International Journal of Biomedical Science and Engineering
2021; 9(2): 11-15
http://www.sciencepublishinggroup.com/j/ijbse
doi: 10.11648/j.ijbse.20210902.11
ISSN: 2376-7227 (Print); ISSN: 2376-7235 (Online)

Pharmacological Analysis and Molecular Docking of *Laurus nobilis (Bay Leaf)* for Lung Cancer with Reference to Sirtuin Drug Targets

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To cite this article:
Seema Rani Padhiary, Kalpana Priyadarsini Das, Meeneri Bobde, Vhatkar Pooja, Sameer Sharma. Pharmacological Analysis and Molecular Docking of *Laurus nobilis (Bay Leaf)* for Lung Cancer with Reference to Sirtuin Drug Targets. *International Journal of Biomedical Science and Engineering.* Vol. 9, No. 2, 2021, pp. 11-15. doi: 10.11648/j.ijbse.20210902.11

Received: March 22, 2021; **Accepted**: April 8, 2021; **Published**: April 20, 2021

Abstract: The aim of this in silico study was to analyze the inhibitory activity of selected phytocompounds from the Bayleaf (*Laurus nobilis*) in contrast to sirtuin proteins using the various pharmacological tools and molecular docking analysis. *Laurus nobilis* is a perennial herbs native to the family *Lauraceae* and it has been cultivated throughout the tropical, European, subtropical, and Asian nations. It has been used for thousands of years for food flavoring, essential oil applications, and in traditional medicine. Mostly, it contains all types of secondary metabolites such as tannins, flavones, flavonoids, alkaloids, eugenol, linalool, methyl chavicol, and anthocyanins. The 3D structures of phytocompounds were retrieved from Pubchem and chemspider databases and subjected to various bioinformatic tools such as SwissADME, Modeller, and Autodock for molecular docking to predict the active binding sites of sirtuin proteins. The comparison of molecular docking score exposed that the targeted phytocompounds showed good binding affinity in contrast to anti-cancer sirtuin proteins. The ADME and Molecular docking properties for drug likeness making them significant agents for biological activities and it is expected to be beneficial and effective for cancer. Bayleaf shows an optimistic results towards the treatment of many diseases. The Bayleaf traditionally has healing properties which has now dragged the attention of science for the betterment of humans. The phytochemical compounds found in and taken in the above research have showed good results with cancer receptors Sirtuin1 and Sirtuin4.

Keywords: Bayleaf, Flavonoids, Cancer, Molecular Docking

1. Introduction

Bay leaf is originated from South Asia as well as it to is related to major and minor Asia and across the globe. Bay leaf (Laur-gus nobilis) is a perennial herb native to the family laurel (Lauraceae). It has been cultivated in European, tropical, subtropical, and Asian countries. Commonly bay leaf used for food flavoring, essential oil applications, food flavoring, and in traditional medicine. It contains most of the flavonoids, tannins, alkaloids, eugenol, linalool, methyl chavicol, and anthocyanins. Bay is commonly using in several industry, from food to cosmetics to pharmaceutical products [1, 2].

There are so many variabilities found in bay leaf due to the leaves, stems, morphology, flower color, growth habitat, and chemical composition. Laurus azorica and L. nobilis are the two species of Bay leaf [3]. Bay leaf has a sharp and bitter taste. The main cause of fragnance and Aroma is due to the oil presence in leaves and other part of the plant. The phenolic compounds extracted from bay leaf contains antioxidant properties. different types of bay leaf species contains different types of chemical constituents [4].

Many herbs and spices are there, which are having some limitations for absorbtion as they have full of antioxidants and various differential compounds. But in case of Bay, It's not still exposed that how much bay leaf should be consumed

to get its health benefits. For the specific amount of use there is no particular recommendations by Researchers. bay is full of antioxidants and is a good source of minerals and dietary fibers [5, 6].

To improving the immune system, Bay leaves are the best used herbs which contains various types of Antioxidants such as vitamin C, vitamin E, and carotenoids are used in many dietary sources and are used to lower blood cholesterol and uric acid level [7, 8].

To cure the infections from viruses, bacteria, fungi, and protozoa, bay leaf is very effective. Bay is also helpful in inhibiting growth of carcinogenic cells. Bay is including phytonutrients, catechins, linalool, and parthenolide, which are the unique combination of antioxidants and organic compounds. This combination specifically shown to restrain the proliferation of cervical cancer cells and it helps to protect the body from the effects of free radicals. Free radicals are the main cause of cancerous cells, free radicals mutated healthy cells to carcinogenic cells. And bay leaves are particularly good at preventing this cancerous cells [9].

Bay leaf is found very beneficial in contrast to many infections from fungi, viruses, bacteria, and protozoa. Bay leaves is also helpful in inhibiting growth of cancer causing cells. The unique combination of antioxidants and organic compounds in bay leaves, including phytonutrients linalool, and parthenolide have good results in treatment of cancer [10]. We have selected the flavonoids (Tangeretin, Epicatechn, 8-heptamethoxyflavone, dihydroquercetin, Quercetin, Nobiletin, Isorhamnetin, Naringenin, Kaempferol, Hesperetin, Apigenin, Gallocatechin) from bayleaf to target the particular sirtuin drug targets.

In this paper, we tried a step ahead to do comparative analysis of the selected phytocompounds from the Bay leaf plant with the medicinal phytocompounds and carried out the pharmacological analysis and molecular docking which analyzed the drug likeness of the selected phytocompound.

2. Materials and Methods

2.1. Ligand Preparation

All the selcted phytocompounds of Bayleaf were retrieved from PubChem databases [11] and Chemspider. And these structures were used for the molecular docking simulation against the sirtuin 1 and 4 protein receptors. All the structures were fetched in the form of Standard Data Format and then converted into Protein Data Bank format using PyMol.

2.2. Retrieval of Receptors

Sirtuin 1 and 4 Protein receptors were used as a receptor against selected phytoligands to inhibit the activity of cancer. All the criteria for the receptors were analyzed by BLAST and PDB analysis [12].

2.3. Homology Modelling for Sirtuin Proteins

The homology modelling for the sirtuin receptors was done by using SwissModel and Modeller. For SwissModel, the Fasta Sequence were retrieved from NCBI database and subjected into the modelling process. The homology of the selected template for the sirtuin proteins was above 90% with respect to percent identity.

2.4. ADMET and Drug-likeness Analysis

The admet and drug likeness analysis was analyzed through SwissADME and pre admet analysis with the respect to five rule of Lipinski filter analysis. To analyze the orally active drug, there are some standard criteria such as cLogP, molecular mass, hydrogen bond donor and acceptor. All the physiochemical properties of phytocompounds were investigated or filtered by SwissADME, which is known for drug discovery tool [13].

2.5. Boiled-Egg

BOILED-Egg is used to predict depend on gastrointestinal absorption and brain barrier for the development of drugs. According to BOILED-Egg plot, if any compounds are rightfully placed in white region of eggs, the probability of GI absorption is higher and brain barrier is higher in case of compound correctly placed in yellow region. In this study, the analysis of the selected compounds for BOILED-Egg was done using SwissADME server [14, 15].

2.6. Molecular Docking Analysis

The objective of the molecular docking analysis is to assume or predict the interaction or inhibitory activity of selected phytocompounds in contrast to targeted sirtuin protein receptors. For Molecular docking, the binding affinity or docking score will give you to the all binding pores of molecules insides the catalytic sites of a protein which leads to the proper interaction between the molecules.

For the molecular docking, Autodock Vina, Patchdock, and PyRx (Virtual Docking Tool) were used to check the inhibitory activity of Phytocompounds with leads to the binding affinity and docking score. Once the docking performed, all the hydrophobic interaction was investigated using PyMol version 1.3 [16-18].

3. Results and Discussion

3.1. Ligands

All the three-dimensional structures of the selected phytocompounds were retrieved from the Pubchem and chemspider databases and leads to the screening through FT Site Server.

3.2. Analysis of Drug Likeness

After completion of Lipinski filter analysis which exposed the rigidity of all compound to be remembered for structure-based drug design and also listed out the compound's properties with similar to their usage using ADME analysis.

Table 1. *Physiochemical Analysis.*

Ligands	Molecular formula.	Molecular weight (g/mol).	Monoisotropic mass (g/mol).	Heavy atom count.	Tropological polar surface area (Angstrom).
Epicatechin	C15H14O6	290.27	290.079038	12	110.38
Gallocatechin	C15H14O7	306.27	306.073953	22	130.61
Apigenin	C15H10O5	270.24	270.052823	20	90.90
Hesperetin	C16H14O6	302.28	302.079038	22	96.22
Kaempferol	C15H10O6	286.24	286.047738	21	111.13
Naringenin	C15H12O5	272.25	272.068473	20	86.99
Tangeretin	C20H20O7	372.37	372.120903	27	76.36
Isorhamnetin	C16H12O7	316.26	316.058303	16	120.36
Nobiletin	C21H22O8	402.39	402.131468	16	85.59
Quercetin	C15H10O7	302.04	302.042653	16	131.36
dihydroquercetin	C15H12O7	304.25	304.058303	22	127.45
8-heptamethoxyflavone	C22H24O9	432.42	432.142032	16	94.82

Table 2. *Lipinski Analysis [13].*

Ligands	Molecular formula	H-Bond donar	H-Bond acceptor	cLogP	Molar Refractivity
Epicatechin	C15H14O6	5	6	0.85	74.33
Gallocatechin	C15H14O7	6	7	0.42	76.36
Apigenin	C15H10O5	3	5	2.11	73.99
Hesperetin	C16H14O6	3	6	1.91	78.06
Kaempferol	C15H10O6	4	6	1.58	76.01
Naringenin	C27H32O14	8	14	-0.79	134.91
Tangeretin	C20H20O7	0	7	3.02	100.38
Isorhamnetin	C16H12O7	4	7	1.65	82.50
Nobiletin	C21H22O8	0	8	3.02	106.87
Quercetin	C15H10O7	5	7	1.23	78.03
dihydroquercetin	C15H12O7	5	7	0.63	74.76
8-heptamethoxyflavone	C22H24O9	0	9	3.04	113.36

Criteria log P≤5.0, molecular weight in the range of 150–500, H-bond donor's ≤5, and H-bond acceptors ≤10. The result come from the above table indicates that the ligands selected were noted to be in acceptable range defined for human use which shows their potential drug like property.

Table 3. *Drug-likeness Analysis.*

Ligands	Blood brain barrier	GI absorption	Permeability glycoprotein substrate	LogS (scale insoluble<-10<poorly<-6<moderately<-4<soluble<-2very<0<highly) [Water solubility]
Epicatechin	no	high	yes	-2.22
Gallocatechin	no	high	no	-2.08
Apigenin	no	high	no	-3.94
Hesperetin	no	high	yes	-3.62
Kaempferol	no	high	no	-3.31
Naringenin	no	low	yes	-2.98
Tangeretin	yes	high	no	-4.11
Isorhamnetin	no	high	no	-3.36
Nobiletin	no	high	no	-4.18
Quercetin	no	high	no	-3.16
dihydroquercetin	no	high	no	-2.66
8-heptamethoxyflavone	no	high	no	-4.38

3.3. Boiled Egg

The prediction also reveals that Tangeretin has high GI absorption followed by Nobiletin, 8 heptamethoxyflavone, apigenin known drugs and Naringenin which is then followed by Epicatechin, dihydroquercetin and Gallocatechin have low GI absorption.

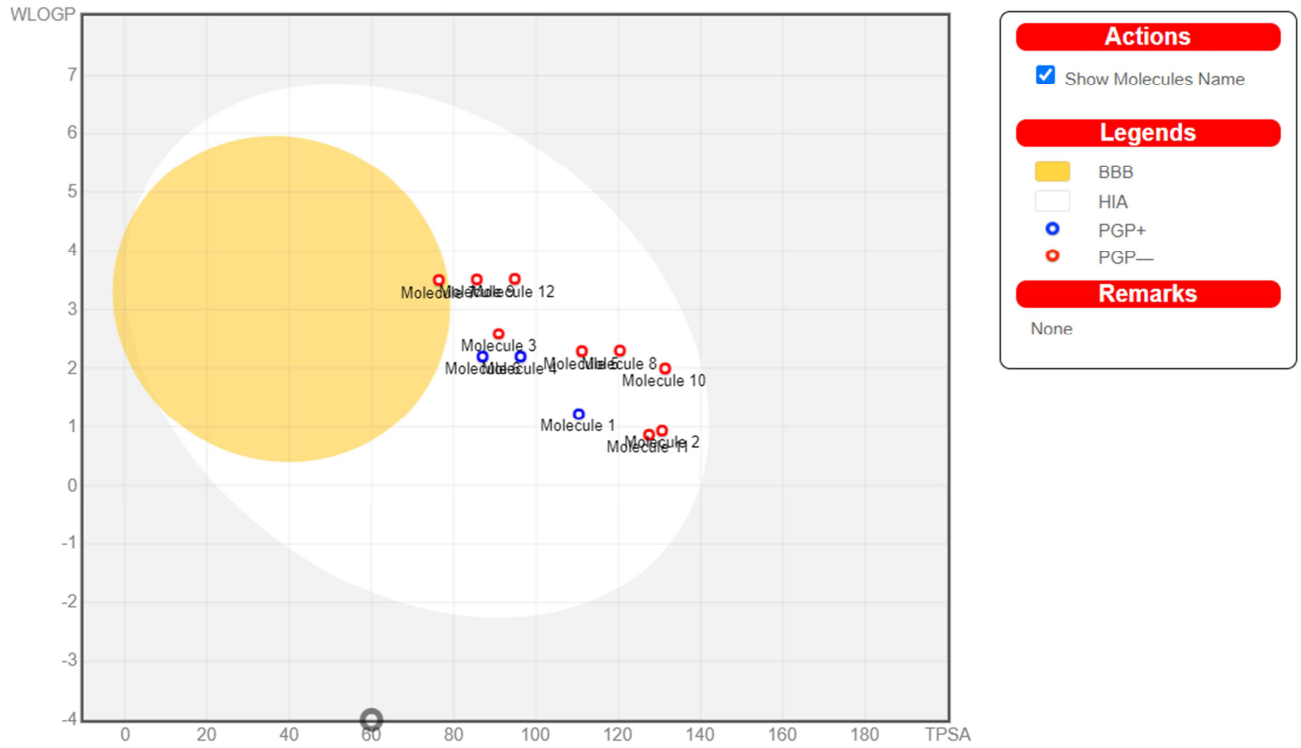

Figure 1. *BOILED-EGG Model: The white region indicates the physico-chemical space of molecules with highest probability of being absorbed by the GI (gastrointestinal tract), & the yellow part indicates the physico-chemical space of molecules with highest probability to permeate to the brain.*

3.4. Molecular Docking Analysis

The results obtained from molecular docking of selected compounds with Sirtuin1 and Sirtuin4 receptors shows that, most of the compounds are exposing better docking score and binding affinity. And this prediction indicates us to believe that the compounds will be suitable or proper for treatment of Cancer. In selected compounds below, the compounds Epicatechin and 8 Heptamethoxyflavone shows high docking score which indicates good ligands capability. The binding affinity of the compound Naringenin a -8.3 which is having a good binding affinity on comparison to other compounds. This compound is then followed by Isorhamnetin and apigenin with affinity of (-7.6 &-7.5).

Table 4. *Molecular docking simulation with Sirtuin1 co-receptor.*

Ligands	Docking Score	Binding Affinity (kcal/mol).
Epicatechin	5864	-7.3
Gallocatechin	4616	-7.1
Apigenin	4220	-7.5
Hesperetin	4584	-7.1
Kaempferol	4406	-7.5
Naringenin	4276	-8.3
Tangeretin	4878	-6.6
Isorhamnetin	4378	-7.6
Nobiletin	4872	-6.5
Quercetin	4280	-6.5
Dihydroquerecetin	4376	-7.3
8-Heptamethoxyflavone	5502	-6.5

Table 5. *Molecular docking simulation with Sirtuin4 co-receptor.*

Ligands	Docking Score	Binding Affinity (kcal/mol).
Epicatechin	4002	-3.1
Gallocatechin	4134	-6.7
Apigenin	3886	-5.4
Hesperetin	4328	-6.8
Kaempferol	3992	-7.3
Naringenin	3820	-6.3
Tangeretin	4792	-4.4
Isorhamnetin	4322	-3.6
Nobiletin	5268	-9.9
Quercetin	3914	-11.2
Dihydroquerecetin	4036	-5.9
8-Heptamethoxyflavone	5540	-8.7

4. Conclusion

Bayleaf shows an optimistic results towards the treatment of many diseases. The Bayleaf traditionally has healing properties which has now dragged the attention of science for the betterment of humans. The phytochemical compounds found in and taken in the above research have showed good results with cancer receptors Sirtuin1 and Sirtuin4. The phytochemical compounds Epicatechin and 8 heptamethoxyflavone shows good Docking Score and Binding affinity with Sirtuin receptors 1and 4. The ADME analysis shows that the compound Tangeretin has high absorption rate. Hence, the phytochemical compounds found in Bayleaf extensively paves a wayout to treat lung cancer which has shown good outcome in in-silico studies.

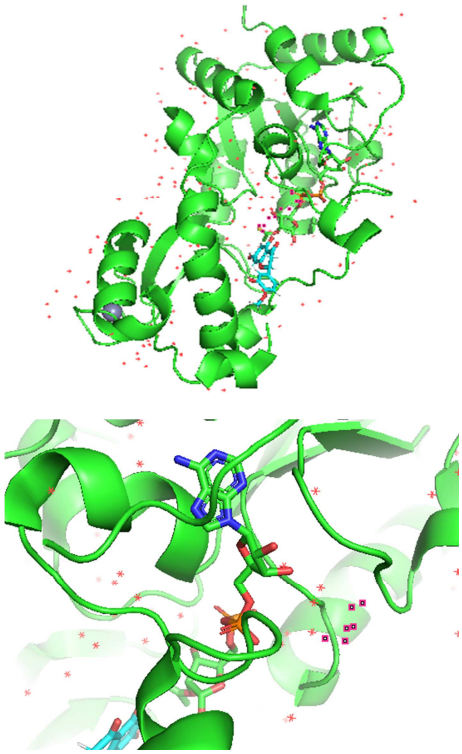

Figure 2. *Molecular Docking interaction of selected phytochemical with targeted sirtuin drugs.*

Acknowledgements

We thank BioNome, Bengaluru for helping us to do research in the field of Bioinformatics.

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