Assessment of ADME and *in silico* Characteristics of Natural-Drugs from Turmeric to Evaluate Significant COX2 Inhibition

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Abstract: Turmeric contains a variety of natural phytoconstituents, effective in reducing the risk of certain diseases and disorders, for example, heart disease, diabetes, neoplastic, and other health disorders. In the present study, ten compounds that occurred in turmeric were evaluated for ADME properties and COX-2 inhibitory potential as anti-inflammatory agents through the *in silico* approach. ADME properties and docking studies revealed that L1, L3, and L4 displayed the best performance and were found suitable to be high-quality COX2 inhibitors. The maximum binding energies were observed in superior mode in comparison to valdecoxib (L, B.E. = -8.7) for ligands L1, B.E. = -8.8; L2, B.E. = -9.7; L3, B.E. = -8.9; L4, B.E. = -9.6. The keto-isomeric form is found more familiar with the COX2 inhibiting activity than the enol-isomeric form. The significant bioavailability scores L1, L3, and L4 suggest that they exhibit good drug-likeness abilities. The results indicate that the curcuminoids in turmeric showed remarkable biological functionalities, particularly COX-2 inhibiting property, which might further be used as oral therapeutics after clinical trials.

Keywords: Turmeric, spice, ADME, drug likeliness, COX2 inhibitor, biological activity.

1. Introduction

In adults, the commonest arthritic states with extremely high pain are osteoand rheumatoid arthritis, which chiefly leads to joint degeneration and sharp inflammation. As a result, patients require significant treatment using good quality pain relievers [1,2]. To combat the severe pain and inflammation through oral and topical with highly effective analgesic characteristics, the commonest examples are non-steroidal anti-inflammatory drugs (NSAIDs) such as traditional NSAIDs (tNSAIDs) and cyclooxygenase 2 inhibitors (COXIBs) [3,4]. The target specificity of pain-reliever drugs associated with converting arachidonic acid into inflammatory prostaglandins, for example, cyclooxygenase (COX) with three main isoforms like COX-1, COX-2, and COX-3 [5]. COX-1 is a common housekeeping enzyme that is observed to be expressed in almost all tissues, whereas COX-2 is expressed during the high inflammations caused by pro-inflammatory molecules including TNF-α, LPS, and IL-1 in some specific organs such as the brain, ovaries, and kidney [6]. The methyl group substitution is quite interesting with respect to larger and more flexible substrate channels and the inhibiting action of drug molecules containing methyl functional groups towards high COX-2 and low
COX-1 inhibiting action [7]. Synthetic drugs that lead to COX-1 inhibition have proven causative to gastrointestinal tract (GIT) side effects [8]. Furthermore, COX-2 inhibitors are widely prescribed anti-inflammatory agents, and even these also possess several side effects that have been reported [9].

Toward the design of novel drugs, computer-aided drug design (CADD) can be combined with wet-lab techniques to elucidate the mechanism of drug resistance in search of promising-antibiotic targets, designed as novel antibiotics for both known and novel targets. On the other hand, many repurposed drugs have already been FDA approved and therefore face a cheaper and quicker journey to the clinic. Considerable CADD-based methods can produce an atomic level structure-activity relationship (SAR) used to facilitate the drug design process, thereby minimizing time and costs. On the other hand, many repurposed drugs have already been FDA approved and therefore face a cheaper and quicker journey to the clinic [10-14]. In the recent era, natural products belonging to a range of chemical classes such as phenolics, quinones, flavonoids, stilbenes, terpenoids, and alkaloids [15-17] have profound effectiveness in COX-inhibiting action [3-5]. Phytoconstituents of natural origin have superior advantages such as eco-friendliness, greater biodegradability, and environmental compatibility to their synthetic counterparts with excellent biological functionalities due to their structural core scaffolds [18-21].

Turmeric (Curcuma longa), commonly known as Haldi, belongs to the ginger family Zingiberaceae, frequently propagated and cultivated in the tropical part of Asia region, including India, Iran, Malaysia, China, Thailand, etc., is often used as a spice and has an effect on the nature, color, and taste of foods. The therapeutically important part is its rhizome. Phytochemicals, including curcuminoids, phenols, aromatic quinines, etc., are reported in turmeric. Particularly, known to have many biological actions such as anti-inflammatory, anticancer, antioxidant, and many more that play a pivotal role in preventing and curing various diseases and ailments, notably from cancer to cardiovascular diseases, diabetic, autoimmune, and neurological [22-24]. Natural-derived drugs are diverse with respect to a chemical moiety and inherent biological effectiveness [19,25,26] and offer greater therapeutic options because of their inherently eco-safe and higher compatibility compared to the synthetic compounds being used conventionally, particularly in drug delivery options [27]. In the current scenario, to make greener drug target as alternates of conventional drugs, the utilization of drugs and bioactive natural products derived of natural origin, especially phytochemical extracts from medicinal flora and fauna, is essentially required. Recent drug discovery and development trends have proven to be immensely valuable due to their wide acceptability and authorization as curing medicines for a number of ailments and infectious diseases. Therefore, in order to reduce adverse side effects during non-steroidal anti-inflammatory treatment compounds obtained from plants or other natural origins to inhibit COX-2, it is an important target for improving therapeutic benefits with nature's gift. The literature survey indicates that the COX inhibiting activity of turmeric ingredients, particularly curcumin, has been evaluated and found to have good anti-inflammatory action. Yet, other phytochemicals in turmeric are believed to be significant COX-2 inhibitory activity unexplored so far. In this work, in order to assess the ADME and anti-inflammatory effects through in silico approach, we have explored the chief phytochemicals of turmeric rhizome for their ADME properties and COX2 inhibitory activity.
2. Materials and Methods

2.1. Preparation of COX2 protein and Ligands optimization.

3D Crystal-structural file of the COX2 Protein (PDB Id: S121P) was downloaded in PDB format from Protein Data Bank (www.rcsb.org). Valdecoxib (L), Chemspider ID:106796, was downloaded from Chemspider's online platform (http://www.chemspider.com) as a reference drug COX2 inhibitor. Ligands L1-L10 (Table 1) were prepared using ChemDraw Ultra (CambridgeSoft Corporation, USA) and generated SMILES for each ligand, and .mol files were saved for docking. To get the theoretical validation, the structures were subjected for their optimization to be considered for ADME and in silico investigation to reach the minimum energy structures using the Avogadro Software v1.2.0. SMILES codes of ligands were computed to assess ADME and other biological activities via the structural input.

2.2. Assessment of ADME properties and Docking studies.

ADME properties were evaluated using SwissADME algorithm (http://www.swissadme.ch) in terms of physicochemical, lipophilicity, water-solubility, pharmacokinetics, drug-likeness and medicinal chemistry in accordance to the Lipinski's Rule of 5 for drug candidates (< 5 H-bond donors, < 10 H-bond acceptors, < 500 Da, and < 5 Log P (CLog P) [28]. We have utilized the CB-Dock Online platform to predict binding energies automatically, a user-friendly and blind docking web server that offers an interactive 3D visualization of results and is available free of charge at http://cao.labshare.cn/cb-dock/ [29].

Table 1. Description of ligands of the study.

| Ligands            | Chemical structures | Molecular weight (Da) |
|--------------------|---------------------|-----------------------|
| L (Valdecoxib)     | ![Chemical structure](image) | 314                   |
| L1 (Curcumin-Keto form) | ![Chemical structure](image) | 368                   |
| L2 (Curcumin-Enol form) | ![Chemical structure](image) | 368                   |
| L3 (Demethoxycurcumin) | ![Chemical structure](image) | 338                   |
| Ligands               | Chemical structures                      | Molecular weight (Da) |
|----------------------|-----------------------------------------|----------------------|
| L4 (Bisdemethoxycurcumin) | ![Structure](image)                      | 308                  |
| L5 (α-Tumerone)      | ![Structure](image)                      | 218                  |
| L6 (β-Tumerone)      | ![Structure](image)                      | 218                  |
| L7 (Bisacurone)      | ![Structure](image)                      | 252                  |
| L8 (Ar-Tumerone)     | ![Structure](image)                      | 214                  |
| L9 (Zingiberene)     | ![Structure](image)                      | 204                  |
| L10 (α-Altantone)    | ![Structure](image)                      | 204                  |

CB-Dock calculates the active centers and cavity sizes with an innovative curvature-based void detection approach using Autodock Vina, a popular docking program. 2.3. Prediction of Anatomical therapeutic chemical (ATC) classification, drug target, cytotoxicity, toxicity, and biological activity score.

Anatomical therapeutic chemical (ATC) classification was performed by the SuperPred web server platform (prediction.charite.de). This platform implies with similar property principle that detects the chemical similarity of drugs with specified molecular targets and therapeutic actions. [30]. Target prediction was assessed by swiss target prediction web service (http://www.swisstargetprediction.ch/). Cytotoxicity prediction was performed by CLC-Pred: Cell Line Cytotoxicity Predictor (http://www.way2drug.com/cell-line/) is a web-based service for in silico prediction of the cytotoxic effects of organic molecules onto non-transformed and cancer cell lines. [29-32].
# Results of ADME and docking studies.

## Ligands

| Ligand | Physicochemical Properties# | Lipophilicity | Water Solubility | Pharmacokinetics | Druglikeness | Medicinal Chemistry | Docking results Binding energies |
|--------|----------------------------|---------------|------------------|------------------|--------------|---------------------|---------------------------------|
| MF=C_{16}H_{12}N_{2}O_{3}S | Log P_{ow} (iLOGP) = 1.78 | Log S (ESOL) = -3.81 | Solubility = 4.83e-02 mg/ml | GI absorption = high | Lipinski = Yes; 0 violation | PAINS = 0 alert | Synthetic accessibility = 3.26 |
| L | MW = 314 Da | | | | | | |
| nHA = 22 | | | | | | | |
| nArHA = 17 | | | | | | | |
| Fraction (Csp3) = 0.06 | | | | | | | |
| nRB = 3 | | | | | | | |
| nHBA = 5 | | | | | | | |
| nHBD = 1 | | | | | | | |
| MR = 83.4 | | | | | | | |
| TPSA = 94.57 Å² | | | | | | | |
| MF=C_{21}H_{20}O_{6} | Log P_{ow} (iLOGP) = 3.27 | Log S (ESOL) = -3.94 | Solubility = 4.22e-02 mg/ml | GI absorption = high | Lipinski = Yes; 0 violation | PAINS = 0 alert | Synthetic accessibility = 2.97 |
| L1 | MW = 368 Da | | | | | | |
| nHA = 27 | | | | | | | |
| nArHA = 12 | | | | | | | |
| Fraction (Csp3) = 0.14 | | | | | | | |
| nRB = 8 | | | | | | | |
| nHBA = 6 | | | | | | | |
| nHBD = 2 | | | | | | | |
| MR = 102.80 | | | | | | | |
| TPSA = 93.06 Å² | | | | | | | |
| MF=C_{21}H_{20}O_{6} | Log P_{ow} (iLOGP) = 3.21 | Log S (ESOL) = -4.50 | Solubility = 1.17e-02 mg/ml | GI absorption = high | Lipinski = Yes; 0 violation | PAINS = 0 alert | Synthetic accessibility = 3.42 |
| L2 | MW = 368 Da | | | | | | |
| nHA = 27 | | | | | | | |
| nArHA = 12 | | | | | | | |
| Fraction (Csp3) = 0.10 | | | | | | | |
| nRB = 7 | | | | | | | |
| nHBA = 6 | | | | | | | |
| nHBD = 3 | | | | | | | |
| MR = 103.70 | | | | | | | |
| TPSA = 96.22 Å² | | | | | | | |
| MF=C_{20}H_{18}O_{5} | Log P_{ow} (iLOGP) = 2.78 | Log S (ESOL) = -3.92 | Solubility = 4.04e-02 mg/ml | GI absorption = high | Lipinski = Yes; 0 violation | PAINS = 0 alert | Synthetic accessibility = 2.82 |
| L3 | MW = 338 Da | | | | | | |
| nHA = 25 | | | | | | | |
| nArHA = 12 | | | | | | | |
| Fraction (Csp3) = 0.10 | | | | | | | |
| nRB = 7 | | | | | | | |
| nHBA = 5 | | | | | | | |
| nHBD = 2 | | | | | | | |
| MR = 96.31 | | | | | | | |
| TPSA = 83.83 Å² | | | | | | | |
| MF=C_{19}H_{16}O_{4} | Log P_{ow} (iLOGP) = 1.75 | Log S (ESOL) = -3.80 | Solubility = 4.94e-02 mg/ml | GI absorption = high | Lipinski = Yes; 0 violation | PAINS = 0 alert | Synthetic accessibility = 2.82 |
| L4 | MW = 308 Da | | | | | | |
| nHA = 23 | | | | | | | |
| nArHA = 12 | | | | | | | |
| Ligands | Physicochemical Properties# | Lipophilicity | ADME Properties | Pharmacokinetics | Druglikeness | Medicinal Chemistry | Docking results |
|--------|-----------------------------|---------------|----------------|-----------------|--------------|-------------------|----------------|
|        | Fraction (Csp3) = 0.05      |               |                |                 |              |                   |                |
|        | nRB = 6                     |               |                |                 |              |                   |                |
|        | nHBA = 4                    |               |                |                 |              |                   |                |
|        | MR = 89.82                  |               |                |                 |              |                   |                |
|        | TPSA = 74.60 Å              |               |                |                 |              |                   |                |
|        |                             | Log \( P_{ow} \) (XLOGP3) = 3.26 | mg/ml : 1.60e-04 mol/l | CYP2C19 inhibitor = No | Egan = Yes | Muegge = Yes | Bioavailability Score = 0.55 | Synthetic accessibility = 2.59 |
| L5     | MF = C\(_{15}\)H\(_{22}\)O | 3.13          | Log \( S \) (ESOL) = -3.30 | GI absorption = high | Lipinski = Yes; 0 violation | | -7.9 |
|        | MW = 218 Da                 |               | Solubility = 1.08e-01 mg/ml : 4.96e-04 mol/l | | | | |
|        | nHA = 16                    |               | Class = soluble | | | | |
|        | nArHA = 0                   |               |                | | | | |
|        | Fraction (Csp3) = 0.53      | 3.77          | Log \( P_{ow} \) (XLOGP3) = 3.77 | | | | |
|        | nRB = 4                     |               |                | | | | |
|        | nHBA = 1                    |               |                | | | | |
|        | nHBD = 0                    |               |                | | | | |
|        | MR = 70.88                  |               |                | | | | |
|        | TPSA = 17.07 Å              |               |                | | | | |
|        |                             | Log \( P_{ow} \) (iLOGP) = 3.14 | Log \( S \) (ESOL) = -3.46 | GI absorption = high | Lipinski = Yes; 0 violation | | -7.3 |
|        |                             |               | Solubility = 7.6e-02 mg/ml : 3.5e-04 mol/l | | | | |
|        |                             |               | Class = soluble | | | | |
|        |                             | Log \( P_{ow} \) (XLOGP3) = 4.01 | | | | |
| L6     | MF = C\(_{15}\)H\(_{22}\)O | 2.66          | Log \( S \) (ESOL) = -2.32 | GI absorption = high | Lipinski = Yes; 0 violation | | -7.8 |
|        | MW = 252 Da                 |               | Solubility = 1.19e+00 mg/ml : 4.73e-03 mol/l | | | | |
|        | nHA = 18                    |               | Class = soluble | | | | |
|        | nArHA = 0                   |               |                | | | | |
|        | Fraction (Csp3) = 0.67      | 1.88          | Log \( P_{ow} \) (XLOGP3) = 1.88 | | | | |
|        | nRB = 4                     |               |                | | | | |
|        | nHBA = 3                    |               |                | | | | |
|        | nHBD = 2                    |               |                | | | | |
|        | MR = 73.72                  |               |                | | | | |
|        | TPSA = 57.53 Å              |               |                | | | | |
|        |                             | Log \( P_{ow} \) (iLOGP) = 2.82 | Log \( S \) (ESOL) = -3.83 | GI absorption = high | Lipinski = Yes; 0 violation | | -8.3 |
|        |                             |               | Solubility = 3.19e-02 mg/ml : 1.49e-04 mol/l | | | | |
|        |                             |               | Class = soluble | | | | |
| L7     | MF = C\(_{15}\)H\(_{18}\)O | 1.88          | Log \( P_{ow} \) (XLOGP3) = 1.88 | | | | |
|        | MW = 214 Da                 |               |                | | | | |
|        | nHA = 16                    |               |                | | | | |
|        | nArHA = 0                   |               |                | | | | |
|        | Fraction (Csp3) = 0.40      | 3.78          | Log \( S \) (ESOL) = -3.83 | GI absorption = high | Lipinski = Yes; 0 violation | | -8.3 |
|        | nRB = 0                     |               | Solubility = 3.19e-02 mg/ml : 1.49e-04 mol/l | | | | |
|        | nHBA = 1                    |               | Class = soluble | | | | |
|        | nHBD = 0                    |               |                | | | | |
|        | MR = 68.59                  |               |                | | | | |
|        |                             | Log \( P_{ow} \) (iLOGP) = 2.82 | Log \( S \) (ESOL) = -3.83 | GI absorption = high | Lipinski = Yes; 0 violation | | -8.3 |
|        |                             |               | Solubility = 3.19e-02 mg/ml : 1.49e-04 mol/l | | | | |
|        |                             |               | Class = soluble | | | | |
| L8     | MF = C\(_{15}\)H\(_{18}\)O | 2.82          | Log \( S \) (ESOL) = -3.83 | GI absorption = high | Lipinski = Yes; 0 violation | | -8.3 |
|        | MW = 214 Da                 |               | Solubility = 3.19e-02 mg/ml : 1.49e-04 mol/l | | | | |
|        | nHA = 16                    |               | Class = soluble | | | | |
|        | nArHA = 0                   |               |                | | | | |
|        | Fraction (Csp3) = 0.40      | 3.78          | Log \( S \) (ESOL) = -3.83 | GI absorption = high | Lipinski = Yes; 0 violation | | -8.3 |
|        | nRB = 0                     |               | Solubility = 3.19e-02 mg/ml : 1.49e-04 mol/l | | | | |
|        | nHBA = 1                    |               | Class = soluble | | | | |
|        | nHBD = 0                    |               |                | | | | |
|        | MR = 68.59                  |               |                | | | | |

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### Physicochemical Properties

| Ligands | MF = C_{15}H_{24} | MW = 204 Da | nHA = 15 | nArHA = 0 | Fraction (Csp3) = 0.60 | nRB = 5 | nHBA = 0 | nHBD = 0 | MR = 70.68 | TPSA = 0.01 Å² |
|---------|-------------------|-------------|---------|-----------|-----------------------|--------|---------|---------|---------|----------------|
| L9      |                   |             |         |           |                       |        |         |         |         |                |

### Lipophilicity

- Log $P_{ow}$ (iLOGP) = 3.80
- Log S (ESOL) = 4.71e-02
- Solubility = 2.31e-04 mol/l
- Class = soluble

### ADME Properties

#### Water Solubility

- Log $P_{ow}$ (iLOGP) = 3.80

#### Pharmacokinetics

- GI absorption = Low
- BBP permeant = No
- P-gp substrate = No
- CYP1A2 inhibitor = Yes
- CYP2C19 inhibitor = No
- Lipinski = Yes; 1 violation:
  - MLOGP>4.15
  - Ghose = Yes
  - Veber = Yes
  - Muegge = No; 1 violation:
    - Heteroatoms<2
  - Bioavailability
  - Score = 0.55
  - Synthetic accessibility = 3.13

#### Druglikeness

- Bioavailability
  - Score = 0.55

#### Medicinal Chemistry

- Synthetic accessibility = 4.09

### Docking results

- Binding energies (kcal/mol)
  - L9: -7.4

### Table 3. Molinspiration-predicted biological characteristics of L, L1-L10.

| Ligands | GPCR ligand | Ion channel modulator | Kinase inhibitor | Nuclear receptor ligand | Protease inhibitor | Enzyme inhibitor |
|---------|-------------|-----------------------|-----------------|------------------------|--------------------|-----------------|
| L       | -0.12       | -0.12                 | -0.19           | -0.07                  | -0.02              | -0.21           |
| L1      | -0.06       | -0.20                 | -0.26           | 0.12                   | -0.14              | 0.08            |
| L2      | -0.09       | -0.39                 | -0.13           | 0.02                   | -0.09              | 0.12            |
| L3      | -0.04       | -0.20                 | -0.26           | 0.18                   | -0.14              | 0.10            |
| L4      | -0.01       | -0.14                 | -0.26           | 0.25                   | -0.08              | 0.15            |
| L5      | -0.48       | -0.20                 | -1.31           | 0.51                   | -0.55              | 0.39            |
| L6      | -0.47       | -0.23                 | -1.42           | 0.58                   | -0.50              | 0.35            |
| L7      | -0.07       | -0.07                 | -0.97           | 0.82                   | -0.14              | 0.69            |
| L8      | -0.47       | -0.28                 | -1.13           | 0.01                   | -0.88              | 0.42            |
| L9      | -0.32       | -0.06                 | -0.94           | 0.13                   | -0.67              | 0.17            |
| L10     | -0.38       | -0.12                 | -1.36           | 0.41                   | -0.51              | 0.38            |

#MF = molecular formula, MW = molecular weight, nHA = No. heavy atoms, nArHA = No. of aromatic heavy atoms, nRB = No. of rotatable bonds, nHBA = No. of H-bond acceptors, nHBD = No. of H-bond donors, MR = Molar refractivity, TPSA = Topological polar surface area.
### Table 4. Anatomical therapeutic chemical (ATC) classification and target prediction of L, L1-L10.

| Ligands | Anatomical therapeutic chemical (ATC) classification | Target prediction |
|---------|------------------------------------------------------|--------------------|
| L       | Coxibs<br>M01AH: 95.05%                              | Lyase<br>Oxidoreductase<br>Primary active transporter |
|         |                                                     | ![Pie chart for L]  |
| L1      | R05CA: 22.08%<br>C01CA: 18.06%                       | Oxidoreductase<br>Enzyme<br>Kinase |
|         |                                                     | ![Pie chart for L1] |
| Ligands | Anatomical therapeutic chemical (ATC) classification | Class (best 3) | Target prediction |
|---------|-----------------------------------------------------|----------------|------------------|
| L2      | R05CA: 19.4%                                        | Lyase          | ![Pie Chart L2](chart.png) |
|         | C01CA: 9.14%                                        | Kinase          |                  |
|         | D10AD: 6.44%                                        | Membrane receptor |               |
|         |                                                     | Oxidoreductase  |                  |
|         |                                                     | ![Pie Chart L2](chart.png) |                  |
| L3      | C01CA: 69.88%                                       | Oxidoreductase  | ![Pie Chart L3](chart.png) |
|         |                                                     | Enzyme          |                  |
|         |                                                     | Protease        |                  |
|         |                                                     | Kinase          |                  |

![Pie Chart L2](chart.png)  
![Pie Chart L3](chart.png)
| Ligands | Anatomical therapeutic chemical (ATC) classification | Class (best 3) | Target prediction |
|---------|--------------------------------------------------|----------------|-----------------|
| L4      | C01CA: 17.56% D01AE: 12.47%                     | ➢ Enzyme       | [Diagram 1]     |
|         |                                                  | ➢ Oxidoreductase|                 |
|         |                                                  | ➢ Kinase        |                 |
| L5      | C01EB: 8.99% R05CB: 7.87%                       | ➢ Oxidoreductase|                 |
|         |                                                  | ➢ Family A G Protein-coupled receptor |             |
|         |                                                  | ➢ Nuclear receptor |             |

[Diagram 1] Pie chart showing the percentage distribution of different target classes for L4 and L5.
| Ligands | Anatomical therapeutic chemical (ATC) classification | Class (best 3) | Target prediction |
|---------|-----------------------------------------------------|----------------|-------------------|
| L6      | M01AE: 5.67% N05CA: 3.11%                         | Oxidoreductase Nuclear receptor Cytochrome P450 | ![Pie chart](chart1.png) |
| L7      | S01EE: 3.76%                                      | Unpredicted    | Unpredicted        |
| L8      | L04AA: 7.06%                                      | Oxidoreductase Family A G protein coupled receptor Protease | ![Pie chart](chart2.png) |
| L9      | R01AA: 7.49% S01EE: 4.76%                        | Unpredicted    | Unpredicted        |
| Ligands | Anatomical therapeutic chemical (ATC) classification | Class (best 3) | Pi-chart |
|---------|-----------------------------------------------------|----------------|---------|
| L10     | G03DB: 5.94% B01AC: 5%                             | Oxidoreductase, Transcription factor, Cytochrome P450 | ![Pie chart](image) |

**SMILES**
Cc1onc(c1c1ccc(cc1)S(=O)(=O)N)c1ccccc1
**Figure 1.** Representation of ADME properties (Bioavailability Radar- LIPO; Lipophilicity, POLAR: Polarity, INSOLU: Insolubility, INSATU: Unsaturation, FLEX: Flexibility. Fraction Csp3; the fraction of carbons in the sp3 hybridization and Boiled egg) and Molecular docking studies of L (Valdecoxib).

**Figure 2.** Representation of ADME properties and Molecular docking studies of L1.
**Figure 3.** Representation of ADME properties and Molecular docking studies of L2.

**Figure 4.** Representation of ADME properties and Molecular docking studies of L3.
Figure 5. Representation of ADME properties and Molecular docking studies of L4.

Figure 6. Representation of ADME properties and Molecular docking studies of L5.
Figure 7. Representation of ADME properties and Molecular docking studies of L6.

Figure 8. Representation of ADME properties and Molecular docking studies of L7.
**Figure 9.** Representation of ADME properties and Molecular docking studies of L.8.

**Figure 10.** Representation of ADME properties and Molecular docking studies of L.9.
Figure 11. Representation of ADME properties and Molecular docking studies of L10.

Table 5. Prediction of cell line cytotoxicities of L, L1-L10.

| Ligands | Pa values | Pi values | Cell-line details                      |
|---------|-----------|-----------|----------------------------------------|
| L       | 0.510     | 0.015     | BT-549: Breast ductal carcinoma        |
| L1      | 0.375     | 0.049     | PC-6: Small cell lung carcinoma        |
| L2      | 0.733     | 0.007     | PC-3: Prostate carcinoma               |
| L3      | 0.392     | 0.043     | PC-6: Small cell lung carcinoma        |
| L4      | 0.530     | 0.047     | Hs-683: Oligodendrogloma               |
| L5      | 0.371     | 0.002     | SHP-77: Small cell lung carcinoma      |
| L6      | 0.436     | 0.010     | NALM-6: Adult B acute lymphoblastic leukemia |
| L7      | 0.445     | 0.090     | NCI-H838: Non-small cell lung cancer, 3 stage |
| L8      | 0.437     | 0.021     | HOP-18: Non-small cell lung carcinoma  |
| L9      | 0.482     | 0.048     | DMS-114: Lung carcinoma                |
| L10     | 0.552     | 0.003     | SGC-7901: Gastric carcinoma            |
Further, the toxicity prediction assay was identified by using the ADME
tool online Web server with respect to hepatotoxicity, hERG (human Ether-à-go-go-Related Gene) blocking, and Ames toxicity. Molinspiration biological characteristics of L, L1-L10 were evaluated Molinspiration Cheminformatics Online Server (https://www.molinspiration.com/) [32] by taking Valdecoxib as a reference standard COX2 inhibitor.

3. Results and Discussion

Principally, for drug development, the unfavorable absorption, distribution, metabolism, and elimination (ADME) properties have been recognized as a major cause of rejection of new molecule as drug candidate [33,34] and is a systematic way to predict essential properties to be a quality drug-using Computer-Aided Drug Discovery (CADD) methodology [35-40]. Therefore, there is increasing interest in the early prediction of any novel drug molecule with respect to the ADME properties. Herein, ADME properties for L1-L10 molecules were evaluated in terms of physicochemical, lipophilicity, water-solubility, pharmacokinetics, drug-likeness and medicinal chemistry in accordance to the Lipinski's Rule of 5 for drug candidates (< 5 H-bond donors, < 10 H-bond acceptors, < 500 Da, and < 5 Log P (CLog P) using L (Valdecoxib) as a standard reference drug. Table 2 depicts the Swissdock-expressed ADME analysis. From the Table 2 it can be observed that considerable ADME properties and binding energies of docked ligands evaluated for ligands- L1 (Lipophilicity = Log P<sub>o/w</sub> (iLOGP) = 3.27 & Log P<sub>o/w</sub> (XLOGP3) = 3.20; Water solubility = soluble; Pharmacokinetics = high GI absorption, CYP1A2 inhibitor; Druglikeness = Lipinski allowed and Medicinal Chemistry = + Leadlikeness & Synthetic accessibility value of 2.97); L3 (Lipophilicity = Log P<sub>o/w</sub> (iLOGP) = 2.78 & Log P<sub>o/w</sub> (XLOGP3) = 3.32; Water solubility = soluble; Pharmacokinetics = high GI absorption, CYP1A2 inhibitor; Druglikeness = Lipinski allowed and Medicinal Chemistry = + Leadlikeness & Synthetic accessibility value of 2.82); L4 (Lipophilicity = Log P<sub>o/w</sub> (iLOGP) = 1.75 & Log P<sub>o/w</sub> (XLOGP3) = 3.26; Water solubility = soluble; Pharmacokinetics = high GI absorption, CYP1A2 inhibitor; Druglikeness = Lipinski allowed and Medicinal Chemistry = + Leadlikeness & Synthetic accessibility value of 2.59).

The maximum binding energies were observed in superior mode compared to valdecoxib (L, B.E. = -8.7) for ligands- L1, B.E. = -8.8; L2, B.E. = -9.7; L3, B.E. = -8.9 & L4, B.E. = -9.6. Figures 1-11 show the docking pattern of the studied drug candidates (L-L10) with respect to Bioavailability Radar- LIPO; Lipophilicity, POLAR: Polarity, INSOLU: Insolubility, INSATU: Unsaturation, FLEX: Flexibility. Fraction Csp3: fraction of carbons in the sp3 hybridization and Boiled egg) and Molecular docking studies of ligands L-L10. Results of ADME properties and docking studies revealed that L1 (Figure 2), L3 (Figure 4), and L4 (Figure 5) displayed the best performance and were found suitable to be high-quality COX2 inhibitors.

From Table 3, it can be seen that the ligands L1 (Figure 2), L3 (Figure 4), and L4 (Figure 5) possessed excellent biological activity scores. The Anatomical Therapeutic Chemical (ATC) Classification System is a drug classification system that categorizes the drug’s targeting activity to the organ with respect to their therapeutic, pharmacological, and chemical properties [34,41]. It is an aid to monitor drug use and for research to improve quality medication use. Anatomical therapeutic chemical (ATC) classification presented in Table 4 were predicted as- L1: R05CA: 22.08% & C01CA: 18.06%, Oxidoreductase / Enzyme / Kinase; L3: C01CA: 69.88%, Oxidoreductase/Enzyme/Protease/Kinase and L4: C01CA:
17.56% & D01AE: 12.47%. Enzyme/Oxidoreductase/Kinase. Table 5 shows the predicted results of cell line cytotoxicities for the ligands L-L10. Having high binding energies, the ligands L1, L3, and L4 have shown PC-6: Small cell lung carcinoma, PC-6: Small cell lung carcinoma, and Hs-683: Oligodendroglioma, respectively, with excellent Pa and pi values. Hence, together with the significant bioavailability scores, L1, L3, and L4 suggest that they exhibit good drug-likeliness properties and thus have a good potential to be developed into an oral drug for therapeutic application.

Medicinal plants and herbs and their derived active phytochemicals/compounds have long been used for the treatment of various disorders and diseases [14,15] due to their enhanced unique abilities of active compounds [19-22,31] such as anti-inflammatory, immunomodulatory, antimicrobial, anticancer, antioxidant, etc. [6-8,32,42]. Our study indicated that the curcuminoids from turmeric can be further consideration to combat high pain. In the present scenario of ecological and drug safety, naturally-derived medicines may surely provide better functionality as well as compatibility.

4. Conclusions

In recent times, global research has focused on using raw and sustainable products with new and cleaner alternatives that allow safety, modality, and activeness. In this work, ten compounds present as chemical ingredients in turmeric were assessed for COX-2 inhibitory potential as anti-inflammatory agents through the in silico approach. Mainly curcuminoids exhibited the best performance and were found suitable to be high-quality COX2 inhibitors. The maximum binding energies were observed in superior mode in comparison to for ligands L1, B.E. = -8.8; L2, B.E. = -9.7; L3, B.E. = -8.9 & L4, B.E. = -9.6. Keto form of curcumin showed greater effectivity than enol-isomer. The significant bioavailability scores L1, L3, and L4 suggest that they exhibit good drug-likeness properties and thus have a good potential to be developed into an oral drug for therapeutic application. A future directional approach is needed on clinical trials and commercialization. Biologically-active extracts and compounds mediating COX-2 inhibitory activities are expected to elucidate further active principles for developing new agents with satisfactory applicability.

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Conflicts of Interest

The authors declare no conflict of interest.

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