The Potency of Secondary Metabolites in *Dracaena angustifolia* for Cyclooxygenase-2 (Cox-2) Inhibitors for The Treatment of Inflammation Disease: An In-Silico Study

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Abstract. Cyclooxygenase-2 (COX-2) plays a critical role in the development of colorectal carcinoma (CRC) and serves as a primary target for reversing colorectal tumorigenesis through the utilization of nonsteroidal anti-inflammatory drugs. The plant *Dracaena angustifolia* has been researched for its potential anti-inflammatory compounds found in its leaves, stem bark, and root bark. This research involved the extraction of leaves, stem bark, and root bark from *D. angustifolia* using methanol as the solvent. The findings of the study revealed variations in the content of flavonoids and total phenols among these extracted components, with the stem bark showing the highest concentration. Additionally, as part of the ongoing doctoral research conducted by the first author, the study incorporated in silico analyses that encompassed molecular docking simulations of multiple compounds naturally occurring in this plant. These compounds include drangustosides A; (R)-2-(3-hydroxy-5-methoxyphenyl)-5-methoxy-8-methylchroman-7-ol; 5,7-dihydroxy-3-(4-hydroxybenzyl)-8-methyl-4H-chromen-4-one; 5,7-dihydroxy-3-(4-hydroxybenzyl)-4H-chromen-4-one; and namonin A, which were evaluated against the COX-2 protein target. Their binding affinities and types of interactions were compared with COX-2 inhibitors such as celecoxib, rofecoxib, and valdecoxib, as well as classical NSAIDs like aspirin, ibuprofen, and indomethacin. As a result, molecular docking indicated that these five compounds have favorable binding affinity energies and exhibit binding site similarity with commonly used drugs. Therefore, these compounds have the potency to act as anti-inflammatory agents targeting COX-2.

Keywords: COX-2 Inhibitor, Dracaena A ngustifolia, Anti-Inflammatory, Molecular Docking

T. Triwiyanto et al. (eds.), *Proceedings of the 6th International Conference of Health Polytechnic Surabaya (ICoHPS 2023)*, Advances in Health Sciences Research 72,
https://doi.org/10.2991/978-94-6463-324-5_19

1 Introduction

Colorectal cancer ranks among the prevalent forms of malignant tumors. Numerous epidemiological studies, along with a substantial body of experimental research, have consistently demonstrated a strong association between chronic inflammation[6] and the initiation and progression of colorectal cancer[28]. Colorectal cancer (CRC) is a diverse disease, encompassing at least three primary variants: hereditary, sporadic, and colitis-associated CRC. Substantial evidence underscores genetic mutations, epigenetic modifications, chronic inflammation, dietary habits, and lifestyle choices as risk factors for CRC[13]. The connection between persistent inflammation and cancer revolves around cytokines and agents within inflammatory pathways, which play roles at various stages of tumorigenesis. Cyclooxygenases (COXs) represent a group of enzymes responsible for facilitating the critical step in prostaglandin production. This enzyme family comprises three members: COX-1, widely found and implicated in maintaining internal balance; COX-2, the inducible form that becomes more active during both inflammation and cancer; and COX-3, expressed in the brain and spinal cord, with functions yet to be fully understood. COX-2 has been observed to regulate cell proliferation and apoptosis primarily in solid tumors, such as colorectal, breast, and prostate cancers, and more recently, in hematological malignancies[23].

The occurrence of colorectal cancer (CRC) often coincides with the excessive activation of the cyclooxygenase-2 (COX-2) gene, with elevated levels most frequently observed in the initial stages of colorectal lesions[12]. COX-2 becomes active when exposed to inflammatory triggers and plays a significant role in the advancement and growth of colorectal cancer (CRC). COX-2 has a significant role in the development of colorectal cancer (CRC) and represents a primary target for the suppression of colorectal tumor formation through non-steroidal anti-inflammatory drugs[17]. The expression of COX-2 is an initial occurrence in the development of rectal cancer[5] and is triggered by inflammatory stimuli[20]. Given the elevated presence of cyclooxygenase-2 (COX-2) in most colorectal cancer tissues and its association with poorer survival in CRC patients, researchers have aimed to assess the impacts of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors (COXIBs) on both the prevention and treatment of CRC[25]. COX-2 is a crucial molecule implicated in the advancement of both sporadic and hereditary colorectal cancer, and the utilization of COX-2 inhibitors presents a promising avenue for the treatment of colorectal cancer[16].

The secondary metabolites of natural products can act as anti-inflammatories. Flavonoids are versatile compounds that have gained growing interest for their anti-inflammatory and pain-relieving characteristics. They inhibit the production of inflammatory agents like IL-1, TNF-α, NO, and COX-2, as well as reduce the expression of VEGF and ICAM-1. Additionally, they suppress the activation of STAT3, NFkB, the NLRP3 inflammasome, and MAP kinase pathways[9]. Phenolic compounds exhibit exceptional pharmacological and nutritional characteristics, including antimicrobial, antibacterial, antiviral, anti-atherosclerosis, antioxidant, and anti-inflammatory properties. Steroidal saponins and sapogenins have garnered considerable interest as significant natural anti-inflammatory agents with the capacity to influence the function of numerous inflammatory cytokines across diverse inflammatory models[19] [15]. Based on this, this article discusses the analysis of flavonoid and polyphenol content in the leaves, stem bark, and root bark of the *D. angustifolia* plant, and an in silico study of

the known compounds in these plant parts is conducted. In this plant have been found several active compounds such as drangustosides A in its leaves[10], R)-2-(3-hydroxy-5-methoxyphenyl)-5-methoxy-8-methylchroman-7-ol; 5,7-dihydroxy-3-(4-hydroxybenzyl)-8-methyl-4H-chromen-4-one; 5,7-dihydroxy-3-(4-hydroxybenzyl)-4H-chromen-4-one in bark[29], and namonin A in root [24], but their potential as anti-inflammatories have not been widely reported.

2 Materials and Methods

The research material used in this study is the simplisia of leaves, stem bark, and root bark *D. angustifolia*, methanol, Folin–Ciocalteu, sodium carbonate, gallic acid, aluminum chloride, quercetin, and ethanol. The tools used in this study were a bottle of maceration (Pyrex), rotary evaporator, vortex, test tubes, analytical balance, and Biochrom spectrophotometer.

Each simplisia was weighed at 100 grams, then mixed with 800 mL of methanol and macerated for 72 hours. Remaceration was performed three times. The macerated result was then concentrated using a rotary evaporator, resulting in a thick extract. Each extract was subsequently analyzed for its flavonoid and total phenol content. The total phenolic analysis was conducted by dissolving 0.05 grams of the extract in 5 ml of 99.9% methanol, homogenized, and centrifuged at 3000 rpm for 15 minutes to obtain the supernatant. The supernatant was filtered to obtain the filtrate. Then, 0.4 ml of the filtrate was pipetted into a reaction tube, added with 0.4 ml of Folin–Ciocalteu reagent, vigorously vortexed until homogenous, and allowed to stand for 5 minutes before adding 4.2 ml of a 5% sodium carbonate solution. The sample was left to stand at room temperature for 30 minutes before measuring the absorbance at a wavelength of 760 nm. A standard curve was created by dissolving gallic acid in distilled water at various concentrations (10-100 mg/L). Total phenol calculation was done using the regression equation formula $y = ax + b$[22]. The flavonoid content analysis was carried out by dissolving 0.05 grams of the extract in 5 ml of 99.9% ethanol, homogenized, and centrifuged at 3000 rpm for 15 minutes to obtain the supernatant. The supernatant was filtered to obtain the filtrate. Then, 0.5 ml of the filtrate was pipetted into a reaction tube, added with 0.5 ml of ethanol and 1.0 ml of 2% $AlCl_3$ reagent, vigorously vortexed until homogenous, and left to stand for 30 minutes at room temperature before measuring the absorbance at a wavelength of 415 nm. A standard curve was created by dissolving quercetin in 99.9% ethanol at various concentrations (0-30 mg/L). Flavonoid calculation was done using the regression equation formula $y = ax + b$.

The material used in this study is the macromolecular crystal structure of the COX-2 receptor with the PDB ID code 3Q7D[27]. The receptor macromolecule was obtained from the Protein Data Bank website (https://www.rcsb.org/structure/3Q7D) and has a resolution of 2.4 Å. The compound used in this study is the drangustosides A, (R)-2-(3-hydroxy-5-methoxyphenyl)-5-methoxy-8-methylchroman-7-ol; 5,7-dihydroxy-3-(4-hydroxybenzyl)-8-methyl-4H-chromen-4-one; 5,7-dihydroxy-3-(4-hydroxybenzyl)-4H-chromen-4-one; and Namonin A compound derived from *D. angustifolia*, the drug compound used in COX-2 inhibitors, such as celecoxib, rofecoxib, and valdecoxib, as well as classical NSAIDs like aspirin, ibuprofen, and indomethacin. The software used in the molecular docking process includes the Windows 10 Operating

System, Pyrex 8.0, Chimera 1.16, Marvinscetch 22.22, BIOVIA Discovery Studio version 2020. To validate the docking technique, the co-crystal ligand was re-docked into the binding pocket of the protein. The optimal configuration of the co-crystal ligand was selected and compared to the original co-crystal ligand before docking, and the Root-Mean-Square Deviation (RMSD) was calculated. Additionally, the structural arrangement of each ligand was analyzed in terms of binding energy and its interactions with amino acids. The computational hardware utilized for these analyses included a computer equipped with an Intel(R) Core(TM) i3-10110U CPU @ 2.10GHz 2.59 GHz processor and 8.00GB of installed RAM.

3 Results

The results of quantitative tests for flavonoid and total content in each part of the *D. angustifolia* plant extract using methanol are presented in Fig. 1.

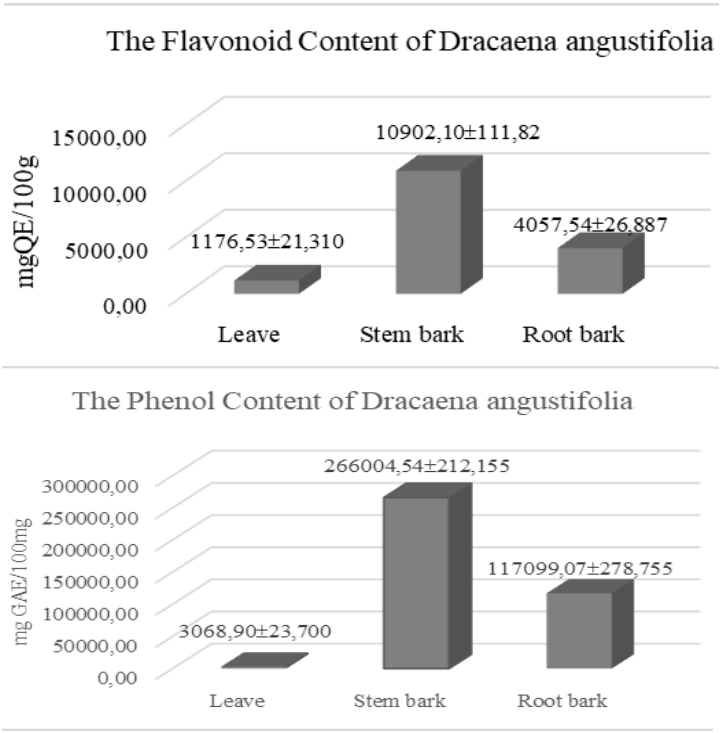


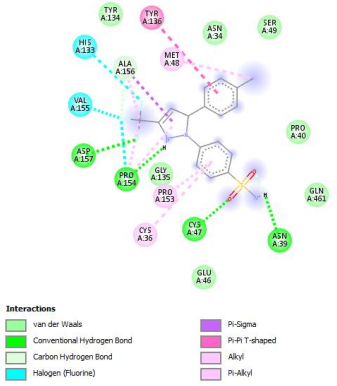
Fig. 1. The flavonoid and phenol content in each part of the Dracaena angustifolia plant extract using methanol

Docking simulation between receptor 3Q7D and compounds with a grid box size of X:-37.1435, Y:44,5656, Z:23.3799, and dimension (Angstrom) X:82.1982, Y:74.0041, Z:65.0858. The results of the docking simulation using Pyrex 8.0 application yielded the binding free energy values, which represent the stability parameter of the

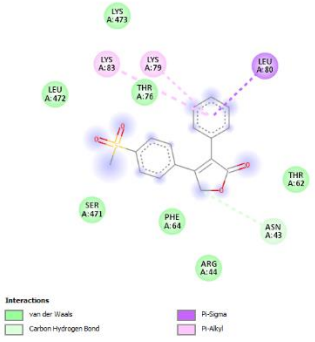
conformations of these compounds on the affinity side with receptor 3Q7D. Molecular interactions with amino acids on the receptor were analyzed using Discovery Studio 2021 application. The results of the simulation can be seen in Table 1 and Fig. 2.

Table 1. Binding affinity compounds with receptor 3Q7D

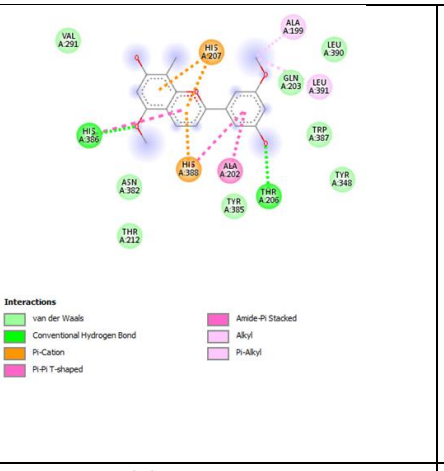
Compounds	molecular formula	molecular weight (g/mol)	binding affinity (kcal/mol)
Celecoxib	$C_{17}H_{14}F_3N_3O_2S$	381.37	-8.2
rofecoxib	$C_{17}H_{14}O_4S$	314.36	-6.9
valdecoxib	$C_{16}H_{14}N_2O_3S$	314.36	-8.4
Aspirin	$C_9H_8O_4$	180.159	-6.5
Ibuprofen	$C_{13}H_{18}O_2$	206.285	-6.7
indomethacin	$C_{19}H_{16}ClNO_4$	357.79	-7.3
drangustosides A	$C_{44}H_{70}O_{17}$	871.027	-10.8
(R)-2-(3-hydroxy-5-methoxy-phenyl)-5-methoxy-8-methylchro-man-7-ol	$C_{18}H_{20}O_5$	316.353	-7.7
5,7-dihydroxy-3-(4-hydroxyben-zyl)-8-methyl-4H-chromen-4-one	$C_{17}H_{14}O_5$	298.294	-7.6
5,7-dihydroxy-3-(4-hydroxyben-zyl)-4H-chromen-4-one	$C_{16}H_{12}O_5$	284.267	-7.5
Namonin A	$C_{57}H_{84}O_{26}$	1185.273	-8.7



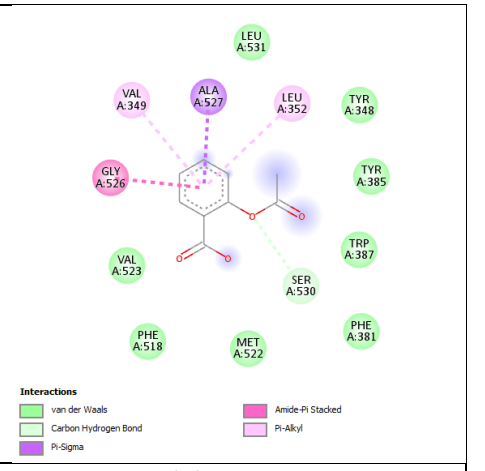
(a) Celecoxib



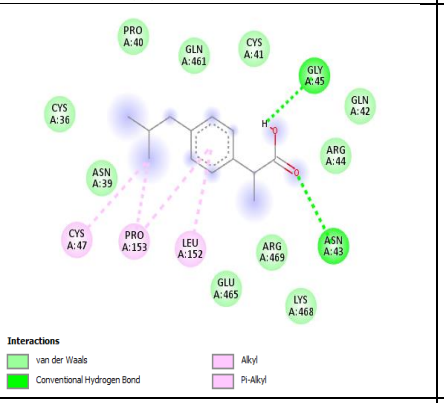
(b) Rofecoxib



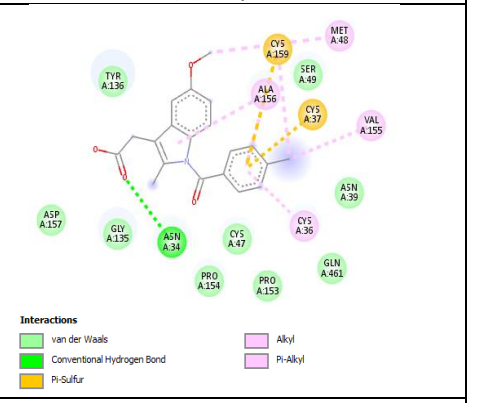
(c) Valdecoxib



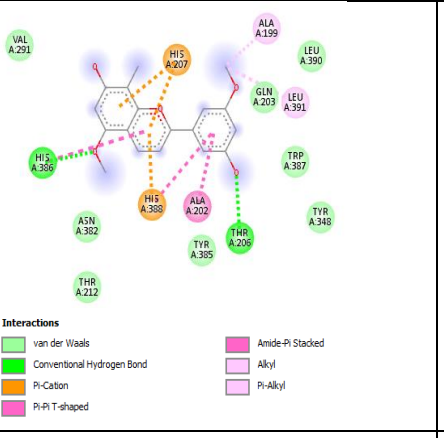
(d) Aspirin



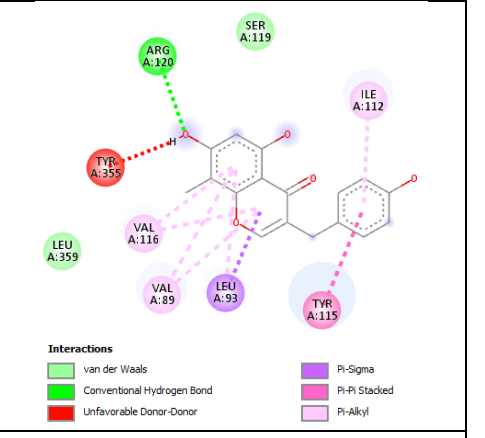
(e) Ibuprofen



(f) Indomethacin



(g) (R)-2-(3-hydroxy-5-methoxyphenyl)-5- methoxy-8-methylchroman-7-ol



(h) 5,7-dihydroxy-3-(4-hydroxybenzyl)-8-methyl-4H-chromen-4-one

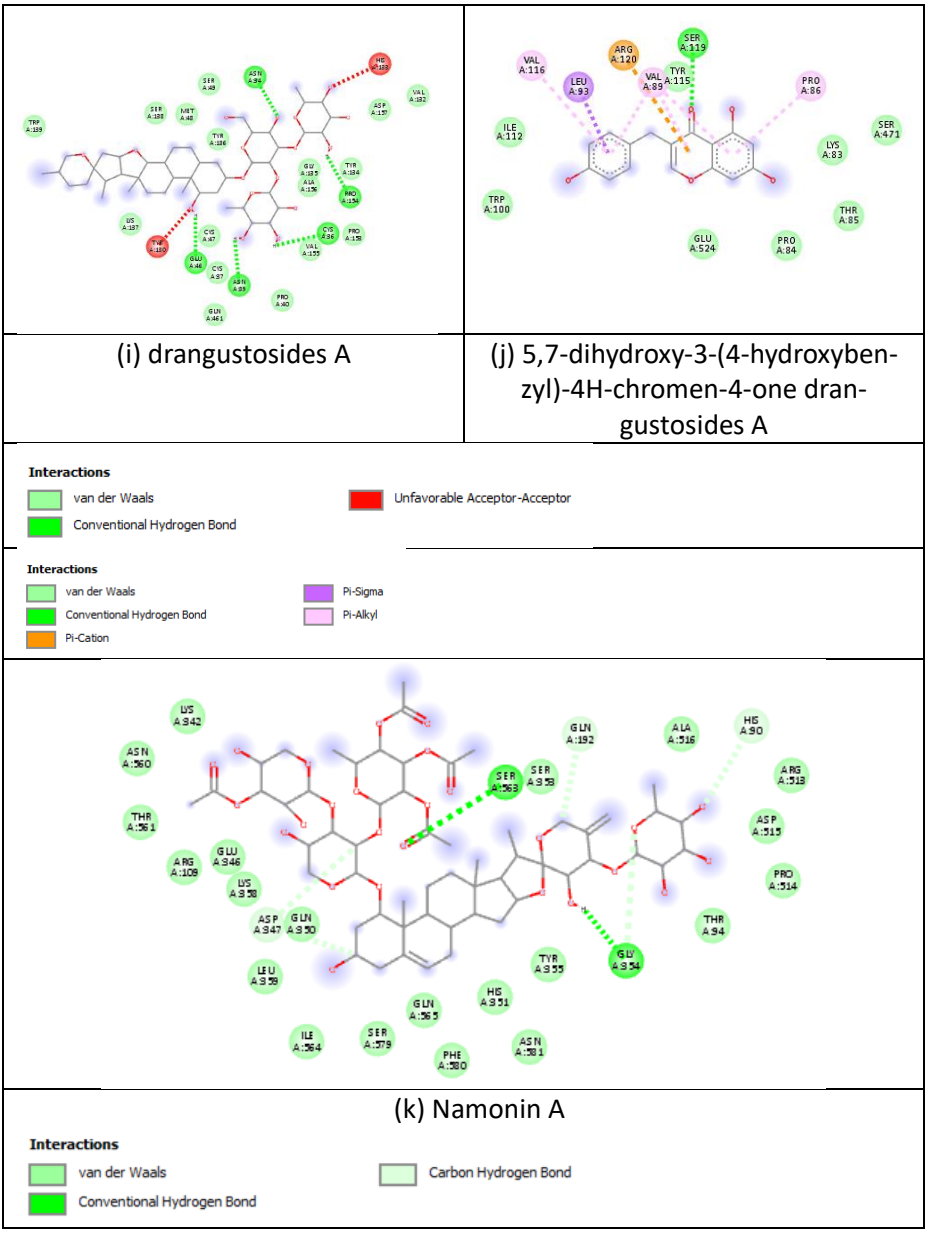


Fig. 2. Visualization of the interaction between the target protein (3Q7D) and its ligand

4 Discussion

Based on Figure 1, the flavonoid and total phenol content in the methanol extract of the stem bark part is higher compared to that in the leaves and root bark. The methanol

extract of the root bark has the highest content of flavonoids and total phenols after the stem bark. Flavonoids come in various classes and, although they have distinct structures, they all share a fundamental framework composed of three rings, collectively known as the flavan nucleus. Structure variations are primarily seen in the arrangement of substitutions within one of these rings. The positioning of the hydroxyl group (–OH) in one of these rings determines how flavonoids function and gives rise to their multifaceted activity. In a wide range of nutraceutical, pharmacological, therapeutic, and cosmetic applications, flavonoids are now seen as an essential component[18]. Flavonoids are widely recognized for their antioxidant, pain-relieving, and anti-inflammatory properties, anti-mutagenic, and anti-carcinogenic effects, and they have established themselves as safe options in both preclinical and clinical settings[9]. Studies show that flavonoids activate antioxidant pathways that render an anti-inflammatory effect. They inhibit the secretions of enzymes such as lysozymes and β-glucuronidase and inhibit the secretion of arachidonic acid, which reduces inflammatory reactions[3].

The validation of Cyclooxygenase (COX-2) as a molecular target for the treatment of inflammatory conditions led to this study, which aimed to identify potential COX-2 inhibitors through the use of pharmacophore modeling. In this article, molecular docking is conducted on compounds known to exist in various parts of the *D. angustifolia* plant. The leaves of this plant contain drangustosides A, which exhibit anti-inflammatory activity as demonstrated by the generation of superoxide and the release of elastase by human neutrophils in response to fMLP/CB[10]. The stem bark of this plant contains flavonoid compounds, including (R)-2-(3-hydroxy-5-methoxyphenyl)-5-methoxy-8-methylchroman-7-ol; 5,7-dihydroxy-3-(4-hydroxybenzyl)-8-methyl-4H-chromen-4-one; 5,7-dihydroxy-3-(4-hydroxybenzyl)-4H-chromen-4-one, which also possesses anti-inflammatory activity[29]. Meanwhile, in its roots, there is a compound called namonin A, which exhibits antiproliferative activity against fibrosarcoma cancer cells[24]. The protein target used in molecular docking is associated with COX-2 and has the PDB ID 3Q7D[21]. This type of receptor has been employed in the evaluation of chemical compounds for anticancer purposes related to COX-2 inhibition[27]. The drug compounds used for comparing the binding include COX-2 inhibitors like celecoxib, rofecoxib, and valdecoxib[8], as well as traditional NSAIDs such as aspirin, ibuprofen, and indomethacin[4]. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly utilized as pain relievers and anti-inflammatory agents for the treatment of diseases characterized by inflammation. These conditions include dysmenorrhea, osteoarthritis, rheumatoid arthritis, gout, ocular inflammation, ankylosing spondylitis, actinic keratosis, tendinitis, and bursitis. However, the prolonged use of traditional NSAIDs (tNSAIDs) such as ibuprofen, indomethacin, diclofenac, ketoprofen, naproxen, piroxicam, and nabumetone is linked to gastrointestinal bleeding, ulceration, and perforation[14]. The interaction between compounds found in *D. angustifolia* and specific proteins presents the possibility of developing medications beyond NSAIDs.

The results of molecular docking indicate differences in binding energy between the ligands and the receptor (Table 1). The optimal docking outcomes can be assessed by contrasting the ΔG. The Gibbs binding energy serves as an indicator of the binding strength between a ligand and receptor (affinity). A lower Gibbs binding energy value (tending toward negative values) signifies a higher level of stability in the bond between the ligand and receptor[2]. In Table 1, the molecular docking results for the ID: 3Q7D protein reveal the compounds with the most favorable docking scores. Specifically,

Aspirin exhibits a ΔG value of -6,5 kcal/mol. On the other hand, the compound that demonstrates the best docking results is drangustosides A, with a ΔG of -10.8 kcal/mol. Compounds from the *D. angustifolia* plant that have been identified demonstrate binding energies that are comparable to those of COX-2 inhibitors and NSAIDs drugs. The ΔG data regarding free binding energy reveals that the most stable compound is drangustosides A, followed by namonin A and 5,7-dihydroxy-3-(4-hydroxybenzyl)-8-methyl-4H-chromen-4-one. The flavonoid compounds found in the stem bark of this plant show consistent binding energies. Compound stability is indicated by its low binding energy, and lower binding energy, along with stronger non-covalent interactions, can lead to more spontaneous reactions between ligands and proteins[2]. The anti-inflammatory properties of flavonoids are achieved through various mechanisms, including the inhibition of proinflammatory enzymes such as lipooxygenase, Cyclooxygenase-2, and iNOS. At the molecular level, flavonoids stimulate protein kinase C, phase II antioxidant and detoxifying enzymes, and mitogen-activated protein kinase (MAPK)[1]. Therefore, they have the potential to be developed as anti-inflammatories in the future.

Flavonoid compounds predominantly exert their effects on iNOS, COX-2, and NFkB by utilizing the PI3K/Akt pathway. These findings lead to two main conclusions. Firstly, flavonoids demonstrate promising potential as effective agents against colon cancer, potentially due to their ability to impede cancer cells through multiple pathways. Secondly, there appears to be a correlation between the chemical structure of flavonoids and specific signaling pathways. Despite sharing a common core ring structure, each compound may target a distinct signaling pathway. Furthermore, while certain flavonoids exhibit potent activity against colon cancer, there is limited information available regarding the specific pathways involved. Further clinical and preclinical investigations are necessary to fully understand the role of flavonoids in combating colon cancer[11].

The observation of amino acid residues resulting from the interaction between the compounds and the target protein serves the purpose of recognizing the interactions that occur, believed to be responsible for the pharmacological effects exhibited by the compounds, such as its role as a COX-2 inhibitor. These interaction bonds encompass hydrogen bonds, hydrophobic interactions, Van der Waals interactions, electrostatic interactions, halogen bonds, and other bonds. Hydrogen bonds have a vital role in both impeding molecular protein complexes and enhancing the stability of protein-ligand complexes, ultimately influencing biological activity[26]. Despite being the strongest among non-covalent bonds, hydrogen bonds are still weaker than ionic or covalent bonds. As a result, the amino acid with the highest number of hydrogen bonds is likely to be the foremost factor contributing to achieving the best level of activity. The types of amino acid residues bound through hydrogen bonds are aspirin (Ser530), ibuprofen (Asn43 and Gly45), indomethacin (Asn34), celecoxib (Asp157, Pro154, Cys47, Asn39), rofecoxib (Asn43), valdecoxib (Asp314, Arg307, Val261, Glu260), drangustosides A (Glu46, Asn39, Pro154, Cys96, Asn94), (R)-2-(3-hydroxy-5-methoxyphenyl)-5-methoxy-8-methylchroman-7-ol (His386, Thr206), 5,7-dihydroxy-3-(4-hydroxybenzyl)-8-methyl-4H-chromen-4-one (Arg120), 5,7-dihydroxy-3-(4-hydroxybenzyl)-4H-chromen-4-one (Ser119), and Namonin A (Ser563, Gly354).

The compounds in the stem bark, which are flavonoids, have numerous other bonds with amino acid residues, in addition to hydrogen bonds. Flavonoids exhibit strong anticancer activity and can potentially exert their effects through multiple mechanisms,

including the inhibition of COX, LOX inhibition, suppression of COX transcription, and other mechanisms that result in reduced levels of inflammatory prostaglandins[7]. Based on the molecular docking results, it is evident that the compounds found in various parts of the *D. angustifolia* plant have the potential as COX inhibitors.

5 Conclusion

The methanol extracts from the leaves, stem bark, and root bark of the *Dracaena angustifolia* plant exhibit variations in flavonoid and polyphenol content. The study's findings show discrepancies in both flavonoid and total phenol content among these extracts, with the stem bark containing the highest concentration, followed by the root bark. Flavonoids and polyphenols have the potential to prevent inflammation that occurs in cases of cancer, including colorectal cancer.

Some compounds found in *D. angustifolia* have the potential as anti-inflammatories against COX-2. Molecular docking approaches are employed to identify compounds with potential anti-inflammatory properties by predicting their interactions with target proteins or receptors. These predictions can provide information about the inhibition of receptor activity by the compounds, which are also compared to drugs commonly used in the treatment of inflammation related to COX-2 and colorectal cancer. Based on the molecular docking results, drangustosides A; (R)-2-(3-hydroxy-5-methoxyphenyl)-5-methoxy-8-methylchroman-7-ol; 5,7-dihydroxy-3-(4-hydroxybenzyl)-8-methyl-4H-chromen-4-one; 5,7-dihydroxy-3-(4-hydroxybenzyl)-4H-chromen-4-one; and namonin A were found to bind to the active site of the COX-2 receptor (PDB ID 3Q7D). Their binding affinities and interaction patterns were assessed in comparison to well-known COX-2 inhibitors like celecoxib, rofecoxib, and valdecoxib, along with traditional NSAIDs such as aspirin, ibuprofen, and indomethacin. The molecular docking analysis revealed that these five compounds displayed favorable binding affinity energies and shared binding site characteristics with commonly prescribed drugs. Consequently, these compounds hold the potential to function as anti-inflammatory agents that target COX-2.

Furthermore, research is necessary for the isolation of compounds found in different parts of the *D. angustifolia* plant that have the potential as anti-inflammatory and anti-colorectal cancer agents. The development of in vitro and in vivo studies regarding the potential of these compounds is essential to obtain more comprehensive data. Molecular docking approaches in other pathways related to anti-inflammatory and anti-colorectal cancer activities of the compounds in *D. angustifolia* should also be conducted, providing more supportive data regarding the plant's potential.

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