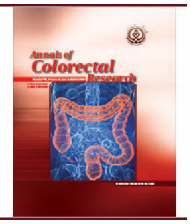
Original Article

*Ann Colorectal Res* 2021;9(1):32-39.



# Bioactive Compounds as a Potential Inhibitor of Colorectal Cancer; an *insilico* Study of Gallic acid and Pyrogallol

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**Received:** 06-01-2021
**Revised:** 19-04-2021
**Accepted:** 20-04-2021

## Abstract

**Introduction:** Colorectal cancer (CRC) is one of the most deadly cancers in the world. The objective of this investigation was to evaluate the protective effect of gallic acid and pyrogallol against CRC development. Previous reports suggest that there is an association present between some tannase-producing bacteria and CRC. Tannase is an enzyme that hydrolyzes tannic acid into gallic acid and pyrogallol. The present study aimed to determine the potential therapeutic effect of these compounds in CRC.
**Methods:** The remedial effects of gallic acid and pyrogallol were studied by determining their descriptor properties and applying molecular docking methods. A total of 100 CRC-causing protein structures were docked in this investigation.
**Results:** The Lipinski Rule of Five and other descriptor properties of the mentioned compounds confirmed their non-toxic and therapeutic nature. According to the molecular docking studies, both GA and pyrogallol showed high binding energies with almost all studied proteins, with maximum values of -38.22 kJ/mol and -33.6 kJ/mol being seen for gallic acid and pyrogallol, respectively.
**Conclusion:** This is the first report on a docking investigation of a large numbers of CRC-related proteins. According to our findings, we conclude that gallic acid and pyrogallol are protective against CRC as they can block the effects of numerous CRC-causing proteins.

**Keywords:** Colorectal cancer, descriptor properties, Molecular docking, Binding energy

*Please cite this paper as:*
Mitra D, Dey A, Biswas I, Das Mohapatra PK. Bioactive Compounds as a Potential Inhibitor of Colorectal Cancer; an *insilico* Study of Gallic acid and Pyrogallol. *Ann Colorectal Res*. 2021;9(1):32-39. doi: 10.30476/ACRR.2021.89642.1080.

## Introduction

Colorectal cancer (CRC) is a very common type of cancer in the world. Worldwide, CRC is ranked second in males and third in females in terms of its frequency. Furthermore, it is ranked fourth in males and third in females for cancer-related death (1).

Genetic alteration is reported as one of the causes of CRC progression (2). Many previous studies have revealed that different pathways are involved in CRC progression such as the Wnt/β-catenin pathway, TGF-β signaling, PI3K signaling, and many genes that control CRC progression (3). CRC progression is divided into five stages, namely early adenoma, intermediate adenoma, late adenoma, colorectal carcinoma, and metastasis. The Wnt/β-catenin

pathway plays an important role in CRC development (4). Loss of function of the adenomatous polyposis coli (APC) gene, gain of function of the K-Ras gene, and loss of function of p53 help to promote CRC development (5). Inactivation of the APC gene stimulates the occurrence of more than 60% of CRC via Wnt/β catenin activation (6). Epidermal growth factors also act as cancer inducers, examples of which are K-Ras and PIK3CA (7). In the development of CRC, some single nucleotide point mutations have been reported in codons 12 and 13 of exon 2 of K-Ras, together constituting 95% of mutation types; the remaining 5% is reported to be present in codons 61, 146, and 154, which are outside of exon 2 (8). Somatic mutations in exon 9 and exon 20 of the *PIK3CA* gene lead to CRC development (9). The PIK3CA mutation is also associated with *mTOR* and *K-Ras* in the regulation of cell growth (10). Cyclooxygenases (COXs) are also an important enzyme for uncontrolled cell proliferation. Overexpression of COX2 leads to the promotion of malignancy (11). Alterations in several pathways can lead to the expression of COX2, which can influence CRC development (12). BRAF is a proto-oncogene that encodes BRAF protein kinase, an efficient activator of MEK. Its mutation is associated with advanced CRC (13). Evidence suggests that CD274 is related to CRC development with the association of many other receptors (14).

Diet can also regulate the initiation and development of CRC and its prevention. A high-protein and high-fat diet can promote CRC progression, while a high-fiber diet can prevent CRC occurrence. This is because high-fiber foods are fermented into short-chain fatty acids (SCFAs), which can inhibit CRC (15, 16). Vegetables contain a high fiber content and different phenolic compounds such as tannin and tannin-like compounds. Tannin is a class of secondary plant metabolites and is an anti-nutritional and antimicrobial compound (17). It can be hydrolyzed by tannase, a microbial enzyme, to produce different bioactive compounds such as gallic acid (GA) and pyrogallol. It is also reported that bioactive compounds can modulate some CRC-related genes (18). A previous report suggests that GA has an inhibitory effect on tumor PD-L1, which causes lung cancer (19). Some bacteria are able to produce the tannase enzyme (20, 21). Hence, these bacteria may help in the reduction of CRC development. Intestinal microbial imbalances can initiate CRC progression. Tannase-producing bacteria are found at the CRC site and are able to degrade tannin into GA and pyrogallol, which may show anti-cancerous activity (22). *Staphylococcus lugdunensis* is a tannase-producing bacterial species and its tannase gene has been identified as tanA. This species was found at the CRC site, with a probable association between *S. lugdunensis* and advanced-stage CRC (23). Another species, *Streptococcus gallolyticus,* is reported to inhibit the anticancerous activity of tannic acid by degrading it, thus encouraging the growth of CRC cells (24).

Docking studies are very important in determining compounds that can be used as a drug as remedies for disease (25-28). The study of descriptor properties is also a very promising technique to analyze a drug molecule (29-31). Previous docking studies with GA and its derivatives have been done on many cancer and diabetic-causing proteins (32, 33). Docking of CRC-causing BRAF genes to derive proteins related to GA has been already studied (34). However, there are lots of other proteins that cause CRC. To determine whether or not GA and pyrogallol have any effects on all those proteins, we docked 100 protein structures with GA and pyrogallol. Using descriptor properties, we also aimed to predict which one is best between GA and pyrogallol. This investigation will help to find out a drug molecule that can act as an inhibitor of CRC.

## Methods

### *Dataset*

Structures were drawn in the BIOVIA DRAW (35) software package (Figure 1). Both ligands were minimized by the semi-empirical method (PM3) by VEGA ZZ (36). All 100 protein structures were retrieved from the RCSB PDB (37) database. Here, we took 7 gene products (i.e., protein structures). We took different resolution structures with different lengths for each target to prove the activity of GA and pyrogallol. Some of those structures showed mutations. Through this study, we can prove that those bioactive compounds can inhibit any target protein of those genes. The amino acid compositions of the mentioned proteins were analyzed using the ProtParam (38) server.

### *Druglikeness Evaluation with Descriptor Properties*

The druglikeness of GA and pyrogallol was evaluated by the Lipinski Rule of Five (39). This rule is important for indicating drug pharmacokinetics in the human body and provides information regarding the use of the ligands as drugs (40-42). We also calculate some other descriptor properties (43) using VEGA ZZ (35).

### *Molecular Docking Studies of all Proteins*

For the molecular docking and preparation of ligands and target proteins, Autodock 4.2 (44) was used. All 100 protein structure docking studies were performed with this software. Nonpolar hydrogen atoms were assembled and rotatable bonds were fixed in both ligands. The root of the ligand was also identified by Autodock 4.2. The active site of each protein structure was identified by the CASTp server (45). The site of docking was placed in a grid box with an appropriate dimension where the ligand will bind properly. Grid space was used as previous

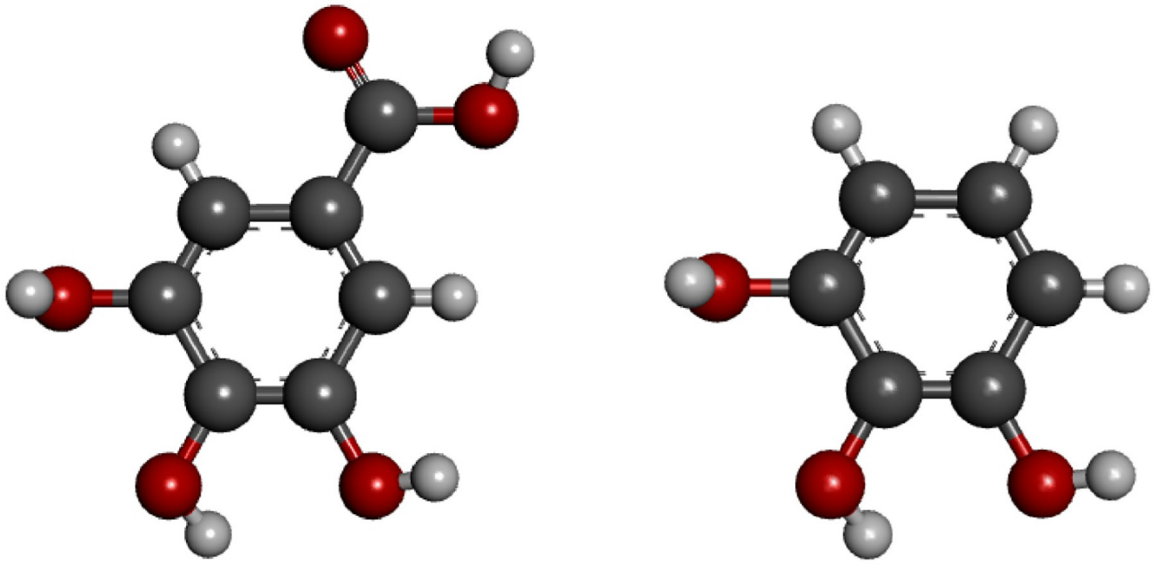


**Figure 1:** Structure of gallic acid and pyrogallol.

research reports (46). The final protein-ligand complex was made by PyMol software (47) to check their bindings. The final 2D and 3D ligand-protein interactions were identified from this complex.

## Results

### *Descriptor Properties of GA and Pyrogallol*

According to Lipinski's Rule of Five, the octanol-water partition coefficient (LogP) of a compound will be in a range between -0.4 to +5, the sum of surface of polar atoms (PSA) of a compound will be ≤140, the number of atoms (natoms) of a compound will be ≤70, the hydrogen bond acceptor (HBA) of a compound will be ≤10, the hydrogen bond donor (HBD) of a compound will be ≤5, the molecular weight (MW) of a compound will be ≤500. All those criteria were fulfilled by both GA and pyrogallol, meaning that they can be used as drug molecules in the human body.

The value of LogP is higher in GA than in pyrogallol (Table 1). The polar surface area of GA is much greater than pyrogallol. The number of atoms, hydrogen bonds, and hydrogen bond acceptors and donors are higher in the case of GA. The volumes of GA and pyrogallol are 138.10 $A^3$ and 108.10 $A^3$, respectively. GA has one rotatable bond whereas pyrogallol does not have any rotatable bond. Due to additional side bonding, GA has a higher molecular weight than pyrogallol. Molar refractivity (M.R) is higher in GA than pyrogallol.

### *Molecular Docking Studies on CRC-Causing Proteins*

We identified seven genes that cause CRC from previous studies. We took 100 gene products (i.e., proteins) from those six genes. The result of docking on these 100 proteins can identify a perfect drug that will stop their activity and cure CRC. We docked all 100 proteins with GA and pyrogallol.

Both GA and pyrogallol showed high binding energy on almost all proteins (Table 2). The highest binding energy was -38.22 kJ/mol in human phosphatidylinositol 4,5-bisphosphate 3-kinase (6PYS) by GA and -33.6 kJ/mol in serine/threonine-protein kinase (5VAM) by pyrogallol. GA also showed very strong binding (-32.34 kj/mol) with the K-ras gene product (4M1W), whereas pyrogallol showed -27.3 kJ/mol with this protein. The CD274 gene influences CRC, and GA showed promising results with the related gene products (-32.76 kJ/mol), while pyrogallol showed -28.98 kJ/mol binding energy.

GA forms three conventional hydrogen bonds, one pi-cation bond, and 11 Van der Waals interactions with human 6PYS. Pyrogallol forms two conventional hydrogen bonds, two amide-pi bonds, two pi-alkyl bonds, and nine Van der Waals interactions with 5VAM. However, one unfavorable accepter-accepter bonding also formed between the hydrogen of para positional oxygen and Leu 577 (Figures 2 and 3).

### *Protein-specific Nature*

In BRAF gene proteins, pyrogallol showed higher

**Table 1:** The properties related to the Lipinski Rule of Five and other molecular descriptor characteristics of gallic acid and pyrogallol.

| Properties | LogP | PSA (Å$^2$) | natoms | nhv | HBA | HBD | Volume (A$^3$) | nrotb | MW (Grams/mol) | M.R |
|---|---|---|---|---|---|---|---|---|---|---|
| Gallic acid | 0.73 | 97.98 | 18 | 12 | 5 | 4 | 138.1 | 1 | 170.12 | 37.42 |
| Pyrogallol | 0.59 | 60.68 | 15 | 9 | 3 | 3 | 108.1 | 0 | 126.11 | 30.79 |

LogP: partition coefficient; PSA: polar surface area; HBA: hydrogen bond acceptor; HBD: hydrogen bond donor; MW: molecular weight; M.R: Molar refractivity

**Table 2:** Genes and their protein products with name, resolution, and binding energy of gallic acid and pyrogallol

| Gene | Molecule name | PDB ID | Resolution (Å) | Gallic acid (kJ/mol) | Pyrogallol (kJ/mol) |
|---|---|---|---|---|---|
| BRAF | B-Raf proto-oncogene serine/threonine-protein kinase | 2FB8 | 2.9 | -32.76 | -31.5 |
| | | 3IDP | 2.7 | -29.82 | -32.34 |
| | | 3PSB | 3.4 | -29.4 | -29.82 |
| | | 3PSD | 3.6 | -29.4 | -29.4 |
| | | 3II5 | 2.79 | -28.56 | -31.5 |
| | Serine/threonine-protein kinase B-raf | 5VAL | 2.3 | -28.14 | -33.6 |
| | | 5VAM | 2.1 | -31.92 | -33.6 |
| | | 6B8U | 2.7 | -28.56 | -33.6 |
| | | 5HID | 2.5 | -28.56 | -33.18 |
| | | 5FD2 | 2.9 | -26.88 | -33.18 |
| | | 6N0P | 2.37 | -28.14 | -32.76 |
| | | 4XV9 | 2 | -32.76 | -32.76 |
| | | 4XV2 | 2.5 | -27.3 | -32.76 |
| | | 4XV1 | 2.47 | -28.14 | -32.76 |
| | | 5C9C | 2.7 | -29.4 | -32.76 |
| | | 4WO5 | 2.83 | -30.66 | -32.76 |
| | | 4RZV | 3.0 | -30.66 | -32.76 |
| | | 4YHT | 3.1 | -32.76 | -32.34 |
| | | 5CSW | 2.7 | -26.88 | -32.34 |
| | | 4XV3 | 2.8 | -30.24 | -32.34 |
| | | 4E26 | 2.6 | -28.98 | -31.92 |
| | | 5JSM | 2.2 | -30.66 | -31.92 |
| | | 4H58 | 3.1 | -33.18 | -31.5 |
| | | 5HI2 | 2.5 | -28.98 | -31.5 |
| | | 4FC0 | 3.0 | -27.3 | -31.5 |
| | | 4FK3 | 2.7 | -28.56 | -31.08 |
| | | 4RZW | 3.493 | -28.98 | -30.66 |
| | | 4PP7 | 3.4 | -27.72 | -30.66 |
| | | 3PRF | 2.9 | -28.98 | -30.66 |
| | | 5JRQ | 2.287 | -30.66 | -30.24 |
| | | 3PPK | 3 | -29.82 | -30.24 |
| | | 4DBN | 3.15 | -31.5 | -29.82 |
| | | 3PRI | 3.5 | -27.72 | -29.4 |
| | | 3Q96 | 3.1 | -28.56 | -28.56 |
| | | 3Q4C | 3.2 | -26.46 | -28.56 |
| | SLC45A3-BRAF FUSION PROTEIN | 4CQE | 2.3 | -26.46 | -31.08 |
| KRAS | GTPase K-ras | 4M1W | 1.58 | -32.34 | -26.04 |
| | | 4DSN | 2.03 | -31.92 | -27.3 |
| | | 4M1T | 1.703 | -31.08 | -26.04 |
| | | 4M1Y | 1.491 | -31.08 | -26.04 |
| | | 4M1O | 1.571 | -30.66 | -26.04 |
| | | 4LYF | 1.568 | -30.66 | -25.62 |
| | | 4LYH | 1.371 | -30.24 | -26.46 |
| | | 4DSO | 1.85 | -30.24 | -25.62 |
| | | 4M1S | 1.552 | -29.82 | -26.46 |
| | | 4M22 | 2.09 | -29.4 | -26.04 |
| | | 4PZY | 1.88 | -28.98 | -26.46 |
| | | 4LUC | 1.29 | -28.98 | -26.04 |
| | | 4EPX | 1.76 | -28.98 | -25.62 |
| | | 4LRW | 2.151 | -28.98 | -25.62 |
| | | 4L8G | 1.521 | -28.56 | -26.04 |
| | | 4LV6 | 1.5 | -28.56 | -26.04 |
| | | 4Q01 | 1.291 | -28.56 | -26.04 |
| | | 4EPT | 2 | -28.14 | -26.88 |

| | | | | | |
|---|---|---|---|---|---|
| PIK3CA | Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform | 6PYS | 2.19 | -38.22 | -33.18 |
| | | 5UK8 | 2.5 | -34.02 | -25.62 |
| | | 5SWR | 3.31 | -32.76 | -26.04 |
| | | 6GVF | 2.5 | -32.34 | -26.04 |
| | | 6GVI | 2.9 | -31.92 | -26.88 |
| | | 3ZIM | 2.85 | -31.92 | -25.62 |
| | | 5FI4 | 2.5 | -31.92 | -25.62 |
| | | 5SWG | 3.11 | -31.5 | -26.46 |
| | | 4JPS | 2.2 | -31.5 | -25.62 |
| | | 5DXT | 2.25 | -31.08 | -26.04 |
| | | 4TUU | 2.64 | -31.08 | -25.62 |
| | | 4TV3 | 2.85 | -31.08 | -25.62 |
| | | 6GVH | 2.74 | -30.66 | -26.88 |
| | | 5XGI | 2.56 | -30.66 | -26.04 |
| | | 5ITD | 3.02 | -30.24 | -26.88 |
| | | 5DXH | 3 | -30.24 | -26.04 |
| | | 5SWP | 3.41 | -30.24 | -26.04 |
| | | 5SWT | 3.49 | -30.24 | -26.04 |
| | | 5XGH | 2.97 | -30.24 | -26.04 |
| | | 5SX9 | 3.52 | -30.24 | -25.62 |
| | | 4L1B | 2.586 | -29.82 | -25.62 |
| | | 5SXF | 3.46 | -29.82 | -25.62 |
| | | 5SXI | 3.4 | -29.82 | -25.62 |
| | | 5UL1 | 3 | -29.4 | -26.88 |
| | | 5SXK | 3.55 | -29.4 | -26.04 |
| | | 5SXB | 3.3 | -29.4 | -25.62 |
| | | 4OVV | 3.5 | -27.72 | -26.46 |
| | | 4WAF | 2.39 | -27.72 | -25.62 |
| | | 2RD0 | 3.05 | -29.4 | -26.46 |
| COX2 | Prostaglandin G/H synthase 2 | 5F19 | 2.04 | -32.34 | -28.14 |
| | | 5F1A | 2.38 | -31.5 | -26.04 |
| | | 5IKR | 2.342 | -31.5 | -25.2 |
| | | 5KIR | 2.697 | -30.66 | -26.04 |
| | | 5IKT | 2.451 | -30.66 | -24.78 |
| | | 5IKV | 2.508 | -30.24 | -24.78 |
| CD274 | Programmed cell death 1 ligand 1 | 5J8O | 2.3 | -32.76 | -28.98 |
| | | 6NOS | 2.701 | -31.92 | -26.88 |
| | | 6NOJ | 2.33 | -31.5 | -29.82 |
| | | 6NM8 | 2.792 | -31.5 | -29.4 |
| | | 5J89 | 2.2 | -30.66 | -28.98 |
| | | 6R3K | 2.2 | -30.66 | -25.62 |
| PARS2 | Proline-tRNA ligase | 4K86 | 2.4 | -29.82 | -27.72 |
| SORT1 | Sortilin | 3F6K | 2 | -28.98 | -26.04 |
| | | 6EHO | 3.5 | -28.98 | -25.62 |
| | | 5MRI | 2 | -28.98 | -25.2 |
| | | 4MSL | 2.7 | -28.14 | -25.2 |

binding energies than GA. However, GA had higher binding energies for the remaining proteins. To determine whether or not any properties present in BRAF gene proteins create a protein-specific nature for pyrogallol, we calculated the physicochemical properties of all proteins.

From the docking interactions, it was found that pyrogallol mostly interacts with the H, R, K, S, G, I amino acids (Figure 4). GA mostly interacts with acidic, aliphatic, and sulfur-containing amino acids (Figures 2 and 3). The amino acid composition reveals that BRAF contains a high number of basic amino acid and also contains a high number of serine (S), glycine (G), and isoleucine (I) residues. For those reasons, pyrogallol showed a protein-specific nature and had higher binding energies with BRAF proteins than other proteins (Figure 4). In other words, all proteins except BRAF products contain high numbers of aliphatic and acidic amino acids. Thus, GA showed higher binding energy in most proteins.

## Discussion

The descriptor properties show the non-toxic nature and high druglikeness of the two bioactive compounds studied, namely GA and pyrogallol.

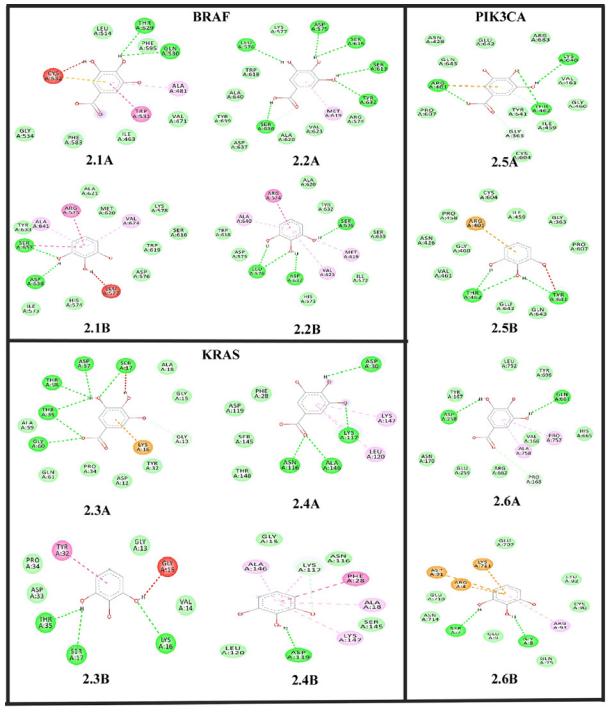


**Figure 2:** Gallic acid and pyrogallol make various types of interactions with BRAF, KRAS, and PIK3CA gene proteins. 2.1A and 2.1B show the interaction of 5VAL with gallic acid and pyrogallol. 2.2A and 2.2B show the interaction of 4H58 with gallic acid and pyrogallol. 2.3A and 2.3B show the interaction of 4DSN with gallic acid and pyrogallol. 2.4A and 2.4B show the interaction of 4M1W with gallic acid and pyrogallol. 2.5A and 2.5B show the interaction of 6PYS with gallic acid and pyrogallol. 2.6A and 2.6B show the interaction of 5UK8 with gallic acid and pyrogallol.

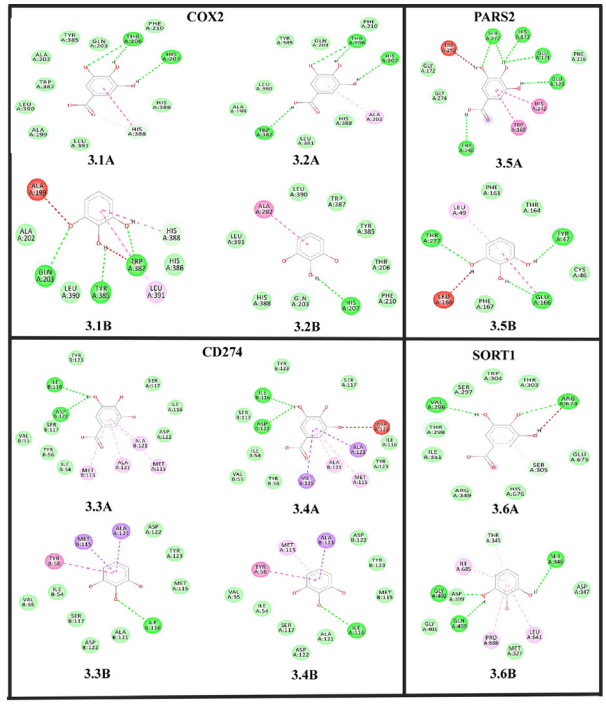


**Figure 3:** Gallic acid and pyrogallol makes various types of interactions with COX2, CD274, PARS2, and SORT1 gene proteins. 3.1A and 3.1B show 5F19 interaction with gallic acid and pyrogallol. 3.2A and 3.2B show 5F1A interaction with gallic acid and pyrogallol. 3.3A and 3.3B show 5J8O interaction with gallic acid and pyrogallol. 3.4A and 3.4B show 6NOJ interaction with gallic acid and pyrogallol. 3.5A and 3.6B show 4K86 interaction with gallic acid and pyrogallol. 3.6A and 3.6B show 3F6K interaction with gallic acid and pyrogallol.

The value of LogP indicates (Table 1) that these compounds are lipophilic. The polar surface area (PSA) values of both compounds were ≤140, which indicates that they can easily permeate across the cell membrane (48, 49). The high number of hydrogen bonds and its accepter/donor nature will increase the binding energy (50, 51) in GA. Molar refractivity (M.R), i.e., the measure of the polarizability of a compound (52, 53), showed a higher value in GA. This means that the polarity of GA is greater relative to pyrogallol. Increasing polarizability also increases the binding energy. For this reason, GA shows more binding energy than pyrogallol in all gene products (proteins) except BRAF gene products. Both GA and pyrogallol showed very good binding energies with all CRC-causing gene products, where pyrogallol showed higher binding energies with those proteins that contained basic amino acids.

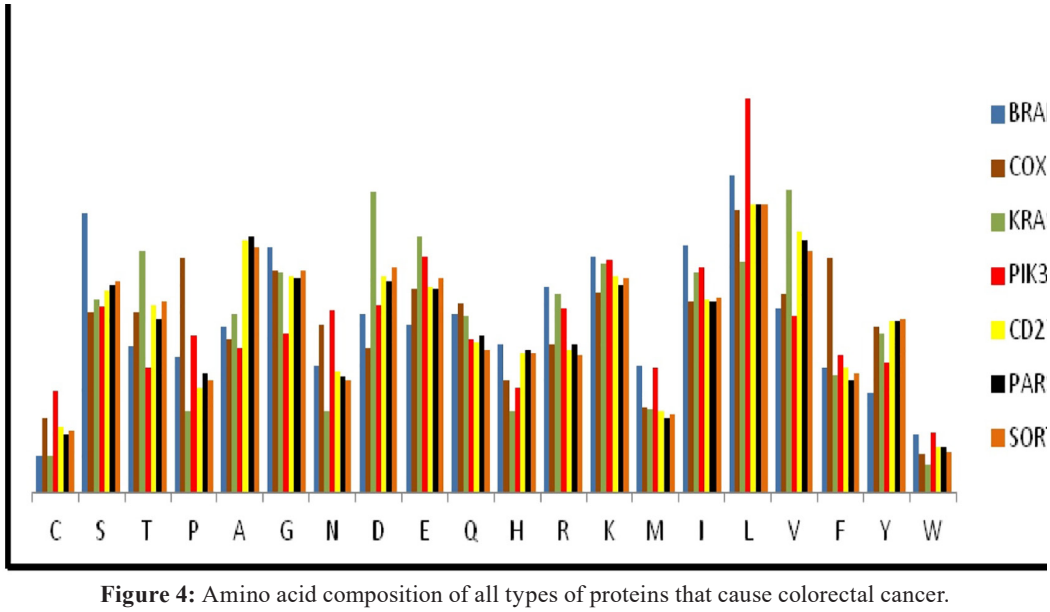


**Figure 4:** Amino acid composition of all types of proteins that cause colorectal cancer.

## Conclusion

The electronic structural properties of GA and pyrogallol were worked out by PM3 minimization. In this investigation, the molecular docking studies of GA and pyrogallol showed maximum binding scores of -38.22 kJ/mol and -33.6 kJ/mol, respectively. A huge number of CRC-causing proteins were docked by GA and pyrogallol, which has never been done before. This is the first such study of a huge number of protein-ligand interactions. Therefore, this investigation concludes that GA and pyrogallol may be used as anticancer drugs for CRC as they can suppress all studied CRC-causing proteins and may stop the development of CRC in humans. In particular, we recommend GA as a potent, safe, and cost-effective drug to prevent premature death in CRC patients.

## Authors contribution

D.M and A.D conceived and designed the project. P.K.D.M. conducted initial manual verifications. Genes were identified by A.D. Proteins were identified and extracted by D.M. Descriptor property calculations and molecular docking was performed by D.M. Draft of the manuscript was prepared by D.M., A.D., and I.B. Final version of manuscript was prepared by P.K.D.M. The whole work was done under the supervision of P.K.D.M.

**Conflicts of interests:** None declared.

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