PREDICTION OF ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION ACTIVITY OF THE COMPONENTS OF MADHUCA LONGIFOLIA AND ITS INHIBITING TARGET MOLECULE

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ABSTRACT

Objectives: Madhuca longifolia is a versatile tropical tree mostly cultivated or harvested in the wild in South Asia for its edible flowers and oil seeds. Mahua trees are vegetatively propagated; they act as soil improvers, and also help in soil reclamation and erosion control. M. longifolia is a plant of great importance due to its scientifically proven uses such as antioxidant activity, immune suppression, and neuroprotective activity, which is because of the various chemical constituents present in different parts of the plant. The aim of our study is to analyze the absorption, distribution, metabolism, and excretion (ADME) properties and pathways analysis of active components of M. longifolia.

Methods: The detailed study of these chemical constituents is done using PubChem and software’s such as Rasmol and Pymol. Swiss ADME was used to find out the ADME properties of the chemical constituents present in the plant. The pathway analysis was done using a literature survey and Swiss Target Prediction.

Results: The research has identify the potentially active compound from the plant with its inhibitory target protein.

Conclusion: The ADME result demonstrates the potential pharmacological activity of the plant compound, which can be studied through in vivo model against its potential inhibitory target molecules.

Keywords: Madhuca longifolia, Rasmol, Pymol, PubChem, Absorption; distribution; metabolism; and excretion properties.

INTRODUCTION

Madhuca longifolia belongs to the Sapotaceae family commonly known as butternut tree, which is a fast-growing tree found widely in Nepal, India, and Sri Lanka. The common Indian name for M. longifolia is Mahua, Mahwa, or Iluppi. It is cultivated in warm and humid regions. It is a deciduous tree that can grow up to 20 m of height. The ethnomedicinal uses of M. longifolia contain various phytochemical compounds such as flavonoids, Vitamins A and C, histidine, glutamic acid, tannins, volatile oil, beta-carotene, and xanthophylls. The aqueous and alcoholic extract of M. longifolia has been reported to show analgesic activity [1].

M. longifolia is a multipurpose tree. Large numbers of Mahua trees are found in India and the estimated production of its flowers is more than 1 million tonne in the country. Tribes of West Bengal, such as Lodhat, Santals, and Mundas, have been using different parts of Mahua as medicine [2]. The presence of some bioactive substances in leaves supports the traditional medicinal uses of M. longifolia. The presence of quercetin was reported in M. longifolia leaf through high-performance thin-layer chromatography technique. Madhucic acid, Madhusazone, and Madhusalmonone were isolated from M. longifolia fruits. A flavone (3,4-dihydroxy-5.2-dimethoxy-6,7-methylenedioxy) was isolated from the fruits of M. longifolia [3].

Recent researches on M. longifolia were against diolofenac-induced toxicity in female Wistar albino rabbits, bio fabrication, and characterization of flavonoid loaded Ag, Au, pyrolysis characteristics, fuel properties, and compositional study of M. longifolia butter [4,5]. Absorption, distribution, metabolism, and excretion (ADME) and toxicological profiling are critical parts of any drug development program, and essential for compliance with regulatory guidelines [6-9]. In this experiment, the ADME properties of each compound were analyzed using SWISS ADME, and the inhibiting target molecule of each compound was found using Swiss Target Prediction. This work would help in analyzing the pharmacological activities of the active compounds of M. longifolia against its inhibitory target molecules.

METHODS

Active compounds of M. longifolia

M. longifolia has various active compounds present in different parts of the plant. Few important ones are Vitamins A and C present in flower, alpha-spinasterol, alpha-terpinene (bark), and important amino acids such as alanine, glycine, cysteine (seeds), alpha- and beta-amyrin acetates (fruit) and xanthophylls, and erthrythrodil (leaves). The active compound of the flower of M. longifolia is Vitamin A (C_{13}H_{18}O) and Vitamin C (C_{6}H_{8}O). The active compound of M. longifolia bark is alpha-amyrin acetate (C_{30}H_{44}O), alpha-terpinene (C_{10}H_{16}), and oleic acid (C_{18}H_{34}O). The active compound of M. longifolia fruits is alpha-amyrin acetate (C_{30}H_{44}O), beta-amyrin acetate (C_{30}H_{44}O), beta-sitosteryl (C_{39}H_{58}O), dihydroquercetin (C_{30}H_{30}O), and quercetin (C_{30}H_{16}O). The active compound of M. longifolia seeds is alamine (C_{13}H_{18}N), arachidic acid (C_{26}H_{52}), cysteine (C_{6}H_{11}NO_{2}), glycine (C_{2}H_{11}NO), leucine (C_{6}H_{13}NO_{2}), linoleic acid (C_{18}H_{34}O), myristic acid (C_{14}H_{28}O), oleic acid (C_{18}H_{34}O), palmitic acid (C_{16}H_{32}O), quercetin (C_{30}H_{16}O), and stearic acid (C_{18}H_{36}O). The active compound of M. longifolia leaves is beta-sitosterol (C_{29}H_{50}), carotene (C_{40}H_{56}), erthrythodil (C_{29}H_{50}), myricitin (C_{30}H_{34}O), n-octacosanol (C_{38}H_{78}O), quercetin (C_{30}H_{16}O), stigmasterol (C_{29}H_{50}), and xanthophyll (C_{30}H_{16}O).

Analysis of ADME property

The ADME properties of each compound were analyzed using SWISS ADME (http://www.swissadme.ch/). The canonical smiles of each compound were taken from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and pasted into SWISS ADME to predict ADME parameters,
pharmacokinetic properties, drug-like nature, and medicinal chemistry of each compound.

**Analysis of inhibitory target molecule**

Analysis of the inhibitory target molecule was done using Swiss TargetPrediction (http://www.swisstargetprediction.ch/) a part of Expasy (https://www.expasy.org/medicinal_chemistry). This website is used to estimate the most probable macromolecular targets of a small molecule.

**RESULTS**

**ADME properties of M. longifolia**

Table 1 represents the ADME analysis of the active compounds of M. longifolia. Many compounds have obeyed the Lipinski rule and few compounds were observed to show high gastrointestinal (GI) absorption. Fig. 1 represents the ADME chart of the compounds. GI absorption in the following compounds was high – Vitamin A, Vitamin C, alpha-terpineol, dihydroquercetin, quercetin, glycol, isoleucine, leucine, linoleic acid, myristic acid, oleic acid, and stearic acid. GI absorption in the following compounds was low – alpha-amyrin acetate, alpha-spinasterol, oleic acid, beta-amyrin acetate, beta-spinasterol, arachidic acid, cysteine, carotene, erythrodiol, myricitin, n-Hexacosanol, n-Octacosanol, Stigmasterol, and xanthophylls.

**Inhibitory analysis of M. longifolia**

Table 2 represents the inhibitory target molecule of the active compound of M. longifolia with its probability and known actives.

**Role of inhibitory target molecules**

The role of inhibitory target molecules was analyzed which is discussed here. Gamma-amino-N-butyrate transaminase is responsible for the catabolism of gamma-aminobutyric acid and inhibition of neurotransmitters in the central nervous system (CNS) [10]. Peroxisome proliferator-activated receptor (PPAR) alpha binds to peroxisome proliferator response elements which initiate the transcriptional regulation of target genes. It may inhibit the ligand-induced transcriptional activity of PPARs alpha and gamma [11]. Fatty acid-binding protein intestinal actively accelerates the transport of lipids to specific parts in the cell. Metabotropic glutamate receptor 2 is the major excitatory neurotransmitter in the CNS and activates both ionotropic and metabotropic glutamate receptors [12]. The active compound Metabotropic glutamate receptor 6 is reported to cause neuronal excitability and synaptic transmission. This is by modulation of a variety of ion channels and other regulatory and signalling proteins. Tyrosine-protein kinase FYN encodes a membrane-associated tyrosine kinase that is involved in controlling cell growth. Tyrosine-protein kinase LCK controls a wide variety of cellular processes. High-affinity choline transporter is involved in pain regulation and pain inhibition [13].

Voltage-gated calcium channel alpha-2/delta subunit 1 plays roles in the trafficking of these channels, both to the plasma membrane and to specific subcellular domains. PPAR-gamma is a key regulator of metabolism, proliferation, inflammation and differentiation, and upregulates tumor suppressor genes. PPAR-alpha is involved in cell proliferation, cell differentiation and in immune and inflammation responses PPAR-alpha, which is a nuclear transcription factor. Free fatty acid receptor 1 is involved in the metabolic regulation of insulin secretion. Fatty acid-binding protein adipocyte is an important mediator of inflammation [14]. Vasopressin V2 receptor has the primary property to respond to the pituitary hormone arginine vasopressin. Aldose reductase is implicated in the development of diabetic complications by catalyzing the reduction of glucose to sorbitol. PPAR-alpha is involved in cell proliferation, cell differentiation and immune, and inflammation responses. Carboxylesterase 2 is responsible for the hydrolysis of various xenobiotics [15]. 11-beta-hydroxysteroid dehydrogenase 1 catalyzes the conversion of the stress hormone cortisol to the inactive metabolite cortisone. Protein-tyrosine phosphatase 1B is essential for catalytic activity. It acts as a negative regulator of insulin signaling by dephosphorylating the phosphotyrosine residues of insulin receptor kinase. Cytochrome P450 51 is involved in drug metabolism and synthesis of cholesterol, steroids, and other lipids. Adenosine A2a receptor plays an important role in cardiac rhythm and circulation, cerebral and renal blood flow, immune function, pain regulation, and sleep. Adenosine A3 receptor is involved in the inhibition of neutrophil degranulation in neutrophil-mediated tissue injury. Butyrylcholinesterase is involved in the detoxification of poisons including organophosphate nerve agents and pesticides, and the metabolism of drugs, including cocaine, heroin, and aspirin [16].

Microtubule-associated protein is associated with several neurodegenerative disorders such as Alzheimer’s disease, pick’s...
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Disease, frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy. Carbonic anhydrase II is associated with osteopetrosis and renal tubular acidosis. Carbonic anhydrase I encodes a cytosolic protein that is found at the highest level in erythrocytes. Transient receptor potential cation channel subfamily M member eight plays a role in prostate cancer cell migration. Niemann-Pick C1-like protein 1 plays a critical role in regulating lipid metabolism. Vitamin D receptor is involved in immune response and cancer. Muscarinic acetylcholine receptor M2 triggers calcium ion release into the cytosol.

DNA polymerase beta translocates to the nucleus on DNA damage.

Plasma retinol-binding protein results in defective delivery and supply to the epidermal cells [17].

**DISCUSSION**

The ethanolic extract of *M. longifolia* has a significant role in nephroprotective and hepatoprotective activity against acetaminophen-induced necrotic damage of hepatic and renal tissue. Ether benzene-95% crude ethanolic extract of leaves and bark of *M. longifolia* shows a remarkable reduction in the time taken to heal a wound [18]. The methanolic extraction proved to have potential benefits of anti-

| Plant parts | Compound          | TPSA (Å) | GIA | NRB | NHBD | NHBA | LIPINSKI | BA | LOG KP (cm/s) |
|-------------|-------------------|----------|-----|-----|------|------|----------|----|---------------|
| Flower      | Vitamin A         | 20.23    | High| 5   | 1    | 1    | YES,1 V  | 0.55| −4.01         |
|             | Vitamin C         | 10.22    | High| 2   | 4    | 6    | YES,0 V  | 0.56| −8.54         |
|             | Alpha-amyrin acetate | 26.30  | Low | 2   | 0    | 2    | YES,1 V  | 0.55| −2.36         |
|             | Alpha-spinasterol | 20.23    | Low | 5   | 1    | 1    | YES,1 V  | 0.55| −2.92         |
|             | Alpha-terpineol   | 20.23    | Low | 1   | 1    | 1    | YES,0 V  | 0.55| −4.83         |
|             | Oleic acid        | 57.53    | Low | 1   | 2    | 3    | YES,1 V  | 0.56| −3.77         |
| Fruit       | Alpha-amyrin acetate | 26.30  | Low | 2   | 0    | 2    | YES,1 V  | 0.55| −2.36         |
|             | Beta-amyrin acetate | 26.30  | Low | 2   | 0    | 2    | YES,1 V  | 0.55| −2.25         |
|             | Beta-sitosterol   | 20.23    | Low | 6   | 1    | 1    | YES,1 V  | 0.55| −2.20         |
|             | Dihydroquercetin  | 127.45   | High| 1   | 5    | 7    | YES,0 V  | 0.55| −7.8          |
| Seeds       | Alamine           | 63.32    | High| 1   | 2    | 3    | YES,0 V  | 0.55| −8.95         |
|             | Arachidic acid    | 37.30    | Low | 18  | 1    | 2    | YES,1 V  | 0.56| −1.61         |
|             | Cysteine          | 177.24   | Low | 7   | 4    | 6    | YES,0 V  | 0.55| −11.37        |
|             | Glycine           | 63.32    | High| 1   | 2    | 3    | YES,0 V  | 0.55| −9.04         |
|             | Isoleucine        | 63.32    | High| 3   | 2    | 3    | YES,0 V  | 0.55| −8.32         |
|             | Leucine           | 63.32    | High| 3   | 2    | 3    | YES,0 V  | 0.55| −8.18         |
|             | Linoleic acid     | 37.30    | High| 14  | 1    | 2    | YES,1 V  | 0.56| −3.05         |
|             | Myristic acid     | 37.30    | High| 12  | 1    | 2    | YES,0 V  | 0.56| −3.35         |
|             | Oleic acid        | 37.30    | High| 15  | 1    | 2    | YES,1 V  | 0.56| −2.60         |
|             | Palmitic acid     | 37.30    | High| 14  | 1    | 2    | YES,1 V  | 0.56| −2.77         |
|             | Quercetin         | 131.36   | High| 1   | 5    | 7    | YES,0 V  | 0.55| −7.05         |
|             | Steric acid       | 37.30    | High| 16  | 1    | 2    | YES,1 V  | 0.56| −2.19         |
| Leaves      | Beta-sitosterol   | 20.23    | Low | 6   | 1    | 1    | YES,1 V  | 0.55| −2.20         |
|             | Carotene          | 0.00     | Low | 10  | 0    | 0    | NO,2 V   | 0.17| 0.12          |
|             | Erythroidiol      | 40.46    | Low | 1   | 2    | 2    | YES,1 V  | 0.55| −3.63         |
|             | Myricitin         | 151.59   | Low | 1   | 6    | 8    | YES,1 V NH or OH=5 | 0.55| −7.40         |
|             | n-Hexacosanol     | 20.23    | Low | 24  | 1    | 1    | YES,1 V  | 0.55| 0.26          |
|             | n-Octacosanol     | 20.23    | Low | 26  | 1    | 1    | YES,1 V  | 0.55| 0.86          |
|             | Quercetin         | 131.36   | High| 1   | 5    | 7    | YES,0 V  | 0.55| −7.05         |
|             | Stigmasterol      | 20.23    | Low | 5   | 1    | 1    | YES,1 V  | 0.55| −2.74         |
|             | Xanthophylls      | 40.46    | Low | 10  | 2    | 2    | YES,1 V  | 0.55| −1.95         |

GIA: Gastrointestinal absorption, NRB: Number of rotatable bond, NHBD: Number of hydrogen bond donor, NHBA: Number of hydrogen bond acceptor, BA: Bioavailability, V: Violation
### Table 2: Analysis of inhibitory target molecule

| Plants parts | Compound | Target | Target class | Probability | Known active (3d/2d) |
|--------------|----------|--------|--------------|-------------|----------------------|
| Flower       | Vitamin A | Plasma binding retinol | Secreted protein | 0.418947321 | 3/2 |
|              | Retinoid X receptor alpha | Nuclear receptor | 0.418947321 | 2/3 |
|              | Retinoid X receptor beta | Nuclear receptor | 0.106099949 | 0/2 |
|              | Vitamin C | Glyoxyn synthase kinase-3 beta | Kinase | 0.141787381 | 0/2 |
|              | Protein kinase C alpha | Kinase | 0 | 0/168 |
|              | Protein-tyrosine phosphatase 1B | Phosphatase | 0 | 0/9 |
| Bark         | Alpha-amyрин | Carboxylesterase 2 | Enzyme | 0.128531578 | 0/12 |
|              | Acetate    | 11-beta-hydroxysteroid dehydrogenase 1 | Enzyme | 0.128531578 | 153/29 |
|              |           | Protein-tyrosine phosphatase | Phosphatase | 0.120225751 | 7/70 |
|              | Alpha-spinasterol | Androgen receptor | Nuclear receptor | 0.705989664 | 23/106 |
|              |           | Muscarinic acetylcholine receptor M2 | Family A G protein-coupled receptor | 0.306043655 | 0/2 |
|              |           | 11-beta-hydroxysteroid dehydrogenase 1 | Enzyme | 0.128531578 | 153/29 |
|              |           | Protein-tyrosine phosphatase | Phosphatase | 0.120225751 | 7/70 |
|              |           | Androgen receptor | Nuclear receptor | 0.705989664 | 23/106 |
|              |           | Muscarinic acetylcholine receptor M2 | Family A G protein-coupled receptor | 0.306043655 | 0/2 |
| Fruit        | Alpha-amyрин | Carboxylesterase 2 | Enzyme | 0.128531578 | 0/12 |
|              | Acetate    | 11-beta-hydroxysteroid dehydrogenase 1 | Enzyme | 0.128531578 | 153/29 |
|              |           | Protein-tyrosine phosphatase | Phosphatase | 0.120225751 | 7/70 |
|              | Beta-amyрин | Prostaglandin E synthase | Enzyme | 0.128531578 | 6/13 |
|              | acetate    | Androgen receptor | Nuclear receptor | 0.120225751 | 12/106 |
|              |           | 11-beta-hydroxysteroid dehydrogenase 2 | Enzyme | 0.120225751 | 6/11 |
|              | Beta-sitosterol | Androgen receptor | Nuclear receptor | 0.120225751 | 12/106 |
|              |           | HMG-CoA reductase | Oxidoreductase | 0.614311102 | 36/7 |
|              |           | Cytochrome P450 51 | Cytochrome P450 | 0.614311102 | 2/2 |
|              | Dihydroquercetin and quercetin | NADPH oxidase 4 | Enzyme | 1 | 7/8 |
| Seeds        | Alanine   | Vasopressin V2 receptor | Family A G protein-coupled receptor | 1 | 1/1 |
|              |           | Aldose reductase | Enzyme | 1 | 17/72 |
|              |           | Gamma-amino-N-butyrate transaminase | Transferase | 0.03397069 | 2/0 |
|              |           | Histone deacyetylase 3 transporter | ERASER | 0 | 0/1 |
|              |           | Betaine transporter | Electrochemical transporter | 0 | 2/0 |
|              | Arachidonic acid | Peroxisome proliferator-activated receptor alpha | Nuclear receptor | 0.364127943 | 77/9 |
|              |           | Peroxisome proliferator-activated receptor delta | Nuclear receptor | 0.364127943 | 30/7 |
|              | Cysteine  | Fatty acid-binding protein intestinal | Fatty acid-binding protein family | 0.34502608 | 0/1 |
|              | Metabotropic glutamate receptor 2 | Family C G protein-coupled receptor | 0 | 3/0 |
|              |           | Metabotropic glutamate receptor 3 | Family C G protein-coupled receptor | 0 | 2/0 |
|              | Metabotropic glutamate receptor 6 | Family C G protein-coupled receptor | 0 | 1/0 |
|              | Glycine   | Tyrosine-protein kinase FYN | Kinase | 0 | 0/1 |
|              |           | Tyrosine-protein kinase LCK | Kinase | 0 | 0/1 |
|              | Isoleucine | Voltage-gated calcium channel alpha-2/delta subunit 1 | Calcium channel auxiliary subunit alpha2delta family | 0.125817531 | 30/5 |
|              |           | Adenosine A3 receptor | Family A G protein-coupled receptor | 0.095255918 | 3/2 |
|              | Leucine   | Excitatory amino acid transporter 3 | Electrochemical transporter | 0.074316474 | 0/3 |
|              |           | Voltage-gated calcium channel alpha-2/delta subunit 1 | Calcium channel auxiliary subunit alpha2delta family | 0.13510518 | 31/5 |
|              |           | Adenosine A3 receptor | Family A G protein-coupled receptor | 0.095255918 | 3/2 |
|              | Linoleic acid | Excitatory amino acid transporter 3 | Electrochemical transporter | 0.074316474 | 0/3 |
|              |           | Peroxisome proliferator-activated receptor gamma | Nuclear receptor | 0.747488284 | 429/22 |
|              |           | Peroxisome proliferator-activated receptor alpha | Nuclear receptor | 0.747488284 | 270/18 |
|              | Myristic acid | Peroxisome proliferator-activated receptor delta | Nuclear receptor | 0.747488284 | 192/10 |

(Contd...)
inflammatory, anti-pyretic, and analgesic properties because of the presence of flavonoids in the plants. The methanolic extract of the bark is known to have antidiabetic and anti-hyperglycemic activity. The aqueous extract of leaves has been preventive to have an effective antiproliferative property. The bark is used for rheumatism, chronic bronchitis, diabetes mellitus, ulcers, tonsillitis, and bleedings. The flowers have been traditionally used as an analgesic, diuretic, cooling agent, tonic, aphrodisiac, astringent, demulcent and for the treatment of helminths, acute and chronic tonsillitis, pharyngitis, and bronchitis. Leaves are expectorant and also used for chronic bronchitis and Cushing's disease [18].

ADME is an abbreviation used in pharmacokinetics and pharmacology for ADME and describes the disposal of a compound within an organism. The path of any new molecule to reach its target involves the passage through many barriers, as well as the survival of the complicated biological systems. A prerequisite in drug discovery and development in conducting drug metabolism and pharmacokinetics studies, often referred to as ADME toxicity studies [19]. Absorption – how much of the drug and how quickly is it absorbed? (bioavailability). Absorption takes place in the GI tract. The surface area and pH of the organ influence the rate of absorption of the compound. Absorption is the movement of drug from the GI tract. The surface area and pH of the organ influence the rate of absorption of the compound. Absorption is the movement of drug from the GI tract.

**Table 2: (Continued)**

| Plants parts | Compound | Target | Target class | Probability | Known active (3d/2d) |
|--------------|----------|--------|--------------|-------------|---------------------|
| Free fatty acid receptor 1 | Oleic acid | Fatty acid-binding protein adipocyte | Family A G protein-coupled receptor | 0.580792647 | 164/3 |
| | Fatty acid-binding protein adipocyte | Fatty acid-binding protein family | 1 | 5/4 |
| | Anandamide amidohydrolase | Enzyme | 1 | 7/17 |
| | Peroxisome proliferator-activated receptor gamma | Nuclear receptor | 1 | 223/24 |
| Palmitic acid | Fatty acid-binding protein adipocyte | Fatty acid-binding protein family | 0.935895337 | 20/3 |
| | Peroxisome proliferator-activated receptor alpha | Nuclear receptor | 0.935895337 | 152/9 |
| | Fatty acid-binding protein adipocyte | Fatty acid-binding protein family | 0.935895337 | 10/5 |
| Quercetin | NADPH oxidase 4 | Enzyme | 1 | 7/8 |
| | Vasopressin V2 receptor | Family A G protein-coupled receptor | 1 | 1/1 |
| | Aldose reductase | Enzyme | 1 | 17/72 |
| | Peroxisome proliferator-activated receptor alpha | Nuclear receptor | 0.929299884 | 121/9 |
| | Peroxisome proliferator-activated receptor delta | Nuclear receptor | 0.929299884 | 135/7 |
| | Fatty acid-binding protein adipocyte | Fatty acid-binding protein family | 0.723067577 | 13/3 |
| Leaves Beta-sitosterol | HMG-CoA reductase | Oxidoreductase | 0.120225751 | 12/106 |
| | Cytochrome P450 51 | Cytochrome P450 | 0.614311102 | 36/7 |
| | Carotene | Adenosine A1 receptor | 0.086885855 | 0/1 |
| | | Family A G protein-coupled receptor | 0.086885855 | 0/1 |
| Erythrodol | Protein-tyrosine phosphatase 1B | Phosphatase | 0.120225751 | 7/70 |
| | Butyrylcholinesterase | Hydrolase | 0.31401521 | 8/2 |
| | Cytochrome P450 19A1 | Cytochrome P450 | 0.22719907 | 12/157 |
| Myricitin | Microtubule-associated protein tau | Unclassified protein | 1 | 1/1 |
| | Lysine-specific demethylase 4D-like | Eraser | 1 | 1/2 |
| | G-protein coupled receptor 35 | Family A G protein-coupled receptor | 1 | 2/4 |
| n-Hexacosanol | Transient receptor potential cation channel subfamily M member 8 | Voltage-gated ion channel | 0.177292204 | 0/1 |
| | Carbonic anhydrase II | Lyase | 0.177292204 | 0/3 |
| | Carbonic anhydrase I | Lyase | 0.177292204 | 0/3 |
| n-Octacosanol | Transient receptor potential cation channel subfamily M member 8 | Voltage-gated ion channel | 0.177292204 | 0/1 |
| | Carbonic anhydrase II | Lyase | 0.177292204 | 0/3 |
| | Carbonic anhydrase I | Lyase | 0.177292204 | 0/3 |
| Quercetin | NADPH oxidase 4 | Enzyme | 1 | 7/8 |
| | Vasopressin V2 receptor | Family A G protein-coupled receptor | 1 | 1/1 |
| | Aldose reductase | Enzyme | 1 | 17/72 |
| Stigmasterol | Androgen Receptor | Nuclear receptor | 0.689284537 | 35/102 |
| | Niemann-pick C1-like protein 1 | Other membrane protein | 0.639333184 | 9/13 |
| Xanthophylls | Vitamin D receptor | Nuclear receptor | 0.082221517 | 0/52 |
| | Androgen receptor | Nuclear receptor | 0.082221517 | 0/52 |
| | Protein-tyrosine phosphatase 1B | Phosphatase | 0.082221517 | 0/16 |
is more soluble [20]. Distribution – where is the drug administered and what is the rate and extent of distribution. After absorption, the drugs are distributed in blood. After GI tract absorption, it is taken up by the hepatic portal system. Lipids are absorbed into the lymphatic system and through thoracic duct, it is delivered into the blood. Lipophilicity plays an important role in distribution [21]. The capillaries in CNS are sealed by connective tissue; hence, only small molecules can cross the blood–brain barrier [22]. Metabolism – how fast is the drug metabolized, what is the mechanism of action and what metabolite is formed and is it active or toxic. It depends on race, age, the health of the patient, depends on whether the patient is taking another drug. The liver is the primary site but it can happen anywhere in the bloodstream. Biotransformation is the process of making a compound more hydrophilic so that it can be excreted out from the body. This happens in two phases, i.e., Phase I metabolism – the compound is modified chemically by the process such as oxidation, reduction, and hydrolysis. These changes create sites for Phase II metabolism. In Phase II conjugation of the Phase I, metabolite takes place with polar groups, for example, glucuronic acid and sulfates. This alters the activity and it becomes more hydrophilic and less lipid soluble so it gets excreted easily. Excretion – how is the drug excreted and how quickly? Some drugs are unchanged but some drugs get changed into urine or bile and are excreted out [23].

Scientists are more interested in estimating the drug-likeness properties that are bioavailability, pharmacokinetics (how body responds to the drug), pharmacodynamics (how drug acts on the body), solubility, toxicity, lipophilicity, permeability, logP, logD, kinetic and thermodynamic solubility, the volume of distribution, and biotransformation [24]. The underlying goal and end-game for all ADME studies are to better understand a compound’s metabolite-mediated toxicity and safety profile to make a concrete decision on whether the compound can progress to late-stage preclinical and clinical studies to enable filling for an investigational new drug, new drug agreement, or a biologics licensing agreement. ADME studies can be used in molecular docking, pharmacophore modeling, de novo designing, fragment-based screening, to find structure-activity relationships [25,26]. Transports play an important role in the ADME of drugs. Recently, various in vitro and in vivo methods have been established for studying transporter function and drug transporter function [9,27].

There are some rules or models for classifying a compound, whether it is a good drug or a bad drug. The most widely accepted one is Lipinski’s rule of 5. Lipinski’s rule – devised by Lipinski and coworkers. If two parameters are out of range, “poor absorption or permeability is possible.” The compound may get absorbed in GI tract if any one of the parameter doesn’t work properly. Hence, the rules are: (1) Molecular weight <500, (2) number of H-bond acceptors<10 (Any O and N atoms), (3) number of H-bond donors <5 (N-H or O-H groups), (4) LogP >5 then it is hydrophobic, and (5) LogP of 0–5 then it is very hydrophilic [28,29].

CONCLUSION

The article has elaborated on the ADME and inhibitory potential of M. longifolia. The role of all target molecules is much essential. The active compound of M. longifolia can be further studied through in vitro and in silico methods for its potential pharmaceutical values.

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The authors declare that there are no conflicts of interest.

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