Identification of Anti-Inflammatory Compounds Present in *Nigella sativa* and Analyzing Their Effects on the Inflammation Pathway Using *In Silico* Techniques

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Abstract

Nigella sativa, also known as black cumin, is an herb native to Asia, the Middle East, and the Mediterranean. The chemical constituents found in *Nigella sativa* seeds have been known to have a wide array of pharmacological actions. Previous studies have primarily focused on identifying the structures of these compounds and their medicinal properties based on physiochemical analysis. There have been few studies that explain how these compounds interact with enzymes found in the human body. Hence, the objective of this study was to identify anti-inflammatory compounds present in *Nigella sativa* from previous literature and see if these compounds can be used to target the cyclooxygenase-2 inflammatory pathway. We compiled a list of twenty-three chemical compounds present in *Nigella sativa* and then constructed a comprehensive molecular database of their three-dimensional structures using chemical modeling approaches. We then docked these compounds into two different cyclooxygenase-2 molecules, using *in silico* techniques, to observe their conformation as well as binding affinity. Furthermore, we analyzed the interaction patterns of the five most stable compounds to understand their effects on the cyclooxygenase binding pocket. In conclusion, using structural bioinformatics approaches, we have identified novel compounds derived from *Nigella sativa* that can be used as possible agents to target inflammation.

1 Introduction

Ethnobotany is the study of traditional customs observed by humans in relation to plants regarding their medicinal, nutritional, and religious values[1]. Historically, plants and the natural compounds they produce have been used differently by different societies; thus ethnobotany has a wide array of applications ranging from plant dyes to guiding drug discovery and development. Previously, researchers have collected plant samples and performed phytochemistry studies that would later be used in clinical studies. Although synthetic biochemistry has greatly reduced the need to use natural compounds derived from plants, ethnobotanical studies have been of extreme academic interest in recent years[2]. This interest stems from the fact that more plant-derived drug interactions have been observed as traditional and herbal medicines become more popular. As of 2019, the World Health Organization reports that about 80% of the world population relies on traditional medicine[3]. Consequently, it is important to have clear regulations on these types of conventional medicine. Studying the possible interactions these natural compounds have on molecules and enzymes in the human body is the first step in establishing these guidelines.

Nigella sativa, also known as black cumin or black seed, is a plant native to Eastern Europe and Western Asia. It has also naturalized over to North Africa and parts of the Middle East[4]. The seeds of *Nigella sativa* have been used in traditional Islamic and Ayurvedic medicine for generations[5]. Traditionally, it is used postpartum to aid with lactation and menstruation[5]. It is also thought to have a wide array of pharmacological actions including anti-microbial, antioxidant, anti-hyperlipidemic, and the focus of our research, anti-inflammatory action[5]. Several

chemical compounds present in *Nigella sativa*, namely thymoquinone, can reduce asthma symptoms and treat rheumatoid arthritis by targeting the inflammatory pathway[5].

Inflammation is a biological immune response that can be triggered by many external factors such as bacteria, viruses, and foreign bodies. Pain, swelling, redness and warmth are some of the symptoms associated with an inflammatory response. On the cellular level, cytokines, small cell-signaling proteins, are released to recruit other immune cells to the site of infection. Vasodilation and increased permeability allow other signaling molecules to diffuse across to address the inflammation. In normal circumstances, an acute defense mechanism is employed to protect cells and eliminate endogenous compounds. However, uncontrolled inflammatory responses may become chronic leading to extreme pain and, in extreme cases, tissue death[6]. There are typically two routes by which inflammation can proceed. One includes cytokine secretion due to the recognition of pathogen-associated molecular patterns (PAMPS) by toll-like receptors (TLRs); the other is bradykinin synthesis, which triggers prostaglandin formation and leads to vasodilation[7]. We focus on the latter pathway here. Arachidonic acid found in poultry and meat is converted by cyclooxygenase-1 and 2 (COX-1 and COX-2) into prostaglandins. These two enzymes can be targeted by traditional non-steroidal anti-inflammatory drugs (NSAIDs). Since COX-1 is an important enzyme for gastric protection and platelet function, selective NSAIDs need to target only COX-2, which is responsible for pain and inflammation[8]. The objective of this research is to create a comprehensive database of chemical constituents present in *Nigella sativa* and analyze their interaction with COX-2 using *in silico* docking methods.

2 Methodology

Construction of molecular database for *Nigella sativa* constituents

PubChem and PubMed were used to compile the database. PubChem is a database that provides information on chemicals and their activity. PubChem Compound, one of PubChem's interlinked databases, shows a wide array of compounds and uses another database, PubChem Bioassay, to compile each chemical's information[9]. PubMed houses an extensive number of biomedical journals and peer-reviewed literature. In addition, it provides access to related entries in other National Center for Biotechnology Information (NCBI) databases[10]. We used PubMed to retrieve the structure of the chemical compounds from scientific literature and compile them into an Excel spreadsheet. After recording twenty-three different chemical compounds, their chemical structures were downloaded as Standard Delay Format (SDF) files from PubChem. The Protein Data Bank (PDB), which is a database containing 3D structures of biological molecules, was then used to obtain three different COX-2 files with inhibitors in their binding pockets. The three targets were 5F1A, 5IKT, and 5KIR with salicylate acid, tolfenamic acid, and Vioxx as the inhibitors, respectively. The three files used differed only in the type of inhibitor that was bound to the COX-2 molecule. Since the focus of the paper is on surrounding the anti-inflammatory properties of these novel compounds, the three files were specifically selected, as all three inhibitors are used in a variety of NSAIDs. Salicylate acid and tolfenamic acid are nonselective, while Vioxx is selective to COX-2.

Molecular modeling studies with Autodock Vina and UCSF Chimera

We then performed molecular docking using UCSF Chimera to study the ligand conformation and binding affinity of the different compounds in the COX-2 binding pocket[11]. The twenty-three ligands (chemical constituents) were then docked into the three targets (COX-2) using Autodock Vina integrated into UCSF Chimera. These two programs visualize interactions and molecular structures by providing high-quality images and docking trajectories[11]. After obtaining the delta G values from the docking, the five most stable ligands were further analyzed in Pymol to study the amino acid interactions in the binding pocket. PyMOL is a cross-plat-

form tool that allows for 3D visualization of macromolecular analysis, protein-ligand docking, and molecular docking simulations among other features[12].

3 Results

Table 1 was compiled from all the different compounds found in the literature. Twenty-three compounds were recorded along with their locations within the plant, pharmacological activity, extract type, and percent yield present in the overall composition of the plant. Table 2 shows the x, y, and z calculations of where the original ligands for both targets can be found. These calculations were used to re-dock the original ligands, salicylate acid and Vioxx, in their respective targets by defining the size of the binding pocket. Tolfenamic acid (5KIT) was excluded from the findings of the paper as there were some issues with the docking of the chemical ligands into that file: appropriate x, y, and z calculations could not be obtained for that target. The delta G values and root mean squared deviation (RMSD) values were also recorded in this table. The RMSD values signify the deviation between the original and redocked ligands. The RMSD value is used as a control to highlight that the original ligand can be redocked into the same target. The best conformation, denoted by the highest delta G value and RMSD < 2.5, was used to compare the remaining 25 ligands and obtain the delta G values, measured in kcal/mol. The delta G values, along with the conformation of each docking for targets, were recorded in Table 3. The average delta G value for both targets was also recorded in these tables. The interactions between the five most stable ligands and the binding pockets of both targets were analyzed and recorded in Table 4. Visualization of these interactions was also recorded to observe the hydrophobicity and hydrophilicity of each interaction. Visualization of these interactions can be observed in Figure 2 and Figure 3.

4 Discussion

Chronic inflammation occurs when an infection remains unresolved. This could lead to a wide array of problems including tissue death and increased risk of cancer[18]. Non-steroidal anti-inflammatory drugs (NSAIDs) have proven to be effective against many types of inflammation. NSAIDs work by inhibiting cyclooxygenase (COX) enzymes and preventing the conversion of arachidonic acid to prostaglandins. Most of the NSAIDs currently on the market are not selective and work by inhibiting both COX-1 and COX-2 enzymes. This can lead to many adverse effects such as decreased platelet formation, which can cause bleeding and gastrointestinal complications[19]. Thus, it is crucial to find a more selective inhibitor for the COX-2 enzyme. *Nigella sativa* has been proven to reduce inflammation along with many other pharmacological actions, but mechanisms by which these natural constituents interact with the inflammatory pathway remain unclear. Identification of the ligand interactions that mediate the anti-inflammatory effect of *Nigella sativa* will facilitate the development of more selective COX-2 inhibitors and help create more comprehensive guidelines on traditional medicine usage.

In this study, we researched the interactions between the chemical constituents and the binding pocket of COX-2 molecules to identify the best compounds for inhibition. Through a combination of in silico docking techniques, we identified five different ligands for each COX-2 molecule that have a more stable interaction than the original inhibitors.

Salicylate acid, the inhibitor found in the 5F1A target, is the active constituent present in aspirin. Although a low dosage of aspirin has been proven to help with age-related diseases, extensive usage has been shown to cause gastrointestinal damage and compromise kidney function[20]. This is due to salicylate acid inhibiting COX-1, which is important in the production of prostaglandin-1, a hormone responsible for maintaining homeostasis and platelet function. Thus, it is important to find alternatives that do not inhibit COX-1 and have stable binding with COX-2. The five compounds observed to have a better binding affinity are thymoquinone, nigellicimine, 4-terpineol, thymol, and carvacrol (Table 4).

Vioxx, the inhibitor of the other COX-2 target, is the active constituent present in Rofecoxib.

Rofecoxib was a drug marketed as a safer alternative to NSAIDs for treating rheumatoid arthritis and migraines. The drug was later withdrawn from the market due to studies showing increased probability of cardiovascular disease in users[21]. Although

TABLE 1: *Chemical constituents present in Nigella sativa. The part of the plant, pharmacological activity, extract, and percentage yield for each compound are also noted.*

Chemical Constituent	Part of Plant	Activity	Extract	Percent yield (%)
Thymoquinone[14]	seed	anti-inflammatory + antifungal + anticancer	methanol	48
Carvacrol[15]	seed	antioxidant + anti-inflammatory	ethanol	12
t-anethole[15]	seed	antioxidant + anti-inflammatory	ethanol	4
4-terpineol[15]	seed	antioxidant + anti-inflammatory	ethanol	7
sesquiterpene longifolene[15]	seed	antibacterial + anti-inflammatory	ethanol	8
α-pinene[16]	seed	anti-inflammatory	ethanol	trace amounts
Thymol[16]	seed	anti-inflammatory	ethanol	trace amounts
Nigellicimine[16]	seed	antifungal	methanol	2
nigellicimine-N-oxide[16]	seed	antifungal	methanol	2
Nigellidine[16]	seed	anti-inflammatory	aqueous	trace amounts
Nigellicine[16]	seed	anti-inflammatory	aqueous	trace amounts
alpha-hederin[16]	seed	antidiabetic	aqueous	trace amounts
Longifolene[16]	leaves/seed	antibacterial + anti-inflammatory	aqueous	trace amounts
Thujene[16]	leaves/seed	antibacterial + anti-inflammatory	aqueous	trace amounts
Sabinene[17]	leaves/seed	antibacterial + anti-inflammatory	aqueous	trace amounts
beta-sitosterol[17]	leaves/seed	antibacterial + anti-inflammatory	aqueous	trace amounts
Phellandrene[17]	leaves/seed	antibacterial + anti-inflammatory	aqueous	trace amounts
α-hederin[17]	leaves/seed	antibacterial + anti-inflammatory	aqueous	trace amounts
Carvone[17]	leaves/seed	antibacterial + anti-inflammatory	aqueous	trace amounts
Limonene[17]	leaves/seed	antibacterial + anti-inflammatory	aqueous	trace amounts
β-pinene[17]	leaves/seed	antibacterial + anti-inflammatory	aqueous	trace amounts
d-citronellol[17]	leaves/seed	antibacterial + anti-inflammatory	aqueous	trace amounts
Saponin[17]	leaves/seed	antibacterial + anti-inflammatory	aqueous	trace amounts

TABLE 2: *XYZ calculations of the original binding site for the two COX-2 targets. These calculations were used to dock the chemical ligands obtained. Redocking of the original ligands and RMSD associated with the ligands were noted.*

Target PDB file	X Y Z	Delta G (kcal/mol)	RMSD
5KIR	23.38 x 1.34 x 34.57	-7.9	1.7
5F1A	1.60 x 24.07 x 240.24	-6.3	2.114

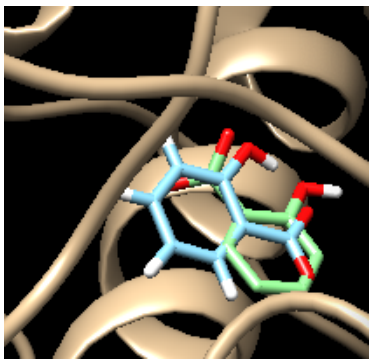


FIGURE 1A.

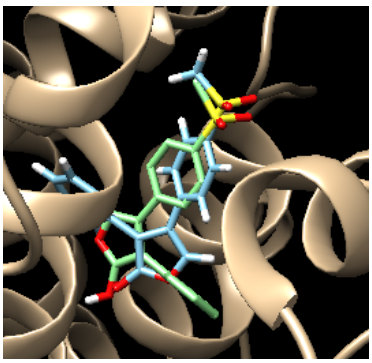


FIGURE 1B.

FIGURE 1. A) *Crystal structure of 5F1A (COX-2) with redocked salicylate acid ligand.* B) *Crystal structure of 5KIR (COX-2) with redocked Vioxx ligand.*

TABLE 3: *Delta G values and of the conformation obtained from the docking of chemical ligands obtained. Average of all dockings was also recorded.*

Ligand	Delta G value for 5F1A(kcal/mol)	Delta G value for 5KIR(kcal/mol)
Thymoquinone	-7	-6.6
carvacrol	-6.3	-6.8
t-anethole	-6.3	-6.4
4-terpineol	-6.6	-6.4
sesquiterpene longifolene	-2.8	-6
α-pinene	-6.2	-6.1
thymol	-6.4	-6.3
nigellicimine	-6.8	-7
nigellicimine-N-oxide	-5	-6
nigellidine	-4	-8.8
nigellicine	-5.2	-8.3
alpha-hederin	-6	-7
Longifolene	-6.3	-6
thujene	-6	-6.1
sabinene	-6.5	-6.1
beta-sitosterol	-2.1	-5.5
α-hederin	-5.7	-6.9
Phellandrene	-6.3	-6.3
carvone	-6.3	-6.8
limonene	-6	-6.3
β-pinene	-5.4	-5
d-citronellol	-5.5	-6
saponin	-5	-5
Average	**-5.6**	**-6.4**

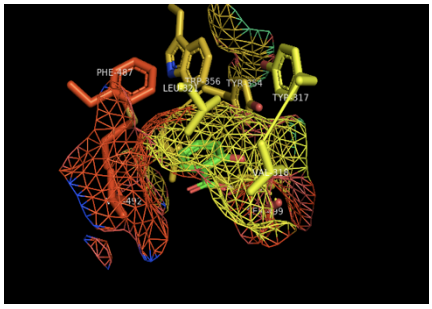


Figure 2A

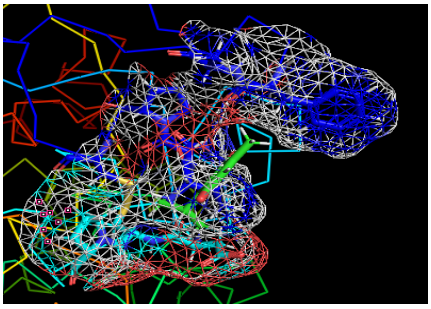


Figure 2B

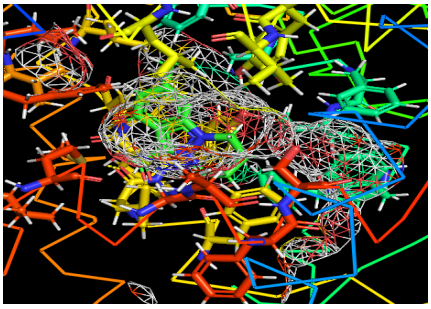
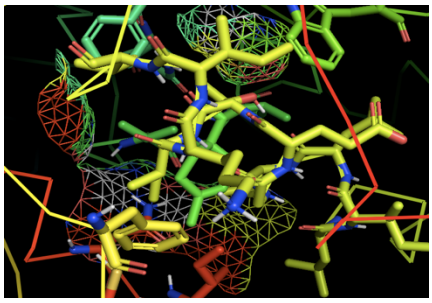


Figure 2C



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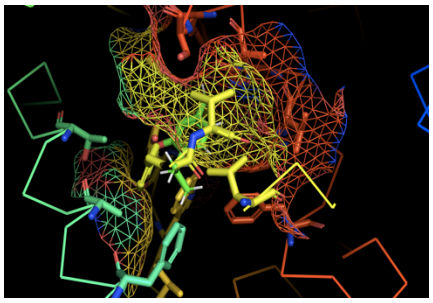

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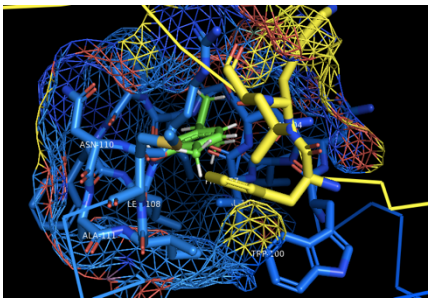


Figure 2F

Figure 2: *Visualization of the amino acid interactions for the five ligands and the original ligand associated with the 5F1A target. Red refers to interactions that are extremely hydrophobic while blue refers to interactions that are extremely hydrophilic. The range of colors determines the level of hydrophobicity or hydrophilicity. a-f) Amino acid interactions for salicylate acid, thymoquinone, nigellicimine, 4-terpineol, thymol and carvacrol respectively.*

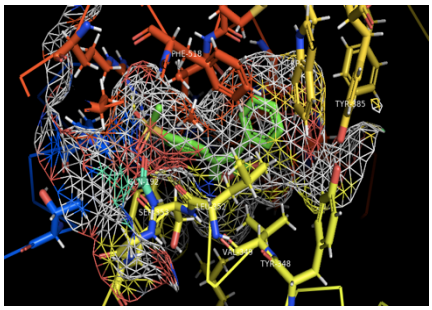


Figure 3A

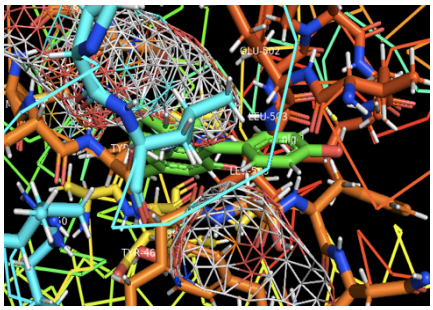
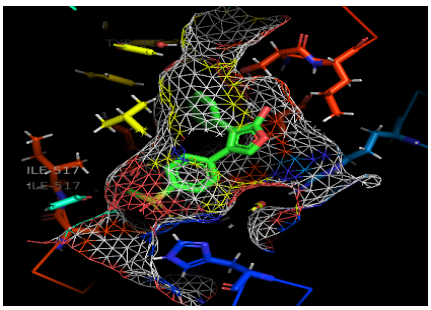


Figure 3B



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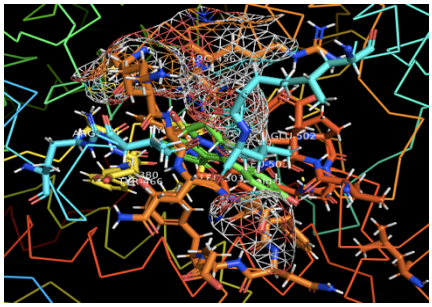

Figure 3D

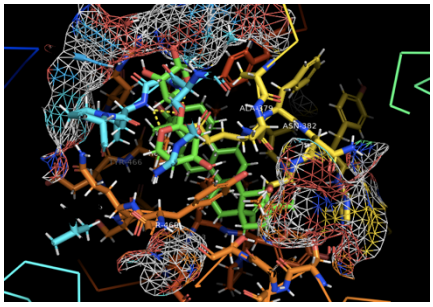

Figure 3E

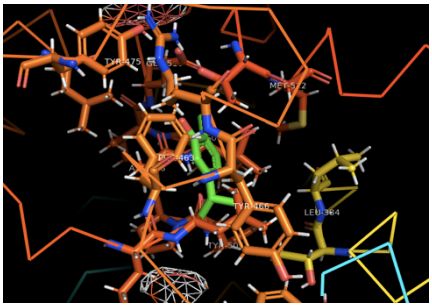

Figure 3F

Figure 3: *Visualization of the amino acid interactions for the five ligands and the original ligand associated with the 5KIR target. Red refers to interactions that are extremely hydrophobic while blue refers to interactions that are extremely hydrophilic. The range of colors determines the level of hydrophobicity or hydrophilicity.* a-f) *Amino acid interactions for Vioxx, nigellidine, nigellicine, nigellicimine, alpha hederin, and carvacrol respectively.*

Table 4: *Amino acid interactions of the five most stable chemical ligands as well as the original ligands docked into the two COX-2 targets. These interactions include hydrophobic, hydrophilic, ionic, and hydrogen bonds.*

Ligand	Interaction pattern in 5F1A	Ligand	Interaction pattern in 5KIR
Original ligand (salicylate acid)	PHE487 TRP356 TYR354. TYR317. LEU321. VAL318. VAL492. PHE 350 SER499	Original ligand (Vioxx)	PHE529. TRP360. TYR466. LEU508. VAL434. PHE463
Thymoquinone	PRO335 PHE487. CYS340. PRO320. LYS470. VAL318. PHE350. SER499	Nigellidine	TYR460. ARG456. GLU380. ARG150. TYR466. LEU503. GLU502
Nigellicimine	TYR348. PHE198. LEU390. TRP387. PHE518. LEU352. PHE529. SER530	Nigellicine	LEU508 PRO389. ALA435. VAL434. LYS436. LEU507.
4-terpineol	PHE335 TRP345 PRO335. CYS340. LEU321. TRP387. LYS470. PHE350	Nigellicimine	TYR466 PHE529 ASN382. LEU508. TYR466. ARG150
Thymol	TYR385. TRP387. PHE198. TYR348. PHE 381. PHE529. LEU390. GLY526	Alpha hederin	ARG150. TYR460. TYR466. LEU503. LEU507. VAL525. PHE529. ASN382
Carvacrol	PHE357 ASN110. ALA111. TRP340. PRO335. LEU321. TRP387. PHE350	Carvacrol	PHE463. TYR466. LEU384. TYR504. LEU507. GLU510. TYR475

Rofecoxib was successful in selectively inhibiting COX-2, its risks outweighed its benefits. The five compounds observed to have a better binding affinity are nigellidine, nigellicine, nigellicimine, alpha hederin, and carvacrol (Table 4).

Thymoquinone

Thymoquinone, the most abundant compound in the *Nigella* seed (Table 1), has been proven to decrease nitric oxide synthesis as well as inhibit prostaglandin formation. Therefore, it could treat asthma and rheumatoid arthritis[22]. Thymoquinone had a higher delta G value than salicylate acid, proving it has the stability to potentially be used as an inhibitor to target the COX-2 enzyme (Table 3). The delta G value denotes the stability of the interaction between the ligand and the target. A higher delta G value indicates that the ligand binds strongly to the target, thus acting as an effective inhibitor. In addition, the interaction of serine and cysteine in the binding pocket shows strong hydrogen bonding between thymoquinone and COX-2 (Table 4). The presence of these hydrophilic amino acids stabilizes thymoquinone in the binding pocket. However, the presence of proline in the set of interactions shows a possibility that thymoquinone might not be stable enough for prolonged interactions, as the cyclic ring in proline can distort the structure. Overall, thymoquinone appears to have numerous hydrophilic interactions that are required for sufficient protein-ligand interactions.

Nigellicimine

Nigellicimine, a novel compound found mainly in the *Nigella* seed, also appears to have a higher delta G value compared to the original ligand of one of the COX-2 targets (5F1A) but not the other (5KIR). Serine, cysteine, and tyrosine appear to be the main amino acids in the interactions between nigellicimine and the 5F1A binding pocket (Table 4). Like thymoquinone, nigellicimine has a stable interaction in the binding pocket. Although there are hydrophilic interactions between nigellicimine and 5KIR, the presence of multiple amino acids (phenylalanine) with aromatic rings may destabilize the structure. Nigellicimine appears to have a higher delta G value compared to some of the other natural compounds present in *Nigella sativa*. The difference

in interactions between the two targets could be attributed to the original ligands (salicylate acid and Vioxx) not sharing the exact same binding pocket. This can be observed through the XYZ calculations denoting that there could be different amino acid interactions involved in each docking (Table 2).

4-terpineol and Thymol

4-terpineol and thymol are compounds that are present in low or trace amounts in the *Nigella* seed (Table 1). It was quite unexpected to observe that they have a higher delta G value compared to salicylate acid (Table 3). The presence of tyrosine and cysteine supports the delta G value regarding the stability of the interaction. Yet, the presence of multiple phenylalanine and tryptophan amino acids in these interactions suggests a temporary binding that cannot be used for extended inhibition of COX-2.

Carvacrol

Carvacrol, the second most abundant compound in the *Nigella* seed (Table 1), is known to reduce inflammation but the mechanism by which it does so remains unclear. Some researchers have hypothesized that its anti-inflammatory activity could be caused by induction of interleukin-10 which in turn reduces other inflammatory cytokines[23]. Carvacrol appears to have a stable interaction with both COX-2 targets, but it does not have a higher delta G value than salicylate acid and Vioxx (Table 3). This could be due to the presence of phenylalanine and tryptophan which cause distortions in the binding structure due to their large side chains that give them a bulky nature. Interactions with 5F1A appear to be more polar compared to interactions with 5KIR (Table 4). Further analysis would be required to know the effects of prolonged interactions of carvacrol on the COX-2 targets in question as the data regarding this compound appear to be inconclusive.

Nigellidine and Nigellicine

Nigellidine and nigellicine were observed to have a higher delta G value compared to Vioxx. Both compounds have been found to reduce inflammation related to viral infections. Most notably, nigellidine and nigellicimine have been found to help reduce COVID-19-related inflammation and inhibit interleukins involved in "cytokine storm"[24]. The presence of asparagine and leucine in the binding pocket interactions suggests that ionic bonds are present which stabilize the structure (Table 4). Similar to other compounds, serine, cystine, and tyrosine are involved as polar contacts for nigellidine and nigellicine (Table 4). The presence of these residues stabilizes the ligand in the pocket of the COX-2 protein. In addition, nigellidine appears to be more stable compared to nigellicine. This could be attributed to the extra aromatic ring present in nigellidine, which is known to increase ligand-receptor binding and lead to increased effectiveness of the compound[25].

Alpha-hederin

Alpha-hederin is found in trace amounts in the *Nigella* seed. Additionally, it has anti-cancer and anti-diabetic pharmacological action (Table 1). Surprisingly, it was one of the five constituents that had a stable interaction with 5KIR. Alpha-hederin appeared to have a high delta G value compared to other constituents but did not exceed that of Vioxx (Table 3). This decrease in delta G could be attributed to the presence of multiple phenylalanine residues as well as basic residues (like lysine) that can cause distortions in the structure. The presence of multiple tyrosine residues in this interaction denotes that there are polar contacts that can stabilize the structure.

In conclusion, thymoquinone and nigellidine were found to have the most stable interaction with COX-2 targets. This research indicates that traditional medicine has the potential to aid in the first step of the drug discovery process: identifying chemical compounds. Using naturally occurring compounds can greatly reduce adverse effects that result from using drugs like NSAIDs. However, further analysis and studies are needed to understand if these compounds can interact unfavorably with other drugs or molecules in the human body■

5 References

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