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Computational exploration of flavonoids from the genus *Knema* with anti-inflammatory potential

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Abstract: Inflammation, a widespread biological process linked to various diseases, poses a significant global health challenge. Recent research targeting the development of new anti-inflammatory drugs has prioritized plant-derived compounds due to their cost-effectiveness and minimal side effects compared to synthetic drugs. Flavonoids, polyphenolic compounds in plants, show potential for treating inflammation-related diseases. This study evaluates the anti-inflammatory activity of flavonoids from the *Knema* genus, a member of the Myristicaceae family. We focused on inhibiting two pro-inflammatory proteins, human and murine interleukin-1B (IL-1) and human interleukin-6 (IL-6). Molecular docking and ADMET prediction identified sulfuretin and (-)-catechin with high binding affinity to IL-6, whereas 4'-hydroxy-7-methoxyflavanone and 7,2'-dihydroxy-6,8-dimethyl-4',5'-methylenedioxyflavan stably bind IL-6. Molecular interaction analyses revealed that hydrogen and pi-sigma bonds contribute to the interaction. Notably, these flavonoids exhibited affinities comparable to celecoxib. Our computational predictions support the suitability of these flavonoids as drug candidates, indicating their promise as natural anti-inflammatory agents capable of modulating pro-inflammatory signaling pathways.

Keywords: printed circuit boards; recycling; shanking table; copper; anova

INTRODUCTION

Inflammation is a complex biological response activated by the immune system to injury, infection, or foreign substances.[1] It is a protective mechanism that helps to remove harmful stimuli and initiate tissue repair.[2] Signs of acute inflammation include redness, warmth, swelling, and pain caused by increased blood flow to the affected area. These bring white blood cells that fight infection

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and remove damaged tissue.[3] Chronic inflammation, on the other hand, is a long-term response that can last for months or even years and is associated with various diseases such as rheumatoid arthritis, asthma and cancer.[4-6] Chronic inflammation can result from several factors, including poor diet, lack of exercise, exposure to toxins and certain medical conditions.[7-9] Anti-inflammatory medications such as celecoxib, ibuprofen, aspirin and corticosteroids can be used to reduce inflammation, but also have side effects.[10-12]

In recent years, natural products have gained significant attention as potential sources of new drugs for various diseases, including those associated with inflammation.[13] The growing interest in natural products is driven by the need for safe and effective alternatives to synthetic drugs, which often have undesirable side effects.[14] Additionally, natural products have evolved over millions of years to interact specifically with biological systems, making them more likely to be effective as drugs.[15] Plants have been used in traditional medicine for years and remain an essential therapeutic agent source. In particular, flavonoids, a large class of natural compounds widely distributed in plants, have diverse biological activities, including anti-inflammatory activity.[16] Flavonoids inhibit the activity of pro-inflammatory enzymes such as cyclooxygenase and lipoxygenases, and modulate the production of pro-inflammatory cytokines such as TNF-alpha, IL6 and IL-1.[17] Furthermore, flavonoids suppress the activation of inflammatory signalling pathways such as the nuclear factor-kappa B (NF-kB) pathway.[18]

The Myristicaceae is a large family of flowering plants that includes over 1000 species. It is widely distributed in tropical regions and has a long history of medicinal use in traditional medicine. Extracts and compounds isolated from Myristicaceae species exhibit various medicinal properties, including anti-inflammatory activity.[19] For example, studies have shown that malabaricone C, isolated from *Myristica fragrans* have shown antioxidant (IC_{50} value 6.56 µg/mL) and anti-inflammatory activities (IC_{50} value 2.06 µg/mL).[20] Similarly, compounds isolated from other species of *M. dactyloides*, *M. malabarica,* and *M. cinnamomea* possess anti-inflammatory, antioxidant, and analgesic properties.[20]

The genus *Knema,* in particular, is a member of the Myristicaceae family with anti-inflammatory, antioxidant, antinematodal, and anticancer properties.[21,22] In this study, we investigated thirty-five flavonoids isolated from the genus *Knema* for their anti-inflammatory activity. Two pro-inflammatory proteins, human and murine interleukin-1B (IL-1) and human interleukin-6 (IL-6), were targeted for potential inhibition using the *Knema* flavonoids. Our findings provide insights into the ability of natural compounds from the Myristicaceae family, particularly those of the genus *Knema*, as possible alternatives to reduce inflammation and prevent the development of chronic diseases associated with excessive or prolonged inflammation.

EXPERIMENTAL

Preparation of ligands

Thirty-five flavonoids isolated from the genus *Knema* were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) as SDF files. The standard drug, celecoxib, was also included in the study as a benchmark for comparison. The openbabel tool[23] embedded in PyRx[24] was used to perform energy minimization for each ligand separately using the default parameters of steepest descent steps 100 with step size 0.02 (Å) and conjugate gradient steps 100 with step size 0.02 (Å), whereas the update interval was fixed at 10.[25]

Preparation of the target protein

The crystal structures of IL-1 and IL-6 with PDB ID 5I1B and 1ALU, respectively, were accessed from the Protein Data Bank (PDB) (http://www.rcsb.org). Before docking, water molecules, other atoms, and ligands cocrystallized with the protein were removed with the Biovia Discovery Studio 2021 Client. [26] The protein structure was minimized by using the conjugate gradient algorithm and the AMBER force field with UCSF Chimera 1.10.1.[27]

Molecular docking

AutoDock 4.2[28] in PyRx virtual screening tool was used for the molecular docking experiment to dock the ligands to the pro-inflammatory receptors. The center and size were adjusted to contain the residue in the binding pocket as reported by [29] and allow the ligands to move freely. The exhaustiveness value was set to 8 to maximize the binding conformational analysis, and the docked compounds were evaluated based on their lowest binding energy (kJ/mol). The binding energy (ΔG) in kJ/mol and the inhibition constants (*Ki*) of isolated ligands and standard drugs were determined by duplicating the docking experiments. The 2D and 3D depictions of the docking complexes were generated using Discovery Studio 2021.[25]

Evaluation of pharmacokinetics and toxicity

Drug candidates are expected to have minimal toxicity and a high pharmacokinetic profile. Therefore, using AdmetLab2 (https://admetmesh.scbdd.com) and SwissADME (http://www.swissadme.ch), the pharmacokinetic profile and toxicity of selected flavonoids were determined.[30]

RESULTS AND DISCUSSION

Cytokine formation is a critical aspect of responding to stimuli that trigger inflammation. Many cytokines and growth factors come from macrophages, which are essential cells in the immune response. However, an uncontrolled inflammatory response can lead to chronic inflammation and further tissue damage. To regulate the inflammation process, macrophages secrete various inflammatory mediators such as nitric oxide (NO), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1), prostaglandins, and IL-6.[29] In addition, suppression of macrophages or their secretions can help repair damages caused by inflammation. Many medicinal plants have been used in traditional medicine to modulate inflammation.[29] Traditional medicine utilizes both steroidal and non-steroidal anti-inflammatory drugs that suppress cyclooxygenase (COX) in treating acute inflammation. However, these treatments are ineffective in persistent

inflammatory disorders like rheumatoid arthritis or osteoarthritis.[4] As a result, there is a desire for alternative therapies with potent and less toxic agents.

Molecular docking is an indispensable tool to investigate bioactive compounds' conformation and binding mechanisms to the catalytic domain of proteins in drug discovery[31]. In the current study, we adopted this method to predict the inhibitory potential of 35 natural flavonoids from the genus *Knema* against interleukin-1(IL-1) and interleukin-6 (IL-6) by evaluating the high binding conformation and affinity. The results of the docking experiment are shown in Table 1, demonstrating that a higher binding affinity correlates with a higher docking score. The binding energies of the docked flavonoids against human IL-6 (1ALU; Figure 1a) and human and murine IL-1 (5I1B; Figure 1b) ranged from -28.79 to -10.38 kJ/mol and from - 26.11 to -14.64 kJ/mol, respectively. Among the flavonoids, sulfuretin had the highest score (-26.11 kJ/mol) against IL-6, followed by (–)-catechin whereas 4'-hydroxy-7-methoxyflavanone (-28.79 kJ/mol) and 7,2'-dihydroxy-6,8-dimethyl-4',5'-methylenedioxyflavan (-28..33 kJ/mol) displayed highest docking score against IL-1. These four compounds from *Knema* species were identified as potential inhibitors of pro-inflammatory proteins, with a binding affinity comparable to celecoxib (Table 1).

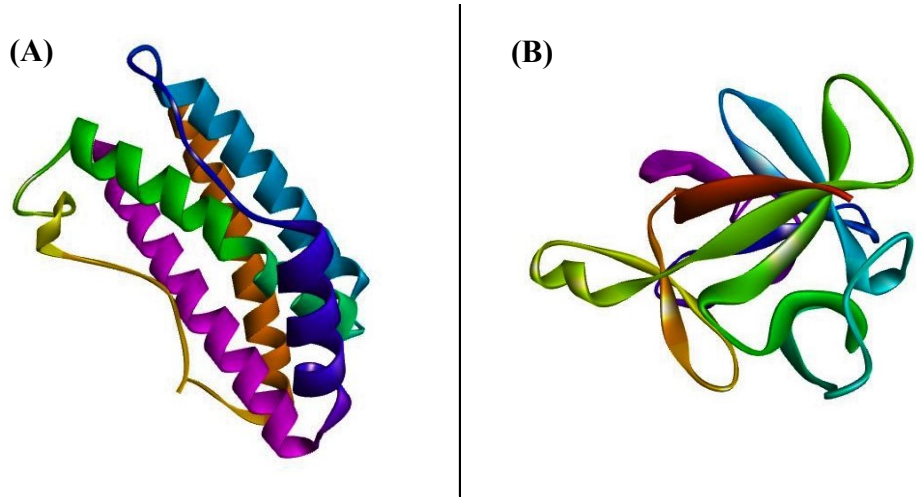

Fig. 1. Crystal structure of **(A)** human interleukin-6 (PDB ID: 1ALU) and **(B)** human and murine interleukin-1B (PDB ID: 5I1B)

Further analyses were performed, including drug-likeness, Absorption, Distribution, Metabolism, Excretion, and toxicity (ADMET). These additional steps provide a comprehensive drug-like assessment of the potential of these compounds.

TABLE I. Docking score and inhibition constant (*Ki*) of interactions between *Knema* flavonoids and pro-inflammatory proteins

No	Compounds	PubChem ID	1ALU			5I1B		
			LBE (kJ/mol)	*Ki* (μM)	nHb	LBE (kJ/mol)	*Ki* (μM)	nHb
1.	Naringenin	932	-23.22	85.33	4	-24.69	46.95	3
2.	(+)-Catechin	9064	-21.97	141.73	6	-25.65	32.24	3
3.	(-)-Catechin	73160	-25.61	32.69	5	-22.89	97.57	4
4.	Sakuranetin	73571	-23.97	62.63	2	-23.05	92.06	3
5.	Butin	92775	-18.54	570.37	4	-24.48	51.22	4
6.	Dihydrokaempferol	122850	-23.10	90.45	3	-22.09	134.59	3
7.	(*S*)-2-(3,4-dihydroxy–phenyl)-5,7-dihydroxy–chroman-4-one	440735	-23.93	63.82	2	-25.44	35.09	5
8.	Fisetinidol	442397	-20.59	248.63	3	-26.15	26.26	5
9.	Myristinin D	497362	-16.95	1.07	3	-17.66	805.35	2
10.	2-(3,4-dihydroxy–phenyl)-3,5,7-trihydroxy-chromen-4-one	5280343	-21.92	144.53	4	-22.34	121.44	5
11.	Biochanin A	5280373	-22.51	114.33	3	-24.98	42.27	2
12.	Formononetin	5280378	-25.10	39.75	3	-24.84	44.14	2
13.	Luteolin	5280445	-21.05	204.36	3	-22.09	134.05	3
14.	Isoquercitrin	5280804	-18.49	572.12	4	-10.38	15.21	3
15.	3-Methylkaempferol	5280862	-23.51	69.66	4	-22.55	111.24	3
16.	Kaempferol	5280863	-22.93	96.30	3	-26.78	20.40	4
17.	Genistein	5280961	-24.02	62.02	3	-25.56	32.98	4
18.	Sulfuretin	5281295	-26.11	25.37	2	-23.35	81.72	2
19.	4',5,7-Trihydroxy-6-methoxyisoflavone	5281811	-23.43	78.96	3	-25.48	34.09	3
20.	2'-Hydroxybiochanin A	5282075	-21.97	140.98	3	-25.48	56.90	2
21.	Astragalin	5282102	-18.24	637.53	5	-16.61	1.23	4
22.	5,7,4'-Trihydroxy-3'-methoxyisoflavone	5319744	-21.88	145.77	1	-22.55	112.69	3
23.	8-O-Methylretusin	5319771	-21.06	207.20	1	-23.81	67.48	1
24.	Proanthocyanidin A1	9872976	-19.62	362.89	2	-22.47	116.56	5
25.	4'-Hydroxy-7-methoxyflavanone	10265122	-22.97	94.38	2	-28.79	9.09	3
26.	4-[3-(2-hydroxy-4-methoxyphenyl)propyl]-2-methoxyphenol	14017333	-19.16	436.07	1	-20.50	257.86	3
27.	7,4'-Dihydroxy-3'-methoxyflavan	14157887	-24.43	52.55	2	-22.89	97.87	2
28.	5,7,3'-Trihydroxy-4'-methoxyflavan	20315197	-21.97	141.21	3	-25.31	36.64	3
29.	Virolane	21722171	-24.10	60.23	1	-24.60	48.90	2
30.	2',7-Dihydroxy-4',5'-methylenedioxy–	23724666	-24.81	44.76	2	-26.04	27.37	3

	isoflavone							
31.	7-Hydroxy-3',4'-methylenedioxyflavan 7-O-β-D-glucopyranoside	44257175	-23.22	85.47	2	-23.01	93.07	3
32.	7,2'-Dihydroxy-6,8-Dimethyl-4',5'-Methylenedioxyflavan	44257181	-23.93	64.01	2	-28.33	10.89	3
33.	2'-Hydroxy-7-methoxy-4',5'-methylene–dioxyflavan	44257183	-24.06	61.39	2	-26.53	22.36	2
34.	3,4',7-Trihydroxy–flavone 7-O-rutinoside	101422354	-14.90	2.46	2	-17.74	776.69	4
35.	Dehydrocatechin	132582811	-22.43	116.83	3	-25.73	31.07	7
36.	Celecoxib	2662	-25.06	40.58	5	-18.70	527.29	3

LBE: Ligand binding Energy; *Ki*: Inhibition constant; nHb: number of hydrogen bonds formed

Molecular interaction analysis of the sulfuretin-IL-6 complex showed two hydrogen bonds formed by Pro65 and Glu172 of IL-6 with sulfuretin at the binding site. This interaction is crucial in regulating the activity of the protein. A pi-donor hydrogen bond observed between sulfuretin and Met67 may contribute to the stability of the protein-sulfuretin complex. In addition, two pi-alkyl bonds were found between sulfuretin and Lys66 residues through ring B and ring C. Van der Waals interactions with six amino acid residues of IL-6 play a role in the overall stability of the complex (Figure 2b). Furthermore, the bioactivity of sulfuretin from *Rhus verniciflua* (Anacardiaceae) cannot be overstated. Sulfuretin, a major flavonoid component isolated from *R. verniciflua*, has demonstrated potent anti-inflammatory effects in macrophage.[32] As in the work of [32] who investigated the effect of sulfuretin on the LPS-induced iNOS and COX-2 expression in RAW264.7 macrophages. They challenged macrophages with LPS (1 μg/mL) in the presence or absence of sulfuretin at non-cytotoxic concentrations ranging from 5 to 40 μM. The results showed that sulfuretin effectively suppressed LPS-induced iNOS and COX-2 protein expression in a dose-dependent manner. Additionally, sulfuretin reduced LPS-induced mRNA expression levels of iNOS and COX-2 in a dose-dependent manner, as assessed by RT-PCR analysis. These findings underscore the remarkable anti-inflammatory potential of sulfuretin and its ability to modulate key inflammatory mediators, providing valuable insights into its therapeutic applications in inflammation-related conditions.

Catechin interacts with human IL-6 with binding energy -25.61 kJ/mol and establishes five hydrogen bonds through residues Pro65, Lys66, Met67, Glu172, and Arg179 which is among the key active residues as described in the work of [33]. These hydrogen bonds, formed between the positively charged hydrogen atom of catechin and negatively charged atoms of the residues, help stabilize the catechin-

IL-6 complex. In addition, a pi-donor hydrogen bond was observed between Met67 and catechin, while a pi-alkyl bond was formed with Phe74. Van der Waal interactions were seen between catechin and amino acid residues of IL-6 (Figure 2a). The structure of catechin-plays a critical role in its interaction with human IL-6 residues. Catechin, being a flavonoid, has a unique molecular structure that allows it to form various interactions with proteins, including hydrogen bonding, pi-pi stacking, and van der Waals interactions. These interactions enhance the stability and specificity of the interaction between catechin and IL-6, which in turn contributes to its efficacy as an anti-inflammatory agent. Catechin has demonstrated significant bioactivity in the context of inflammation, as supported by the research conducted by [34]. Their findings reveal that catechin plays a crucial role in attenuating inflammation induced by TNF-α in mature adipocytes through the activation of the AMPK/SIRT1 pathway. Celecoxib interacts with human IL-6, forming hydrogen bonds with Cys73, Lys66, Gln75, and Arg179 residues. Carbon-hydrogen bonds, pi-alkyl, and halogen bonds were also observed. However, an unfavourable interaction was also detected with Gln183 (Figure 2c). Notably, celecoxib formed fewer hydrogen bonds and favourable interactions with IL-6. Catechin and sulfuretin showed a more extensive network of interactions including pi-alkyl bonding and van der Waal's interaction. This suggests that they may have a stronger ability to regulate the inflammatory response compared to celecoxib.

Analysis of 4'-hydroxy-7-methoxyflavanone interaction with IL-1B revealed three hydrogen bonds via Leu134, Val132, and Phe133. The compound also formed a pi-donor hydrogen bond with Leu134 and a pi-alkyl interaction with Leu80. Additionally, three alkyl interactions were observed with Val132, Leu26, and Leu80. 4'-hydroxy-7-methoxyflavanone also formed a pi-anion interaction and a pi-sigma interaction with Glu25. Furthermore, eight amino acid residues of IL-1B in the binding pocket displayed van der Waals' interaction with 4'-hydroxy-7-methoxyflavanone (Figure 3A). Alkyl interactions between the ligand and Val40, Leu62, Lys65, and Met20 were observed (Figure 3b). Similarly, 7,2'-dihydroxy-6,8-dimethyl-4',5'-methylenedioxyflavan exhibited hydrogen bonds with residues Met20, Gln38 and Lys63 as well as a pi-donor hydrogen bond with Val41 whereas pi-alkyl interactions were seen with Val19 and Val40. Additionally, it's worth noting that an earlier study by [35] reported the cytotoxic potential of 4'-hydroxy-7-methoxyflavanone, isolated from the leaves of *M. calabura*, in inhibiting the growth of HT-29 (colon cancer) cell lines.

Celecoxib, an anti-inflammatory drug used as a control in this study, established hydrogen bonds with Leu20 and Tyr24. Additionally, pi-alkyl interactions with Pro131 and Phe133 and hydrophobic bonds with Pro131 and Met130 were observed. An unfavorable donor-donor interaction was found with Leu82 and van der Waals interactions with residues such as Glu25 and Leu80

(Figure 3c). Comparing the binding affinities and inhibition constants, celecoxib (-18.70 kJ/mol and 527.29 μM) had the best binding affinity and inhibition constant than 4'-hydroxy-7-methoxyflavanone (-28.79 kJ/mol and 9.09 μM), followed by 7,2'-dihydroxy-6,8-dimethyl-4',5'-methylenedioxyflavan (-28.33 kJ/mol and 10.89 μM). However, celecoxib is a small molecule and does not have similar chemical structure like catechin and sulfuretin. The structure of the flavonoids allows them to form various interactions with proteins. However, celecoxib can tightly bind IL-1B and IL-6 to effectively regulate the body's inflammatory response.

Evaluating the pharmacokinetics profile of natural compounds plays a crucial role in predicting their biological activity, as these properties are often the reason for failure of drugs in clinical trials. Several rules have been proposed to determine the suitability of small molecules as therapeutic agents, with the Lipinski rule of five (RO5) being the most widely used.[36] RO5 states that for a compound to be a good candidate for drug development, it should not violate more than one of the following criteria: molecular weight less than 500 Da, octane-water partition coefficient less than 5, hydrogen bond donor less than or equal to 5, hydrogen bond acceptor less than or equal to 10.[37] This study evaluated the selected flavonoids from *Knema* species for their adsorption, distribution, metabolism, excretion (ADME) properties, and drug likeness potential on Swissadme server.

The results show that all selected compounds fulfilled the Lipinski rule (Table 2), indicating that they have potential as therapeutic agents. Furthermore, the pharmacokinetic profile was evaluated using human intestinal absorption (HIA), blood/brain barrier (BBB), P-glycoprotein substrate (P-gp-sub), P-glycoprotein inhibitor (P-gp inh) clearance, and human colon adenocarcinoma cell line permeability (Caco-2). The results presented in Table 3 indicate that all phytochemicals fall within the recommended range for these parameters. An effective prediction of human intestinal absorption of drug molecules has been demonstrated using Caco-2 cell lines, and the blood/brain partition coefficient is crucial in evaluating drugs for the central nervous system.[31] In addition, organ toxicological evaluation for each compound was also carried out, and the results are presented in Table 4.

Most of the compounds were found to be negative for carcinogenesis, Ames toxicity, hepatotoxicity, and eye corrosion, indicating their less toxicity. These findings highlight the importance of comprehensively evaluating pharmacokinetics and toxicity for developing natural compounds as novel pharmaceutical agents.

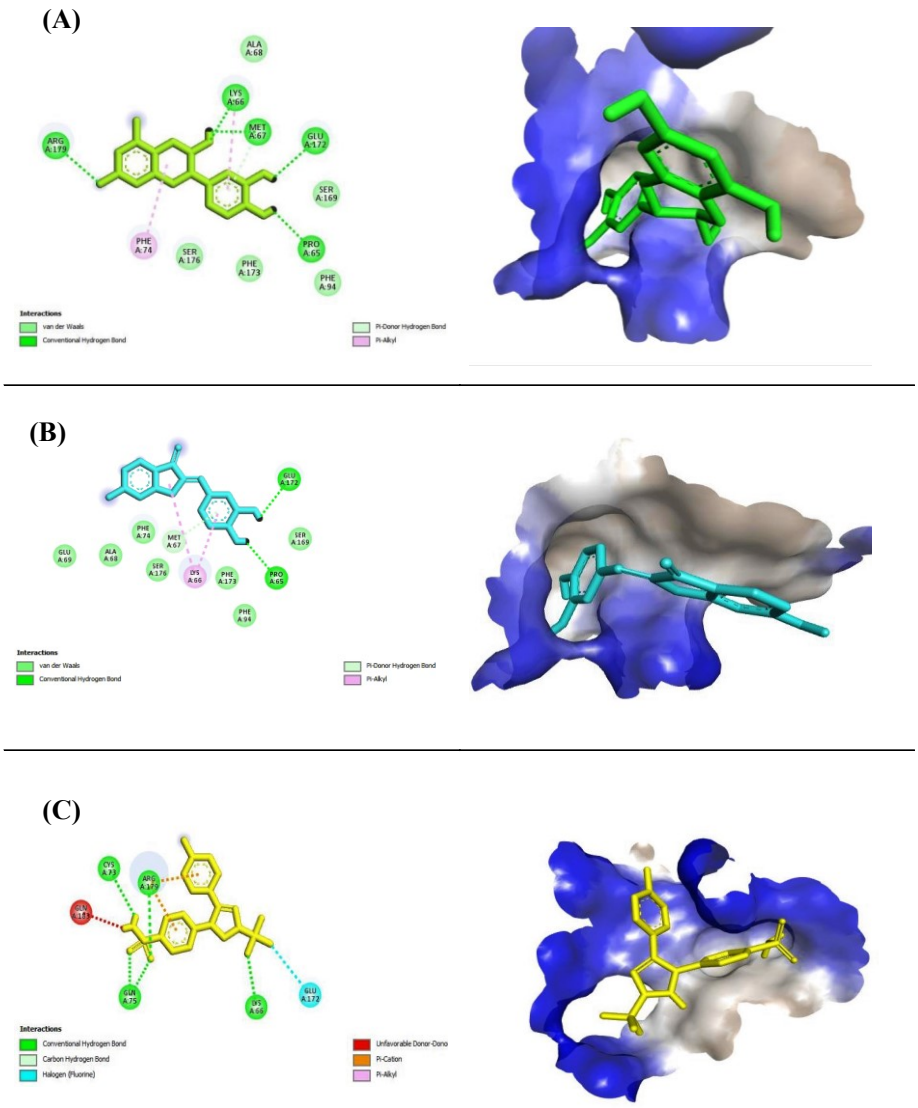

Fig. 2. A 2D and 3D interaction map of **(A)** (-)-catechin, **(B)** sulfuretin, **(C)** celecoxib with IL-1. The protein binding pocket is shown as surface representation and the ligands are presented as stick; (-)-catechin (green), sulfuretin (blue), and celecoxib (yellow).

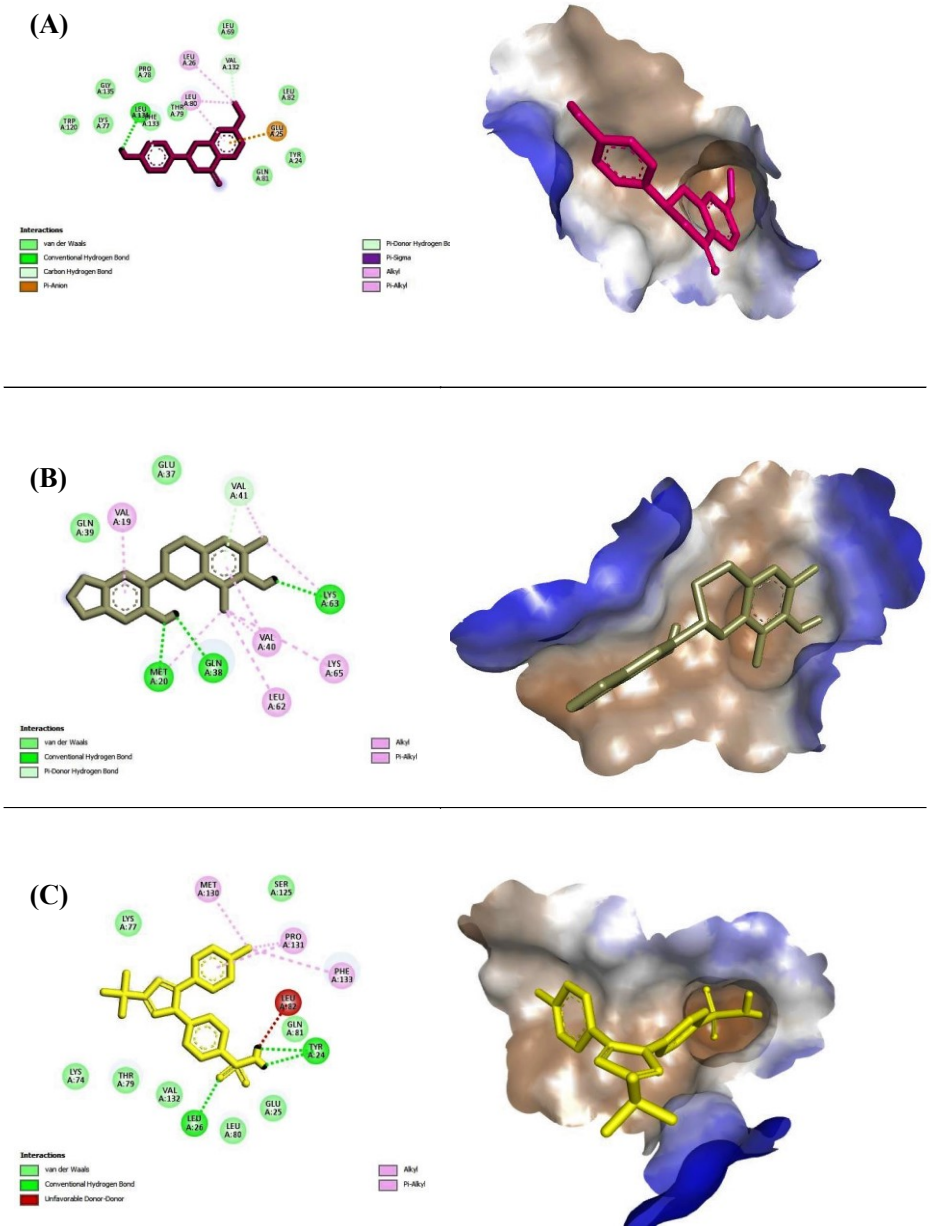

Fig 3. A 2D and 3D interaction map of **(A)** 4′-hydroxy-7-methoxyflavanone; **(B)** 7,2′-dihydroxy-6,8-dimethyl-4′,5′-methylenedioxyflavan; **(C)** celecoxib. The protein binding pocket is shown as a surface representation and the ligands are presented as sticks; 4′-hydroxy-7-methoxyflavanone (red), 7,2′-dihydroxy-6,8-dimethyl-4′,5′-methylenedioxyflavan (green) and celecoxib (yellow).

TABLE II. Drug-likeness properties of the selected *Knema* flavonoids and standard drug were calculated using Swissadme online webtool

Phytochemicals	MW	WLOGP	TPSA	HBa	HBd	RO5
(-)-Catechin	290.27	1.22	110.38	6	5	0
Sulfuretin	270.24	2.31	86.99	5	3	0
7,2'-Dihydroxy-6,8-dimethyl-4',5'-methylenedioxyflavan	314.33	3.19	68.15	5	2	0
4'-Hydroxy-7-methoxyflavanone	270.28	2.78	55.76	4	1	0
Celecoxib	381.37	5.75	86.36	7	1	0

MW: Molecular weight (130.0–725.0); HBd: Hydrogen bond donor (0.0–6.0); HBa: Hydrogen bond acceptor (2.0–20.0); TPSA: Topological polar surface area (7.0 to 200.0); RO5: Rule of five (Maximum violation: 2)

TABLE III. Pharmacokinetic profiles of the selected *Knema* flavonoids and standard drugs calculated using AdmetLab2 online webtool

Phytochemicals	Pgp-inh	Pgp-sub	HIA	Caco-2	BBB	CL
(-)-Catechin	0.008	0.032	0.016	-5.846	0.018	17.07
Sulfuretin	0.007	0.002	0.01	-5.011	0.039	11.10
7,2'-Dihydroxy-6,8-dimethyl-4',5'-methylenedioxyflavan	0.017	0.007	0.002	-4.85	0.078	19.86
4'-Hydroxy-7-methoxyflavanone	0.206	0.001	0.005	-4.583	0.175	14.7
Celecoxib	0.084	0.005	0.003	-4.767	0.586	0.99

Pgp-inh: P-glycoprotein inhibition; Pgp-sub: P-glycoprotein substrate; HIA – Human intestinal absorption; Caco-2 - human colon adenocarcinoma cell line permeability; BBB - blood–brain barrier; CL: clearance

TABLE IV. Organ toxicity prediction of the selected *Knema* flavonoids and standard drug was calculated using AdmetLab2 (online webtool)

Phytochemicals	Carc	EC	AM	HT
(-)-Catechin	0.136	0.004	0.531	0.111
Sulfuretin	0.782	0.004	0.804	0.251
7,2'-Dihydroxy-6,8-dimethyl-4',5'-methylenedioxyflavan	0.885	0.003	0.027	0.245
4'-Hydroxy-7-methoxyflavanone	0.799	0.034	0.59	0.386
Celecoxib	0.139	0.003	0.016	0.641

Carc: Carcinogenicity; EC: Eye corrosion; AM: Ames mutagenesis; HT: Hepatotoxicity

CONCLUSION

This study investigated the anti-inflammatory potential of 35 flavonoids isolated from the *Knema* genus using molecular docking against two pro-inflammatory proteins, human and murine interleukin-1B and human interleukin-6. The findings suggest that sulfuretin and (-)-catechin have high binding affinities against human interleukin-6. Moreover, 4'-hydroxy-7-methoxyflavanone and 7,2'-dihydroxy-6,8-dimethyl-4',5'-methylenedioxyflavan, displayed high binding

affinities against human and murine interleukin-1B and may act as promising natural anti-inflammatory agents by modulating pro-inflammatory signalling pathways. The significance of this study extends beyond the identification of specific flavonoids. It contributes to the growing body of evidence supporting the utilization of flavonoids as therapeutic agents for inflammatory diseases. Moreover, the highlighted compounds offer potential leads for future drug development in the quest for effective anti-inflammatory treatments. As a stepping stone, future investigations, including rigorous *in vitro* and *in vivo* experiments, are warranted to validate and expand upon the findings presented here, ultimately advancing the translational potential of these natural compounds in the realm of anti-inflammatory drug development.

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И З В О Д

РАЧУНАРСКО ИСТРАЖИВАЊЕ ФЛАВАНОИДА ИЗ РОДА *KNEMA* КОЈИ ИМАЈУ АНТИИНФЛАМАТОРНИ ПОТЕНЦИЈАЛ

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Запаљење, је раширени биолошки процес повезан са разним болестима, и представља значајан изазов за здравље у свету. Скорија истраживања која циљају нове антиинфламаторне лекове дају предност једињењима добијеним из биљака због њихове исплативости и минималних споредних ефеката у поређењу са синтетичким лековима. Флавоноиди, полифенолна једињења у биљкама, показују потенцијал за третирање болести повезаних са запаљењима. Овај рад процењује антиинфламаторну активност флавоноида из рода *Knema* (Кнема), из породице *Myristicaceae*. Фокусирали смо се на инхибирање два проинфламаторна протеина, хуманог и и мишјег интерлеукина-1Б (IL-1) и хуманог интерлеукина-6 (IL-6). Молекулски докинг и ADMET предвиђање су идентификовали сулфуретин и (-)-катехин са високим везивним афинитетом за IL-6, док 4'-хидрокси-7-метоксифлаванон и 7,2'-дихирокси-6,8-диметил-4',5'-метилендиокси-флаван стабилно везују IL-6. Анализе молекулских интеракција откривају да водоничне и *pi-sigma* везе доприносе интеракцији. Посебно, ови флаваноиди испољавају афинитете упоредиве са селекоксибом. Наша рачунарска предвиђања подржавају прикладност ових флавоноида као кандидата за лекове, указујући да су они обећавајући природни протуупални агенси способни да модулирају проинфламаторне сигналне путеве.

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