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Structure-Based Docking to Identify Anti-Inflammatory Phytochemicals Binding to Cox-2 and 5-Lox

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Abstract:

The process of inflammation is a complicated physiological reaction to noxious stimuli and is the work of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX), and is thought to be the cause of chronic inflammatory diseases, including arthritis, asthma, and inflammatory bowel disease. Phytochemicals such as flavonoids, terpenoids, alkaloids have been proposed to be a promising multi-target anti-inflammatory agent, which is safer than traditional NSAIDs because it is associated with gastrointestinal, renal, and cardiovascular side effects. The preclinical animal studies prove that such compounds are effective in reducing paw edema, leukocyte infiltration, and pro-inflammatory cytokines. The complementary structure-based molecular docking experiments identify that there is great hydrogen bonding, hydrophobic and high binding affinities with the important catalytic residues of COX-2 and 5-LOX, which support their dual-inhibitory capacity. Also, phytochemicals of various classes could be used with the help of combinatorics to obtain additive or synergistic effects, to increase efficacy with minimal doses and toxicity. The lack of bioavailability, species-specific differences, and long-term safety data are some challenges that require optimization of formulations and translation studies. The combination of in silico docking with in vivo preclinical models is, in general, a powerful platform of prioritization of phytochemical candidates and their progression to safe and effective multi-targeted anti-inflammatory drugs.

Keywords: Phytochemicals, Anti-inflammatory, COX-2, 5-LOX, Flavonoids, Terpenoids, Structure-based Docking, Preclinical Studies.

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1. INTRODUCTION

Inflammatory process is a complicated physiological reaction, which is provoked by pathogenic infections, tissue damage, or chemical irritants and is marked by the activation of

various signaling pathways and the formation of pro-inflammatory mediators. Two of the most important arachidonic acid pathway enzymes include cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX), which control the production of prostaglandins and leukotrienes respectively, which are involved in mediating inflammation, pain and tissue injury[1]. The abnormal functioning of these enzymes is also a factor in chronic inflammatory diseases, such as arthritis, inflammatory bowel disease and asthma. Traditional anti-inflammatory agents especially non-steroidal anti-inflammatory drugs (NSAIDs) typically anti-COX enzymes, but tend to have minimal effects on multi-pathway inflammation and may have side effects including gastrointestinal irritation, cardiovascular side effects, and renal toxicity. As a result, more interest is on finding safer and more efficient alternatives that can be utilized to modulate various inflammatory targets at the same time.

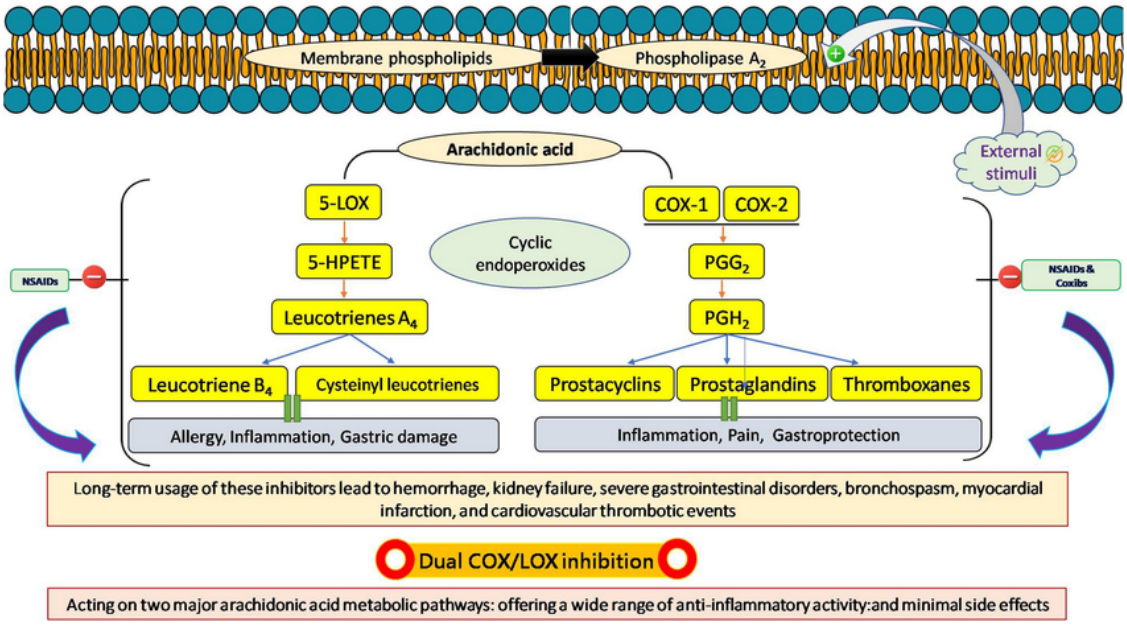

Figure 1: COX-2 AND 5-LOX[2]

Plant-derived bioactive compounds, which can be found as phytochemicals, have become potential agents of multi-target anti-inflammatory treatment. Flavonoids, terpenoids and alkaloids are also classes that have shown inhibitory effects on COX-2 and 5-LOX in preclinical research and this reduces the inflammation with minimum side effects. The discovery of structure-based molecular docking and enhanced computational methods has enabled the discovery of phytochemical interactions with target enzymes and the determination of binding affinity, key interactions and the possible simultaneous inhibition[3]. Integrating in silico docking with animal based studies will offer a good model on ranking the most promising compounds to undergo further experimental validation and therapeutic development as it will streamline the preclinical discovery process and reduce trial and error in experiments.

1.1 Background and Context

The inflammation is a defensive mechanism of the body; however, chronic or uncontrolled inflammation is one of the causes of numerous diseases. COX-2 and 5-LOX are at the centre of the inflammatory cascade and mediate the generation of prostaglandins and leukotrienes, which enhance immune responses and tissue destruction. The idea of inhibiting these enzymes has traditionally been used in the management of inflammation, and although traditional pharmacological inhibitors offer many advantages, they tend not to offer multi-pathway inhibition, and they also have significant adverse effects. A safer alternative is natural phytochemical with its structural diversity and multi-target potential. They are highly fit to be used as a complex inflammatory condition due to their ability to affect several inflammatory mediators at the same time[4].

1.2 Objectives of the Review

This review aims:

- To evaluate the dual inhibitory potential of phytochemicals, including flavonoids, terpenoids, and alkaloids, against COX-2 and 5-LOX enzymes using structure-based docking and animal models.
- To analyze the molecular interactions and binding affinities of selected phytochemicals with COX-2 and 5-LOX enzymes through in silico docking studies.
- To assess the anti-inflammatory efficacy of phytochemicals in preclinical animal models, including reductions in paw edema, leukocyte infiltration, and pro-inflammatory cytokine levels.
- To investigate the pharmacokinetics, bioavailability, tissue distribution, metabolism, and safety profile of phytochemicals in animal models.
- To explore combinatorial and synergistic effects of multiple phytochemicals for enhanced multi-target anti-inflammatory activity and identify strategies for future translational research.

1.3 Importance of the Topic

The research of phytochemicals as dual-COX-2 and 5-LOX inhibitors is of great importance since the current anti-inflammatory treatments have limitations and safer and multi-target agents are required. The molecular interaction and in vivo activity of these naturally occurring compounds are not only important in providing the mechanism concept regarding the anti-inflammatory effect of these compounds but also in choice and optimization of potential therapeutic agents. This combined methodology incorporating computational predictions with animal testing is essential in developing natural products into clinically applicable anti-inflammatory drug therapies[5].

2. PRECLINICAL INSIGHTS ON PHYTOCHEMICAL ANTI-INFLAMMATORIES

Animal models have shown that phytochemicals (flavonoids (quercetin, luteolin), terpenoids (curcumin, boswellic acids), and alkaloids (berberine, piperine)) have the ability to inhibit COX-2 and COX-5 pathways as well as regulate pro-inflammatory mediators to reduce inflammation. Structure-based docking these findings with modes, key interactions and dual inhibition potential prediction complements preclinical testing[6]. The most common methods involve the use of in vivo models such as paw edema and arthritis with computational docking software such as AutoDock and Schrodinger Suite and the results of docking are correlated with biological results. Although this integrative method gives mechanistic information and points to the safer alternatives of NSAIDs, there are drawbacks such as predictive uncertainty, species specificity and variations in bioavailability that stress that interpretation and subsequent validation should be observed closely.

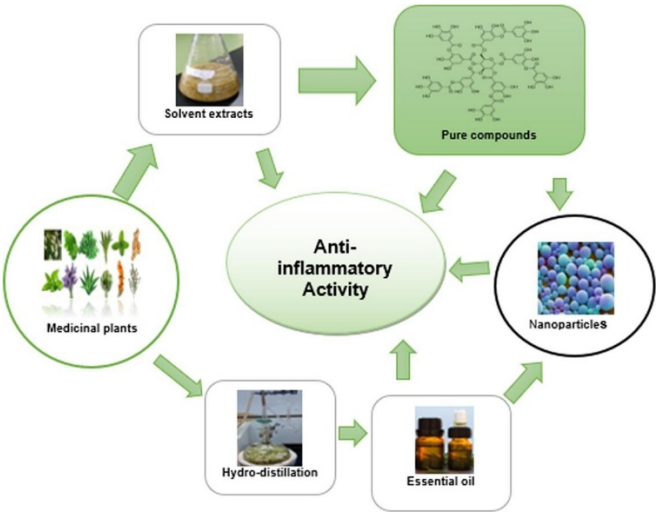

Figure 2: Anti-Inflammatory Activity[7]

2.1 Anti-inflammatory Phytochemicals in Animal Models

It has been demonstrated by animal studies that a large variety of phytochemicals can be successfully used to reduce inflammation through the modulation of the COX-2 and 5-LOX pathways[8].

- **Flavonoids:** The compounds, quercetin, luteolin, and kaempferol have been widely tested in rodent models. These flavonoids helped a great deal in reducing paw edema in carrageinan-induced inflammatory models as well as formalin-induced models, in addition to reducing levels of pro-inflammatory cytokines, such as TNF-a, IL-1b and IL-6. Their anti-inflammatory actions are credited to their inhibition of COX-2-induced production of prostaglandins and the 5-LOX-induced production of leukotrienes[9].
- **Terpenoids:** Phytochemicals such as boswellic acids and curcumin were capable of inhibiting COX-2 and 5-LOX in murine paw edema, arthritis and chronic inflammation. The boswellic acids were also found to reduce the production of leukotrienes and curcumin inhibited the production of the prostaglandins and infiltration of the

inflammatory cells in the joint tissues. Antioxidative properties were also observed with these compounds and this also contributes to their anti-inflammatory effect.

- **Alkaloids:** Alkaloids like berberine and piperine had a great decline in leukotriene levels as well as other markers of inflammation in rat models of induced inflammation. These compounds also blocked COX-2 and 5-LOX in addition to modulating signaling pathways including NF- 5, which further decreased the expression of inflammatory mediators. Together, these studies have indicated that phytochemicals may be efficient natural anti-inflammatory agents in preclinical animals.

2.2 Structure-based Docking Studies

Molecular docking based on structure gives a significant idea on the interaction of phytochemicals and inflammatory enzymes, which complement in vivo observations[10].

The binding modes and affinity of phytochemicals to the active sites of COX-2 and 5-LOX are predicted by docking studies. The predictive ability of in silico techniques is supported by the strong inhibitory activity that compounds with a high docking score has in animal models. Hydrogen bonding with catalytic residues, 5 stacking of the 5, and hydrophobic interactions are some of the key interactions that stabilize the ligand-enzyme complex.

Multi-target docking has demonstrated that some phytochemicals include curcumin and quercetin which may bind to both COX-2 and 5-LOX, thus potentially causing dual inhibition. This dual-targeting feature is especially beneficial because it can increase the anti-inflammatory activity and decrease the risk of the compensatory response of the alternative pathways. The docking studies are also used to determine important structural features that lead to enzyme binding which can be used to design more potent derivatives to undergo preclinical tests[11].

2.3 Methodologies

Integration of in vivo/in silico combination is commonly used to assess the anti-inflammatory activity of phytochemicals[12].

- **In vivo assays:** The anti-inflammatory activity is often evaluated using rodent models. Typical experimental models are the induction of paw edema with carrageenan, formalin, or histamine, and model of chronic inflammations (e.g. adjuvant-induced arthritis). Inflammatory responses can be measured using these models through edema volume, cytokine levels, leukocyte infiltration and the histopathology of the tissues.
- **In silico docking:** Ligand binding affinity, interaction patterns, and potential inhibitory efficacy can be predicted with the help of such computational tools as AutoDock, GOLD, and Schrodinger Suite. Docking simulations offer an economical approach to screening a variety of phytochemicals, rank candidates to be tested in vivo, and learn about the molecular mechanism of enzyme inhibition[13].

- **Validation:** The best method of validation is the correlation of docking scores and predicted binding interactions and in vivo efficacy data. Phytochemicals with high affinity to essential catalytic sites are frequently associated with a marked decrease in inflammation among animal models, which justifies the translational importance of structure-based docking. By joining these methodologies, it becomes faster to discover promising agents against inflammation and fewer experiments are carried out to reduce trial-and-error.

2.4 Critical Evaluation

- **Strengths:**

Docking of animal models and structures coupled with structure-based docking bring forth important mechanistic insights into the anti-inflammatory effects of phytochemicals. Docking studies can help researchers to determine how these compounds bind to the active sites of COX-2 and 5-LOX, determining which residues play a role in binding and stabilization. Combined with in vivo studies, e.g. rodent paw edema or arthritis models, these predictive measures are checked against real biological behaviour, developing a strong platform on preclinical testing. Moreover, phytochemicals tend to have fewer side effects than standard non-steroidal anti-inflammatory drugs (NSAIDs), thus, making them safer alternatives to be used in the treatment of animals in the long term, thus, demonstrating their therapeutic potential[14].

- **Weakness:**

Although this approach has its benefits, it has drawbacks of its own. The results of docking are mostly predictive and they do not necessarily give a true picture of the in vivo efficacy, and so they have to be properly experimentally validated. In addition, species differences in enzyme structure and metabolism may restrict the direct transfer of results in animals to humans. The bioavailability, absorption and metabolism of phytochemicals in animals may vary greatly compared to that in humans, which can influence efficacy and safety. These considerations are important enough to warrant the caution in regard to result interpretation as well as the necessity to have complementary studies that will help fill the gaps between in silico prediction and in vivo observation[15].

3. PHYTOCHEMICAL STRATEGIES FOR COX-2 AND 5-LOX INHIBITION IN ANIMAL MODELS

Flavonoid, such as quercetin, luteolin, kaempferol, show a high level of anti-inflammatory properties on animal models at both COX-2 and 5-LOX. The experiments of docking based on the structures exhibit high levels of hydrogen bonding and hydrophobic activity with key residues, which justify their dual effect of inhibition. These results are in line with the results in vivo which showed that flavonoid intervention decreased paw edema, leukocyte infiltration and pro-inflammatory cytokines, and this demonstrates that flavonoid can effectively regulate the prostaglandin and leukotrienes pathways[16].

Terpenoids, including boswellic acids and curcumin, also exhibit dual COX-2/5-LOX inhibition in docking and animal models to lower the levels of prostaglandins and leukotrienes in rodent inflammation models. In addition, the integration of phytochemicals of various classes, such as flavonoids and terpenoids, increases anti-inflammatory activity, which results in additive or synergistic effects at active sites of enzymes. These combinatorial approaches are promising in the development of multi-target natural anti-inflammatory therapy and should be investigated further in preclinical studies[17].

3.1 Flavonoid-Based COX-2 and 5-LOX Inhibition

Flavonoid agents such as quercetin, luteolin and kaempferol have shown great anti-inflammatory properties in inflammatory animal models by inhibiting both COX-2 and 5-LOX enzymes. Docking studies using structures indicate that these compounds bind to these enzymes with strong hydrogen bonds to key residues in the active sites of both the enzymes, as well as stabilizing hydrophobic interactions that are found to increase the binding affinity[18]. Such in silico studies are consistent with in vivo studies of rodents of paw edema and arthritis, in which flavonoid administration resulted in a significant decrease in edema, leukocyte infiltration, and pro-inflammatory cytokine release. The fact that flavonoids can dual inhibit both COX-2 and 5-LOX supports the idea that flavonoids are multi-targeted anti-inflammatory molecules that can regulate the prostaglandin and leukotrienes cascades[19].

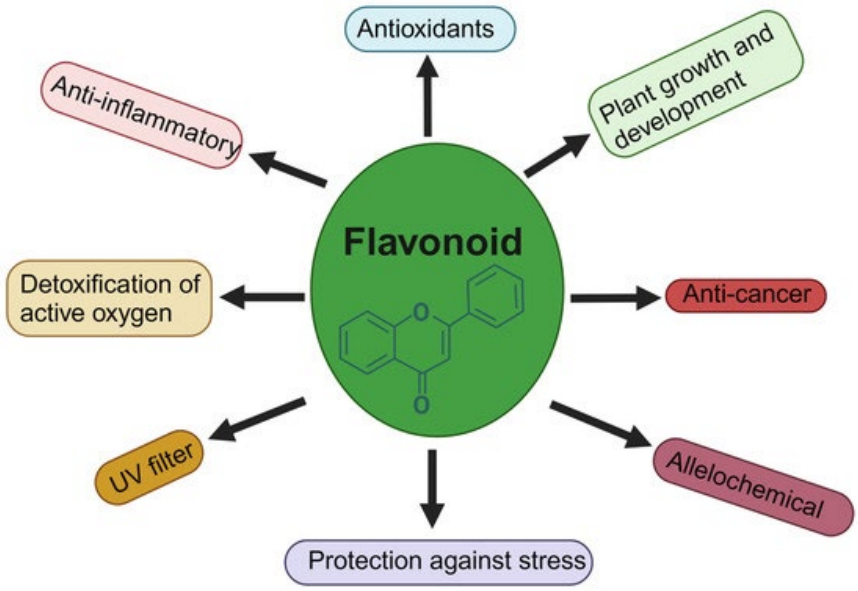

Figure 3: Flavonoids[20]

3.2 Terpenoid-Based Multi-target Inhibition

Computational and animal studies have demonstrated that terpenoids like boswellic acids and curcumin react with dual COX-2/5-LOX inhibition[21]. Docking studies reveal that these compounds have a high binding affinity to the active sites of the two enzymes, create hydrogen

bonds and hydrophobic interactions that increase stability and inhibitory capabilities. These predictions are confirmed by animal experiments, which indicate the reduction of the levels of prostaglandins and leukotrienes in terpenoid treated animals and the reduction of inflammation in paw edema and arthritis models. The terpenoids have shown the capability of preventing several inflammatory processes simultaneously, which underscores their usefulness as multi-purpose natural anti-inflammatory agents and justifies their further exploratory use in preclinical trials[22].

3.3 Synergistic Effects of Phytochemical Combinations

The anti-inflammatory effect has been reported to be stronger when various classes of phytochemicals are used (ie flavonoids and terpenoids) in animal models. Docking studies indicate that such combinations have the potential to generate additive or synergistic effects at the enzyme active sites potentiating interactions with COX- 2 and 5-LOX and increasing the inhibitory capacity[23]. These findings are supported in vivo studies which indicate that greater edema, cytokine, and leukocyte infiltration reductions are achieved when a combination of multiple phytochemicals is used as opposed to single compounds. These anti-inflammatory therapies that target multiple targets and are based on such combinatorial approaches are promising strategies and should be pursued more systematically in preclinical models[24].

4. PHARMACOKINETICS AND SAFETY PROFILE OF PHYTOCHEMICALS IN ANIMAL MODELS

Phytochemicals pharmacokinetics is an important area of preclinical research because it is the factor that determines the absorption, distribution, metabolism, and excretion (ADME) of these compounds in animal systems. The oral bioavailability of flavonoids including quercetin, luteolin and kaempferol typically has moderate levels in rodents because of low solubility and high levels of first-pass metabolism in the liver[25]. Such compounds can quickly undergo metabolism into glucuronide and sulfate conjugates, which can be biologically active but have an effect on the systemic exposure levels. Boswellic acids and curcumin are terpenoids and possess low bioavailability, which is mainly caused by low aqueous solubility and short half-lives. These challenges have been overcome in animal research through the use of numerous methods of formulation, including nanoencapsulation, liposomal delivery, and co-delivery with bioavailability enhancers, which have a great effect on improving systemic absorption and therapeutic efficacy[26].

Phytochemicals also significantly affect their distribution in the animal model through the physicochemical characteristics and binding affinity with proteins. Flavonoids are more apt to build in highly perfused areas like liver, kidney and spleen whereas terpenoids tend to be more widely distributed as they are more lipophilic. This type of tissue-specific accumulation is beneficial in the targeting of inflammatory locations, especially in arthritis or paw edema models, where local anti-inflammatory ability is essential. Nonetheless, the differences in the distribution profiles of various compounds and between animals put more emphasis on the fact

that the extrapolation of pharmacokinetic results to the possible human use requires a close interpretation[27].

Metabolism is a very important phenomenon in the efficacy and safety profile of phytochemicals. Phase I reactions in rodents (such as oxidation and hydroxylation) are commonly preceded with phase II conjugation reactions, giving rise to glucuronides, sulfates or methylated derivatives[28]. These metabolites have the capability to maintain the anti-inflammatory activity, though they may have different powers or half-life. Pharmacological profile of the co-administered compounds can also be affected by enzyme induction or inhibition especially of cytochrome P450 isoforms. Thus, it is critical to know the metabolic mechanisms of phytochemicals in animal models to anticipate the therapeutic effects, help to optimize drug regimens, and minimize the likelihood of drug interactions during preclinical research[29].

Animal-model safety assessment has shown that venues of the phytochemicals are well tolerated with low acute toxicity in the majority of cases, with optimum anti-inflammatory concentrations. Rat research has cited insignificant side effects of flavonoids, terpenoids and alkaloids even at doses which are multiple times higher than treatment doses. However, chronic administration-studies depict the fact that at high doses of specific compounds, including berberine or curcumin, mild levels of hepatotoxicity, gastrointestinal disturbances or enzyme activity changes may emerge, which illustrates the significance of overdosing[30]. All in all, a combination of pharmacokinetic data and safety tests in animal models is very promising as it gives a solid ground to the next step of translational studies and the ultimate clinical trial of promising phytochemicals.

Table 1: Summary of Literature on Natural and Synthetic Compounds Targeting Inflammatory Enzymes[31]

Author(s) & Year	Study Focus	Focus Area	Methodology	Key Findings
Sarmah et al. (2024)[32]	Screening of potent inhibitors from Aquilaria malaccensis Lam.	Anti-inflammatory, arachidonic acid–related enzymes	Molecular docking, ADMET analysis, molecular dynamics simulation, MM-PBSA	Identified phytocompounds with stable interactions with target enzymes, showing potential as anti-inflammatory agents

Shoribo & Pateh. (2025)[33]	Evaluation of β-sitosterol, stigmasterol, and 2-hydroxyhexadecanoic acid methyl ester against COX and LOX	Pain inhibition, inflammatory pathways	In-silico docking studies	Compounds showed significant binding affinities and inhibitory potential, indicating natural analgesic activity
Singh et al. (2018)[34]	Natural products as anticancer therapeutic molecules	Anticancer and anti-inflammatory enzymatic targets (Topoisomerase, COX, LOX, aromatase)	Literature review	Bioactive phytochemicals selectively interacted with target enzymes, showing dual anti-inflammatory and anticancer potential
Suleman et al. (2025)[35]	Phytocompounds as COX-2 inhibitors in dermatology	Atopic-prone skin, COX-2 mediated inflammation	Literature review	Natural compounds targeted COX-2 effectively, providing potential therapeutic options for inflammatory skin conditions
Toumi et al. (2023)[36]	Synthesis and evaluation of tetracyclic spirooxindole-pyrrolidine-engrafted hydantoin scaffolds	Anti-inflammatory, antimicrobial, analgesic	Crystallographic analysis, molecular docking, biological activity assays	Synthesized scaffolds exhibited notable anti-inflammatory, analgesic, and antimicrobial activities, supporting multifunctional therapeutic potential

5. DISCUSSION

Phytochemicals, such as flavonoids and terpenoid, inhibit COX-2/5 -LOX in animal models, and docking experiments confirm this claim. They provide safer and multi-target analogs of NSAIDs, but are not directly translatable due to bioavailability and species differences. Further studies are required to improve delivery, study combinations, as well as relate animal results to clinical uses[37].

5.1 Interpretation of Findings

The animal preclinical research findings have shown that phytochemicals like flavonoid, terpenoid and alkaloids have an ability to reduce inflammatory effects by inhibiting the COX-

2 and the 5-LOX enzymes. Evidence indicated by structure-based docking studies confirm these results, showing that there is strong binding affinity, hydrophobic and hydrogen bonding with key catalytic residues. The bilateral block of COX-2 and 5-LOX contribute to the attained effects of reduce paw edema, leukocytes infiltration and pro-inflammatory cytokines in rodents. These findings show the promise of this approach with phytochemicals as multi-target anti-inflammatory agents and ultimately confirm the combination of in silico and in vivo methodology in preclinical screening[38].

5.2 Implications and Significance

The results highlight the pharmacotherapy of phytochemicals as safer options than traditional NSAIDs which can usually provoke gastrointestinal, renal, and cardiovascular adverse side effects. Dual-target inhibition can be used to stimulate both prostaglandin and leukotriene systems, which can be considered an advantageous approach in managing complicated inflammatory states. In addition, a combination of phytochemicals with various classes (e.g., flavonoids and terpenoids) can also increase anti-inflammatory activity of such combinations with additive or synergistic effects and lower effective doses and decrease risks of toxicity. This multi-target is an extension of the increased interest in natural product-based treatments of chronic inflammation.

5.3 Limitations and Gaps

In spite of the positive results, there are some limitations. As an informative approach, docking prediction cannot completely model the dynamic aspects related to enzymes, tissue distribution, or metabolisms in vivo, and its complexities. Bioavailability (e.g., curcumin, quercetin) and species-specific differences may supply only limited extrapolation of findings to humans, and limit systemic bioavailability. Also, there is a lack of long-term safety data, cumulative toxicity, and organ-specific effects were not studied completely. These loopholes explain why the results of preclinical trials should be carefully interpreted[39].

5.4 Future Research Directions

Future studies should aim at enhancing the bioavailability of phytochemicals by using advanced formulation approaches like nanoencapsulation or liposomal formulation. Systematic evaluation of combinatorial phytochemical therapies can be further used to boost anti-inflammatory efficacy. Mechanistic investigations about upstream signaling pathways (NF-kB, mitigate, mitogen-activated protein kinase, etc.) would yield deeper insights towards molecular mechanisms. Finally, translational studies that bridge the gap between animal models and clinical relevance are difficult to achieve and important to bring phytochemical-based dual inhibitors to safe and effective anti-inflammatory therapeutics[40].

6. CONCLUSION

Phytochemicals, such as flavonoids, terpenoids, and alkaloids, have shown a great potential as multi-target anti-inflammatory agents by acting on the COX-2 and 5-LOX enzymes at the same time through both structure-based molecular docking and preclinical animal studies. These are natural compounds that are effective in reducing paw edema, leukocyte infiltration and pro-inflammatory cytokines while generally having lesser levels of adverse effects in comparison to conventional NSAIDs. Structure-based docking leads to mechanistic information about important molecular interactions for dual inhibition and selection of promising candidates for further evaluation. Combinatorial strategies of phytochemicals from various classes exhibit additive or synergistic properties and can increase efficacy and potentially lower doses required. Despite such limitations, such as low bioavailability, species-specific variations and long-term safety data, advancements in formulation approaches and translational research provide opportunities for optimizing therapeutic outcomes. Overall, combining in silico and in vivo approaches forms a solid platform for the creation of safe, efficacious and multi-target phytochemical-based anti-inflammatory therapies, making them a dream to implement in the future for clinical patient treatment.

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