Inhibition of KRAS Gene Using Different Biochemical Active Compounds

Saif Qahtan Salman

Lecturer of Biochemistry, College of Environmental Science, Al-Qasim Green University, Babylon, Iraq.

Abstract

The KRAS gene is classified as a type of genes called oncogenes. In case of mutation oncogenes have an ability to stimulate the proliferation in cells and make them cancerous. The mutation at 12th position changing the existing amino acid to arginine has been reported in lung cancer. KRAS gene expresses a protein that known as KR which play a role in signaling pathway called RAS/MAPK. The role of the protein is to transfer signals into the nucleus of the cells. Which are responsible of cell growth and proliferation? In this study, Kras protein sequence, structure and functional analysis were performed. The antioxidants selected for the study are ascorbic acid, 3, 7, dihydroxyflavone, isoflavone and quercetin. The chemical structures of those antioxidants were studied to be used for binding to the mutational site of KRAS. Based on the binding efficiency the best antioxidant which can be used in lung cancer treatment is determined.

Keywords: KRAS gene, Kras protein, Antioxidants, Ascorbic acid, 3, 7, Dihydroxyflavone, Isoflavone, quercetin.

Introduction

Ras Mutations in Lung Cancer

The RAS gene family includes HRAS, KRAS and NRAS and specified for a protein (21 KD a) that bind to GTP and regulate cell growth. This protein has the ability to interact with multiple effectors such as phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), and signal transducer and activator of transcription (STAT) protein (Figure 1). In case of mutation, an amino acid will be replaced at 12th, 13th or 16th position; RAS proteins will obtain transforming capability [1]. Such mutations can lead to impaired GTP ASE activity. Commonly mutations in KRAS gene occur in non-small cell lung carcinoma (NSCLC) [2]. Adenocarcinoma is about (20–30%) while (7%) found in squamous cell carcinoma [3].

Figure 1: The activation and deactivation of RAS cycle by guanine exchange factors and GTP ase activating proteins
Lung Cancer Prevention by Antioxidants

Many studies found that humans with low antioxidant have a tangible increase of cancer risk [4]. Recently, many patients with cancer combine some types of alternative and complementary therapies with conventional therapies. Antioxidants are the most common therapies. At this time, antioxidants show some benefit especially when they combined with specific types of chemotherapy [5].

Recently In vitro studies found that the effect of chemotherapeutics can by stimulated by using antioxidants. Many clinical studies were initiated to check the efficiency of high-dose of antioxidants to chemotherapy (carboplatin and paclitaxel) in NSCLC. Studies do not support hypothesis that antioxidants protect tumor cells that may be damaged by free radicals which may be generated by chemotherapy.

Many studies must be performed to prove if high-dose multiple antioxidants in addition to chemotherapeutics enhance the response and/or the time of survival in lung cancer [6].

Materials and Methods
Drug Designing Tools and Data Bases

Argus Lab

Argus Lab is considered as a drug designing tool with three-dimensional builder and a simple molecular mechanics. Argus Lab can also be used for protein docking.

Pub Chem

Pub Chem is one of the most important data bases that give data on the activities of the biological molecules.

It includes bioactivity, compound structures and substance information data in three main databases, PC bio Assay, PC compound and PC substance respectively.

Dundee Pro drg Server

It induces topologies for use, and energy coordinates in many formats by taking a description of molecules (like MDL Molfile, PDB coordinates and text drawing).

Results and Discussion

Kras Protein

MTEYKLVVGAGGVGKSALTIRQQLIQNHFV DEYDPTIEDSYRKQVVIDGETCLLDILDLTA GQEEYSAMRDQYMRTGECGFCLCVAINNT KSFEDIHYYREIQIKRKDSEDVPMVLCGN KCDLPITRVTQKQADLSYGIPFIETSA KTRQREDAFYTILREIRQYRLKKIKSKEEK TPGCVKIKKCIIM

Structure Visualization using Argus Lab

Highlighting the Mutational site G12D

Figure 1: Highlighting the mutational site G12D
Optimization

Figure 2: KRAS structure optimization was done. The energy of the protein structure is 1151.78 kcal/mol

Binding Results

Dihydroxyisoflavone

Binding results (Figure 3) showed the binding KRAS protein mutation with antioxidant (3, 7 dihydroxyisoflavone) closely through the use of simulation system Argus lab. The high-energy showed the binding in this compound for two reasons, first, the high receptor for KRAS protein mutation, site (12D), second The high susceptibility of the 3,7 dihydroxyisoflavone.

Figure 3: KRAS protein and 3,7 dihydroxyisoflavone binding. High binding energy is -6.63067 kcal/mol this shape explains the binding between 3,7 dihydroxyisoflavone (violet color) and KRAS protein in site 12D (yellow color)

Isoflavone

Isoflavone Binding results (Figure 4) showed the binding KRAS protein mutation with antioxidant Flavones closely through the use of simulation system Argus lab. The high-energy showed the binding in this compound for two reasons, first, the high receptor for KRAS protein mutation, site (12D), second The high susceptibility of the Flavones.
Ascorbic Acid
Ascorbic acid have high binding energy with KRAS protein in the activate 12D which are responsible about KRAS mutation. This binding (Figure 5) showed the high ability for ascorbic acid to link with KRAS protein. Through used Agrus lab showed clear binding occurring between the antioxidants compounds with KRAS protein in the site 12D, this binding showed the antioxidants activity for inhibiting the KRAS mutation.

Quercitin
Quercitin have high binding energy with KRAS protein in the activate 12D which are responsible about KRAS mutation. This binding (Figure 6) showed the high ability for Quercitin to link with KRAS protein. Through used Agrus lab showed clear binding occurring between the antioxidants compounds with KRAS protein in the site 12D, this binding showed the antioxidants activity for inhibiting the KRAS mutation.
Figure 6: KRAS and quercitin binding appears high binding energy: -5.89287 kcal/mol this shape explains the binding between quercitin (violet color) and KRAS protein in site 12D (yellow color)

<table>
<thead>
<tr>
<th>Antioxidant</th>
<th>Protein structure</th>
<th>Binding Energy</th>
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</thead>
<tbody>
<tr>
<td>3,7 dihydroxyisoflavone</td>
<td>Kras</td>
<td>-6.63067 kcal/mol</td>
</tr>
<tr>
<td>Isoflavone</td>
<td>Kras</td>
<td>-6.23017 kcal/mol</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Kras</td>
<td>-5.89287 kcal/mol</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Kras</td>
<td>-5.78191 kcal/mol</td>
</tr>
</tbody>
</table>

**Table 1: Binding energy between KRAS protein and Antioxidants compounds**

**Summary and Conclusion**

From the computational analysis, Kras protein was found to be hydrophilic, Aliphatic, Stable, negatively charged having the PI 6.33 and molecular weight 21655.8 daltons. Antioxidants (Ascorbic acid, 3,7, dihydroxyflavone, Isoflavone and Quercetin) were tested for drug likeliness and toxicity.

From the binding energies between the mutational site 12D and the various antioxidants, the antioxidant named 3, 7, dihydroxyisoflavone showed the efficient binding -6.63067 kcal/mol, when compared with other antioxidants. Thus 3, 7 dihydroxyisoflavone can be taken as an effective antioxidant in the inhibition of Lung cancer proliferation.

**References**