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Natural and virtually designed flavonoids: Potential anti-HCV targets *in silico* approach

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ABSTRACT

The present work is a computational approach which predicts potential anti hepatitis C activity of flavonoids by inhibiting NS5B polymerase of HCV virus in silico. PDB ID 3D5M was selected for docking of flavonoids against HCV NS5B polymerase as target in silico analysis. Currently there are very few antiviral therapies available for hepatitis C. Thus there is a scope to develop new drugs for treating hepatitis C. Molecular modeling approach was used to determine the potency of some naturally occurring and virtually designed flavonoid moieties against hepatitis C. Using glide software and ribavirin as a standard drug, excellent docking scores were achieved suggesting drug like characteristics of flavonoids against hepatitis C virus NS5B polymerase.

Keywords: Flavonoids, Hepatitis C virus, NS5B Polymerase, Glide, Docking, 3D5M.

INTRODUCTION

The word "hepatitis" means inflammation of the liver caused by enveloped, positive-sense single-stranded RNA virus of the family *flaviviridae*. [1] The condition can be self-limiting or can progress to fibrosis (scarring), cirrhosis or liver cancer. Hepatitis viruses are the most common cause of hepatitis in the world but other infections, toxic substances (e.g. alcohol, certain drugs), and autoimmune diseases can also cause hepatitis. [2] There are 5 main hepatitis viruses, referred to as types A, B, C, D and E. It is of greatest concern because of the burden of illness and death they cause and the potential for outbreaks and epidemic spread. [3] In particular, types B and C lead to chronic disease in hundreds of millions of people and, together, are the most common cause of liver cirrhosis and cancer. [4]

Hepatitis C virus (HCV) infects an estimated 200 million individuals worldwide. Approximately 80% of acutely infected HCV patients progress to chronic infection, 20% of whom develop cirrhosis within 25 years, with 25% of patients with cirrhosis developing hepatocellular carcinoma and/or decompensated liver disease. [5] Hepatitis C virus has three structural proteins and seven nonstructural proteins. The structural proteins are HCV core protein, E1 and E2 envelope glycoproteins and frameshift Protein. The nonstructural proteins are P7, NS2, NS3-NS4A-protease, NS3 helicase-NTpase, NS4B, NS5A and NS5B RdRp. [6] HCV replication is thought to be semi-conservative and asymmetric with two steps, both of which are catalyzed by the NS5B RdRp. The positive-strand genome RNA serves as a template for the synthesis of a negative-strand intermediate of replication during the first step. In the second step, negative-strand RNA serves as a template to produce numerous strands of positive polarity that will subsequently be used for polyprotein translation, synthesis of new intermediates of replication or packaging into new virus particles. [7-9] Thus NS5B RdRp plays a central role in replication of hepatitis C virus. Currently there

are very few drugs available on hepatitis C, which drives the medicinal chemist to arrive at potent antihepatitic agent. [10]

Flavonoids are widely spread in nature and possess diversified biological activities like anticancer [11], antifungal [12], antioxidant [13], antiallergic [14], anticoagulative [15] and vasorelaxant [16] activities. They are abundantly available in nature particularly in fruits, vegetables, nuts, seeds, flowers and are regular part of our diet. [17]

Herein we report the in *silico* interaction of various flavonoid derivatives against hepatitis C virus NS5B RdRp (PDB ID-3D5M) [18]

EXPERIMENTAL SECTION

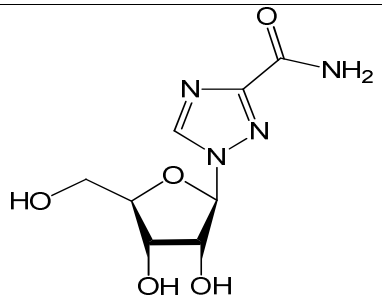
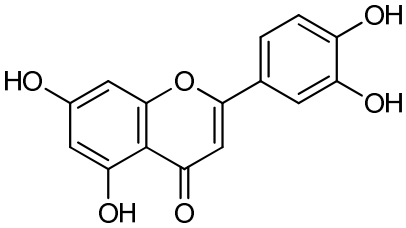
All the molecular modeling studies described herein were performed on Lenovo UltraBook Laptop (Intel® Core™ i5 CPU @ 1.70 GHz, RAM 4 GB) running Windows 7 Home Basic Operating System. Schrödinger Small-Molecule Drug Discovery Suite Release 2013-1 Glide version 5.7, as implemented in Schrödinger suite 2013-1, was used for performing molecular docking studies of the standard inhibitor drugs (NS5B RdRp) along with the flavonoid derivatives. For HCV NS5B-RdRp crystal structure, search in the Protein Data Bank (www.rcsb.org) yielded several structures. High-resolution (2.20 Å) structure of NS5B (PDB ID 3D5M) was used for docking studies. In addition, ribavirin (RBV), an anti HCV drug was also docked in the active site of polymerase. Since the crystal structure ligand was present, it was used for placing the enclosing box during receptor grid generation. For docking studies *Extra Precision* (XP) mode was used.

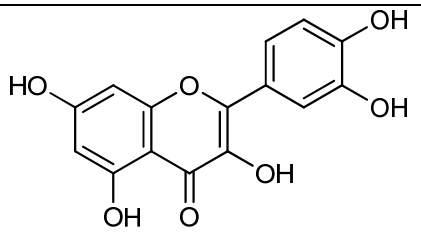
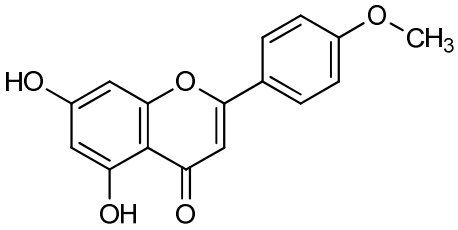
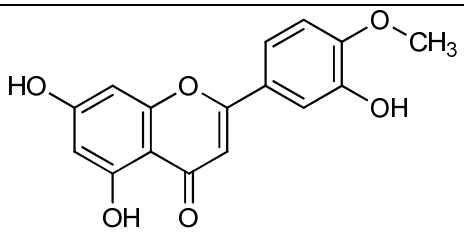
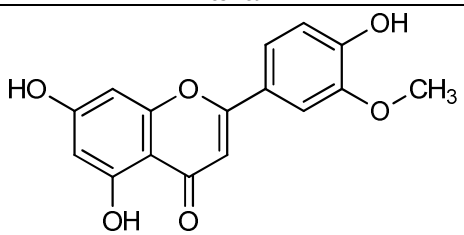
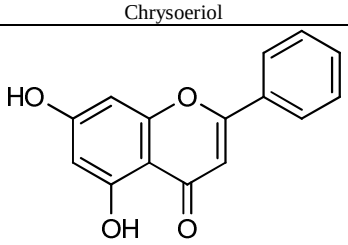
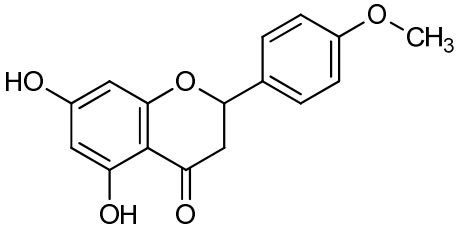
RESULTS AND DISCUSSION

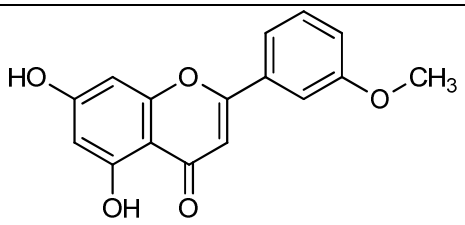
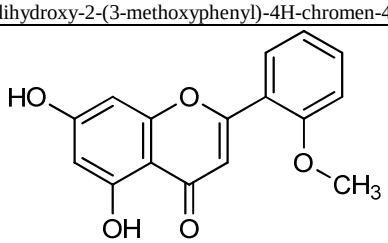
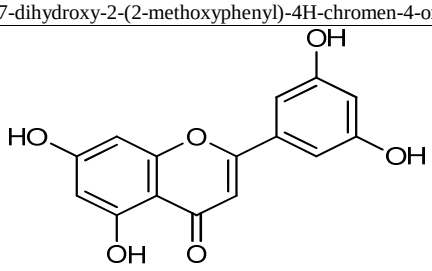
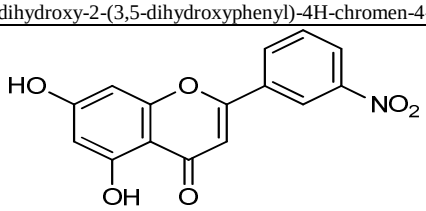
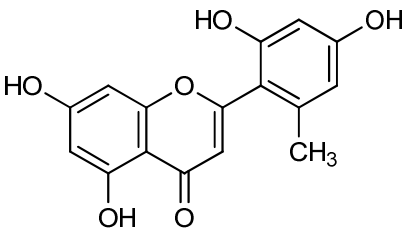
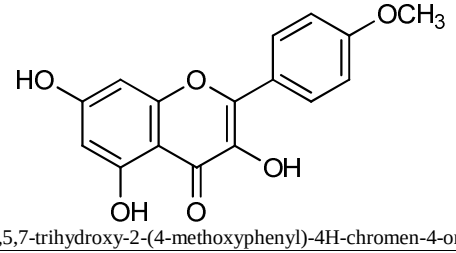
Various flavonoids were docked against hepatitis C virus NS5B polymerase on PDB ID-3D5M. (Table 1) Ribavirin (RBV) was used as a standard drug to compare the docking results. Ribavirin shows -6.8 docking score against HCV NS5B polymerase (PDB ID-3D5M). Docked flavonoids show higher dock score than ribavirin whereas majority of the flavonoids show comparable docking scores with ribavirin.

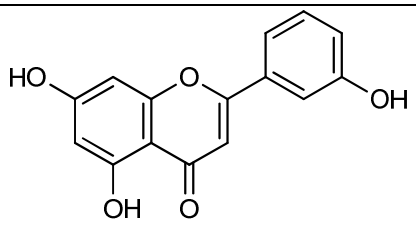
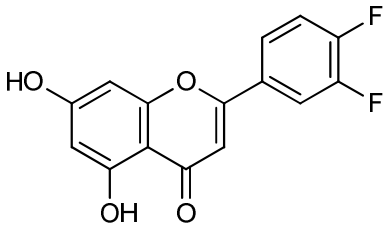
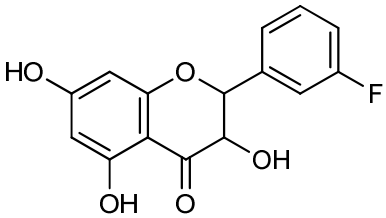
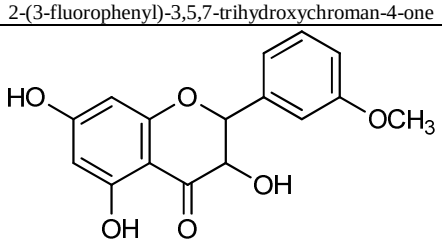
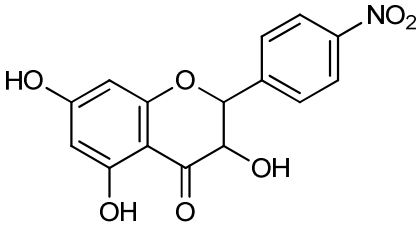
Quercetin shows highest docking score hence exhibiting potential anti HCV characteristics in *silico*.

Table 1. Results showing the docking score of all ligands and standard drug with the receptor.

Entry	Name and structure of molecule	Docking score* (Glide Score)
1	 Ribavirin	-6.8
2[a]	 Luteolin	-7.58

3[a]	 Quercetin	-7.70
4[a]	 Acacetin	-6.00
5[a]	 Diosmetin	-6.10
6[a]	 Chrysoeriol	-6.48
7[a]	 Chrysin	-6.47
8[a]	 5,7-dihydroxy-2-(4-methoxyphenyl) chroman-4-one	-6.12

9[a]	 5,7-dihydroxy-2-(3-methoxyphenyl)-4H-chromen-4-one	-5.86
10[a]	 5,7-dihydroxy-2-(2-methoxyphenyl)-4H-chromen-4-one	-5.45
11[a]	 5,7-dihydroxy-2-(3,5-dihydroxyphenyl)-4H-chromen-4-one	-6.12
12[b]	 5,7-dihydroxy-2-(3-nitrophenyl)-4H-chromen-4-one	-5.23
13[b]	 2-(2,4-dihydroxy-6-methylphenyl)-5,7-dihydroxy-4H-chromen-4-one	-6.35
14[a]	 3,5,7-trihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one	-5.60

15[a]	 5,7-dihydroxy-2-(3-hydroxyphenyl)-4H-chromen-4-one	-5.87
16[b]	 2-(3,4-difluorophenyl)-5,7-dihydroxy-4H-chromen-4-one	-7.60
17[b]	 2-(3-fluorophenyl)-3,5,7-trihydroxychroman-4-one	-6.49
18[b]	 3,5,7-trihydroxy-2-(3-methoxyphenyl)chroman-4-one	-7.30
19[b]	 3,5,7-trihydroxy-2-(4-nitrophenyl)chroman-4-one	-7.00

****** *All the flavonoids were docked on PDB ID-3D5M*
[a] *Naturally occurring flavonoids*
[b] *Virtually designed flavonoids*

Flavonoids show docking score greater than ribavirin. (Table1. Entry 2, 3, 16, 18, 19) Therefore this result (Table 1) reveals that, there are good binding interactions between flavonoids and anti HCV protein. Due to these binding interactions, it may hinder the working functions of the NS5B RdRp. Some flavonoids having comparable docking score with standard (Table 1. Entry 6, 7, 11, 13, 17) have the potential to be drug candidate after some refinement.

CONCLUSION

Naturally occurring and virtually designed flavonoid derivatives have excellent docking scores compared with ribavirin. Thus, we can conclude that, various natural and virtually designed flavonoids exhibit potential anti hepatitis characteristics in *silico*.

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