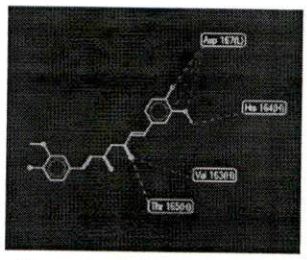



**Figure 2:** Hydrogen bond interaction (dashed blue-line) and Steric-Van der Walls bond interaction (dashed red-line) between Standard Ligand and Curcumin on the active site of HCV protein (4GAG.pdb).

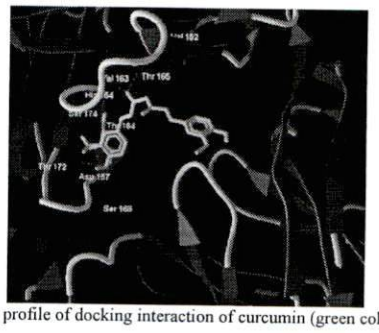
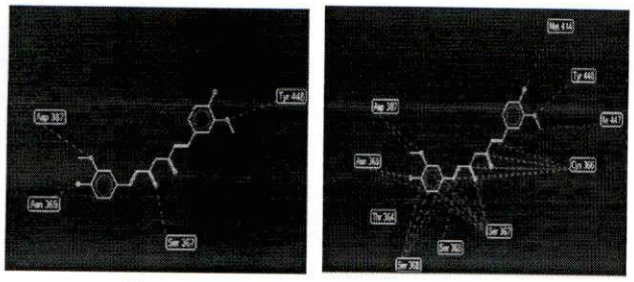



**Figure 3:** The 3D profile of docking interaction of curcumin (green color) with 4GAG protein.

Further analysis was done to observe the possible interaction with other proteins. We obtained a strong interaction between 4EAW.pdb and curcumin. 4EWA is a protein of HCV NS5B, considered to be involved in the replication step of HCV life cycle, a potential therapeutic target in HCV treatment. The rerank score of curcumin was -102.169 kcal/mol, which is similar to the rerank



(A) (B)

**Figure 4:** Hydrogen bond interaction (dashed blue-line) and Steric-Van der Walls bond interaction (dashed red-line) between (A) Standard Ligand and (B) Curcumin on the active site of HCV protein (4EAW.pdb).

score of standard ligand -103.24 kkal/mol. This result indicated a strong interaction between curcumin and receptor and resulting good therapeutic activity. Curcumin revealed more interaction with amino acid of Tyr 448, Ser 367, Asp387, and Asn 369 with hydrogen binding interaction than the standard ligand which only binds with three amino acids, Tyr 448, Asp 318, and Asn 291 (Figure 4). These results indicated that curcumin has strong interaction with 4EAW that might serve as a potential target for HCV inhibition. The 3D profile of curcumin docking interaction is shown in Figure 5.

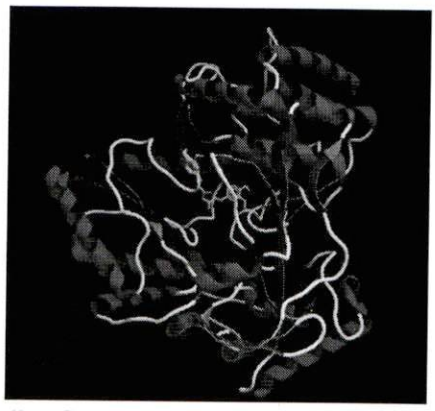


**Figure 5:** The 3D profile of docking interaction of curcumin (green color) with 4EWA protein.

## Experimental

***Extraction and sample preparation:*** The rhizomes of *Curcuma domestica, Curcuma xanthorrhiza,* and *Curcuma heyneana* were verified by a licensed botanist of Botanical garden, Purwodadi, Indonesia. The dried powder of the rhizome was extracted with ethanol. The obtained filtrates were evaporated to yield the ethanol extracts *C. domestica, C. xanthorrhiza,* and *C heyneana*. Stock solution was prepared by dissolving the extract in dimethyl sulfoxide (DMSO) to obtain a stock concentration of 100 mg/mL. Serial dilutions of extracts were prepared to yield the concentrations of extracts 100, 50, 10, 1, 0.1 and 0.01 µg/mL.

***Cells and viruses:*** Huh7it cells were cultivated in Dulbeco's Modified Eagle Medium (GIBCO Invitrogen, Carlsbad, CS, USA) supplemented with 10% Fetal Bovine Serum (Biowest, Nualle, France), 0.15 mg/mL Kanamycin (Sigma–Aldrich, St. Louis, MO, USA) and non-essential amino acids (GIBCO-Invitrogen) in 5% CO2 at 37$^0$C. The culture cells were cultivated and maintained by periodically re-feeding with new medium. The adapted HCV variant was propagated in Huh7it [27]. Culture supernatant from the infected cells was collected at day 2 and day 5 post infection and concentrated using Amicon Ultra centrifugal filter unit. Virus titers were determined for antiviral assay [28, 29].

***Antiviral activity assay:*** Antiviral activity assay was conducted as described previously [7, 8, 28, 29]. Huh7it cells (5.4 x $10^4$) were seeded for 24 hours. The HCV at multiplication of infection (MOI) of 0.1 in the presence of different concentrations of sample were inoculated to the culture cells. The mixture of extract and virus was incubated for 2 hours. After virus absorption for 2 h, the cells were rinsed with the medium and were further incubated in the medium containing the same sample for 46 hours. Mode of action analysis was performed by time-of-addition experiments. Three series of studies were done. First, the culture was treated with the extract both in pre- and post- inoculation. Second, the culture was only treated with the extract at inoculation steps (2 hours). The third extract was added only after inoculation to examine the action of substance in the post-entry steps of HCV life cycle. Culture supernatants were collected for virus titration. The 50% inhibitory effect ($IC_{50}$) was calculated by SPSS probit analysis [7, 8].

***Virus titration and immunostaining:*** Huh7it-1 cells (2 x $10^4$ cells/well) were seeded in a 96-well plate and incubated for 24 hours. Virus supernatants were diluted in the medium and inoculated onto the Huh7it culture cells and incubated for 4 hours. After virus absorption, the cells were cultured with medium containing 0.4% methylcellulose (Sigma–Aldrich) following 41 hours incubation. Infected cells were analyzed with immunostaining using anti-HCV patient anti-serum (250 time dilution on 2% BlockAce/1%BSA/PBS) and HRP-goat antihuman Ig antibody (300x on 2% lockAce/1%BSA/PBS). The HCV antigen positive cells were visualized with Metal Enhanced DAB substrate kits (Thermo Fisher Scientific, Rockford, USA). The infected cells were counted under microscopes and calculated the percentage inhibition.

***MTT assay:*** The cytotoxicity analysis was conducted to determine whether the extract mediated any cytotoxicity effects. MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) assay was done by inoculating 100, 50, 10, 1 and 0.1 µg/mL of extract in 96 wells plate culture cells which have seeded for 24 hours. After 48 h incubation, the medium was replaced with MTT reagent containing medium and incubated for 4 h. Absorbance sample was evaluated under microplate reader at 450 and 600 nm, which is correlated with the amount of cell viability. The percentage of cell toxicity was calculated by comparing with untreated cells and further determine its 50% cytotoxic concentration ($CC_{50}$) values [7, 8, 27].

***Docking analysis:*** The ligand was prepared by making 2D and 3D structures of the curcumin using ChemBioOffice program Ultra 11.0 and its energy was minimized using MMF94. The docking analysis continued by Molegro Virtual Docking ver 5.5 program Ver 5.5, resulted in rerank score describing the minimal energy by the ligand in interaction with the receptor.

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