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

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ABSTARCT

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 TargetPrediction.

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.

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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 Iluppai. 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. longifolig* 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 Lodhas, 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, Madhushazone, and Madhusalmone were isolated from M. longifolia fruits. A isoflavone (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 diclofenac-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 TargetPrediction. 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-terpineol (bark), and important amino acids such as alanine, glycine, cysteine (seeds), alpha- and beta-amyrin acetates (fruit) and xanthophylls, and erythrodiol (leaves).

The active compound of the flower of *M. longifolia* is Vitamin A ($C_{20}H_{30}O$) and Vitamin C ($C_6H_8O_6$). The active compound of *M. longifolia* bark is alpha-amyrin acetate ($C_{32}H_{52}O_2$), alpha-spinasterol ($C_{29}H_{48}O$), alphaterpineol ($C_{10}H_{18}O$), and oleic acid ($C_{30}H_{48}O_3$). The active compound of *M. longifolia* fruits is alpha-amyrin acetate ($C_{32}H_{52}O_2$), beta-amyrin acetate ($C_{32}H_{52}O_2$), beta-amyrin acetate ($C_{32}H_{52}O_2$), beta-amyrin acetate ($C_{32}H_{52}O_2$), beta-sitosterol ($C_{29}H_{50}O$), dihydroquercetin ($C_{25}H_{34}N_2O_7$), and quercetin ($C_{15}H_{10}O_7$). The active compound of *M. longifolia* seeds is alanine ($C_{3}H_7NO_2$), arachidic acid ($C_{20}H_{40}O2$), cysteine ($C_{3}H_7NO_2$ S), glycine ($C_{2}H_{50}O_2$), isoleucine ($C_{6}H_{13}NO_2$), leucine ($C_{6}H_{13}NO_2$), linoleic acid ($C_{16}H_{32}O_2$), quercetin ($C_{15}H_{10}O_7$), and stearic acid ($C_{18}H_{36}O_2$). The active compound of *M. longifolia* leaves is betasitosterol ($C_{29}H_{50}O_7$), and stearic acid ($C_{19}H_{36}O_2$). The active compound of *M. longifolia* leaves is betasitosterol ($C_{29}H_{50}O_7$), carotene ($C_{40}H_{56}$), erythrodiol ($C_{30}H_{50}O_2$), myricitin ($C_{15}H_{10}O_8$), n-hexacosanol ($C_{29}H_{48}O$), and xanthophylls ($C_{40}H_{56}O_2$).

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, glycine, isoleucine, leucine, linoleic acid, myristic acid, oleic acid, palmitic 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 acidbinding 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 $kin ase. Cytochrome P450\,51\,is involved in drug metabolism and synthesis$ 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



Fig. 1: Absorption, distribution, metabolism, and excretion analysis

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
			0				MLOGP>4.15		
	Vitamin C	10.22	High	2	4	6	YES,0 V	0.56	-8.54
Bark	Alpha-amyrin acetate	26.30	Low	2	0	2	YES,1 V	0.55	-2.36
Durn	1 5						MLOGP>4.15		
	Alpha-spinasterol	20.23	Low	5	1	1	YES,1 V	0.55	-2.92
	X X						MLOGP>4.15		
	Alpha-terpineol	20.23	High	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
							MLOGP>4.15		
Fruit	Alpha-amyrin acetate	26.30	Low	2	0	2	YES,1 V	0.55	-2.36
							MLOGP>4.15		
	Beta-amyrin acetate	26.30	Low	2	0	2	YES,1 V	0.55	-2.25
	-						MLOGP>4.15		
	Beta-sitosterol	20.23	Low	6	1	1	YES,1 V	0.55	-2.20
							MLOGP>4.15		
	Dihydroquercetin	127.45	High	1	5	7	YES, 0 V	0.55	-7.8
	Quercetin	131.36	High	1	5	7	YES, 0 V	0.55	-7.05
Seeds	Alanine	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
							MLOGP>4.15		
	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
							MLOGP>4.15		
	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
							MLOGP>4.15		
	Palmitic acid	37.30	High	14	1	2	YES,1 V	0.56	-2.77
							MLOGP>4.15		
	Quercetin	131.36	High	1	5	7	YES, 0 V	0.55	-7.05
	Stearic acid	37.30	High	16	1	2	YES,1 V	0.56	-2.19
							MLOGP>4.15		
Leaves	Beta-sitosterol	20.23	Low	6	1	1	YES, 1 V	0.55	-2.20
							MLOGP>4.15		
	Carotene	0.00	Low	10	0	0	NO, 2 V	0.17	0.12
							MW>500.		
							MLOGP>4.15		
	Erythrodiol	40.4 6	Low	1	2	2	YES, 1 V	0.55	-3.63
							MLOGP>4.15		
	Myricitin	151.59	Low	1	6	8	YES, 1 V NH or	0.55	-7.40
							OH>5		
	n-Hexacosanol	20.23	Low	24	1	1	YES,1 V	0.55	0.26
							MLOGP>4.15		
	n-Octacosanol	20.23	Low	26	1	1	YES,1 V	0.55	0.86
							MLOGP>4.15		
	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
							MLOGP>4.15		
	Xanthophylls	40.46	Low	10	2	2	NO, 2 V	0.17	-1.95
							MW>500		
							MLOGP>4.15		

Table 1: Absorption, distribution, metabolism, and excretion analysis of active compounds of Madhuca longifolia

GIA: Gastrointestinal absorption, NRB: Number of rotatable bond, NHBD: Number of hydrogen bond donor, NHBA: Number of hydrogen bond acceptor, BA: Bioavailability, V: Violation

disease, frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy. Carbonic anhydrase II is associated with osteopetrosis and renal tubular acidosis. Carbonic anhydrase I encode 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 it 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 acetaminopheninduced 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-

Table 2: Analysis	of inhibitory	target molecule
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Fruit Alpha-amyrin acetate Carboxylesterase 2 Enzyme 0.128531578 0/12 acetate 11-beta-hydroxysteroid dehydrogenase 1 Protein-tyrosine phosphatase 1B Enzyme 0.128531578 6/13 Beta-amyrin Androgen receptor Enzyme 0.120225751 12/106 11-beta-hydroxysteroid dehydrogenase 2 Enzyme 0.120225751 12/106 Beta-sitosteroi 11-beta-hydroxysteroid dehydrogenase 2 Nuclear receptor 0.120225751 12/106 11-beta-hydroxysteroid dehydrogenase 2 Nuclear receptor 0.120225751 12/106 11-beta-hydroxysteroid dehydrogenase 2 Nuclear receptor 0.120225751 12/106 11-beta-hydroxysteroid dehydrogenase 2 Cytochrome P450 0.614311102 36/7 Cytochrome P450 0.614311102 36/7 7/8 Vasopressin V2 receptor Family A G protein-coupled 1 1/1 receptor Aldose reductase 0.03397069 7/0 Arachidic acid Peroxisome proliferator-activated receptor alpha Nuclear receptor 0.364127943 30/7 Cysteine Histone deacetylase 3 ransporter Enzyme 0 2/0 0			Aldo-keto reductase family 1 member B10	Enzyme	0.754299393	7/7
acetate II-beta-hydroxysternid dehydrogenase 1 Protein-tyrosine phosphatase 1B Protein-tyrosine phosphatase 1D Protein-tyrosine phosphatase 2D Protein-tyrosine phosphatase 1D Protein-tyrosine phosphatase 2D Protein-tyrosine phosphatase 2D Protein-tyrosin	Fruit	Alpha-amyrin	Carboxylesterase 2	Enzyme	0.128531578	0/12
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Beta-amyrin acetate Prostaglandin E synthase Enzyme 0.12023751 12/106 acetate Androgen receptor Enzyme 0.120225751 12/106 Beta-sitosterol Androgen receptor Nuclear receptor 0.120225751 12/106 Beta-sitosterol Androgen receptor Nuclear receptor 0.120225751 12/106 Beta-sitosterol NAPI order deutase Oxidoreductase 0.614311102 2/2 Cytochrome P450 51 Cytochrome P450 0.614311102 2/2 Androgen receptor Farmily A G protein-coupled 1.1 7/2 Seeda Alanine Aldose reductase Enzyme 1.3 7/7 Seeda Alanine Aldose reductase Enzyme 1.3 7/7 Seeda Alanine Aldose reductase Sampa-sinino-N-butyrate transaminase Enzyme 0.3 0/1 Tyros receptor Enzyme 1.3 7/7 7/7 7/7 Seeda Alanine Holdsoreductase dreceptor or transferase 0.3 0/1 Cysteine			Protein-tyrosine phosphatase 1B	Phosphatase	0.120225751	7/70
acetate		Beta-amyrin	Prostaglandin E synthase	Enzyme	0.128531578	6/13
Andragen receptor 0.120225751 6/11 Nuclear receptor 0.120225751 6/12 Beta-sitosterol Androgen receptor 0.120225751 6/12 HMG-CoA reductase 0.01201225751 6/12 UMG-CoA reductase 0.01201225751 6/12 UMG-CoA reductase 0.014311102 3/7 and quercetin ADPH oxidase 4 Enzyme 1 1 7/8 and quercetin Vasopressit V2 receptor 7 Aldose reductase 10.03397069 2/0 Family A G protein-coupled 1 1/1/7 Response Protein N-butyrate transaminase 17 ansFerase 0.03397069 2/0 Histone deacetylase 3 transporter EKASER 0 0/1 Betaine transporter 0.260397079 2/0 Histone deacetylase 3 transporter EKASER 0.030397069 2/0 Peroxisome proliferator-activated receptor alpha Peroxisome proliferator-activated receptor 0.364127943 30/7 Peroxisome proliferator-activated receptor alpha Peroxisome proliferator-activated receptor alpha Peroxisome proliferator-activated receptor 6 Metabotropic glutamate receptor 2 Metabotropic glutamate receptor 6 Family C G protein-coupled 0.2/0 Metabotropic glutamate receptor 6 Family C G protein-coupled 0.2/0 receptor Family C G protein-coupled 0.0/1 High-filmit, tholine transporter 0.0/1 High-filmit, tholine transporter 2 Family A G protein-coupled 0.0/1 High-filmit, tholine transporter 3 Excitatory amino acid trans		acetate				
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HMG-CoA reductaseOxidoreductaseOxidoreductaseOxidoreductaseOxidoreductaseOxidoreductaseOxidoreductaseOxidoreductaseOxidoreductaseOxidoreductaseOxidoreductaseOxidoreductaseIn7/8SeedsAlanineAldose reductaseEnzyme11/17/721/772SeedsAlanineGamma-amino-N-butyrate transaminaseTransferase0.033970692/01/0Arachidic acidPeroxisome proliferator-activated receptor alphaNuclear receptor0.3641279433/7Arachidic acidPeroxisome proliferator-activated receptor alphaNuclear receptor0.3641279433/7Arachidic acidPeroxisome proliferator-activated receptor alphaNuclear receptor0.3641279433/07Fatty acid-binding protein intestinal Peroxisome proliferator-activated receptor dela Metabotropic glutamate receptor 2Fatty acid-binding protein family Peroxisome proliferator-activated receptor 601/0Metabotropic glutamate receptor 6Fatty acid-binding protein-coupled receptor01/0Metabotropic glutamate receptor 7Family C G protein-coupled Peroxisome proliferator-activated receptor 601/0Righting Cogagate calcium channel alpha-2/delta subunit 1Adenosine A3 receptor01/1Adenosine A3 receptorElectrochemical transporter0.0743164740/3LeucineVoltage-gated calcium channel alpha-2/delta subunit 1Alpha-2/delta family Adenosine A3 receptor0.0743164740/3LeucineVoltage-gated calcium channel		Beta-sitosterol	Androgen receptor	Nuclear receptor	0.120225751	12/106
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NumberHistone deacetylase 3 transporter Betaine transporter Betaine transporterERASER000/1Arachidic acidPeroxisome proliferator-activated receptor alpha Peroxisome proliferator-activated receptor delta Fatty acid-binding protein intestinal Fatty acid-binding protein family 0.34052608 Ol03/0CysteineMetabotropic glutamate receptor 2 Metabotropic glutamate receptor 3 Metabotropic glutamate receptor 6 Tyrosine-protein kinase FYN High-affinity choline transporter Subunit 1 Adenosine A3 receptorFamily C G protein-coupled Calcium channel alpha-2/delta alpha2delta family Adenosine A3 receptor01/0LeucineExcitatory amino acid transporter 3 subunit 1 Adenosine A3 receptorElectrochemical transporter Calcium channel alpha-2/delta subunit 1 Adenosine A3 receptor0.095255918 Al23/2 receptorLinoleic acidPeroxisome proliferator-activated receptor alpha Peroxisome proliferator-activated receptor alphaNuclear receptor Nuclear receptor0.74316474 O/3Linoleic acidPeroxisome proliferator-activated receptor alpha Peroxisome prolifera	Seeds	Alanine	Gamma-amino-N-butyrate transaminase	Transferase	0.03397069	2/0
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Peroxisome proliferator-activated receptor delta Nuclear receptor 0.5326355 225/5		Myristic acid	Peroxisome profilerator-activated receptor alpha	Nuclear receptor	095528599	229/9
		.,	Peroxisome proliferator-activated receptor delta	Nuclear receptor	0.580792647	138/7

(Contd...)

Table 2: (Continued)

Plants parts	Compound	Target	Target class	Probability	Known active (3d/2d)
-		Free fatty acid recentor 1	Family A G protein-coupled	0 580792647	164/3
			receptor	0.000772017	101/0
	Oleic acid	Fatty acid-binding protein adipocyte	Fatty acid-binding protein family	1	5/4
		Anandamide amidohydrolase	Enzyme	1	7/17
		Peroxisome proliferator-activated receptor	Nuclear receptor	1	223/24
		gamma			
	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 muscle	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	1	1/1
			receptor		
		Aldose reductase	Enzyme	1	17/72
	Stearic acid	Peroxisome proliferator-activated receptor alpha	Nuclear receptor	0.929299884	121/9
		Peroxisome proliferator-activated receptor delta	Nuclear receptor	0.929299884	135/7
	D 1	Fatty acid-binding protein adipocyte	Fatty acid-binding protein family	0.723067577	13/3
Leaves	Beta-sitosterol	Androgen Receptor	Nuclear receptor	0.120225751	12/106
		HMG-COA reductase	Oxidoreductase	0.614311102	36/7
	Caratana	Cytochrome P450 51	Cytochrome P450	0.006005055	2/2
	Carotelle	Adenosine A1 receptor	Fainity A G protein-coupled	0.0000000000000000000000000000000000000	0/1
		Adapasina Ala recontar	Ference Constant counted	0.006005055	0/1
		Adenosine Aza receptor	Fainity A G protein-coupled	0.0000000000000000000000000000000000000	0/1
		Adapasing A2 recentor	Femily A C protein coupled	0.006005055	0/2
		Adenositie AS receptor	receptor	0.000003033	0/3
	Frythrodial	Protoin-turosino phosphataso 18	Phoenhatasa	0 120225751	7/70
	Erythroutor	Buturylcholinesterase	Hydrolase	0.120225751	8/2
		Cytochrome P450 1941	Cytochrome P45	0.222719907	12/157
	Myricitin	Microtubule-associated protein tau	Unclassified protein	1	1/1
	Nyrieitin	Lysine-specific demethylase 4D-like	Eraser	1	1/1
		G-protein coupled receptor 35	Family A G protein-coupled	1	2/4
		- F	recentor	-	_, -
	n-Hexacosanol	Transient receptor potential cation channel	Voltage-gated ion channel	0.177292204	0/1
		subfamily M member 8			- /
		Carbonic anhydrase II	Lvase	0.177292204	0/3
		Carbonic anhydrase I	Lvase	0.177292204	0/3
	n-Octacosanol	Transient receptor potential cation channel	Voltage-gated ion channel	0.177292204	0/1
		subfamily M member 8	0.0		,
		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	1	1/1
			receptor		
		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
		HMG-CoA reductase	Oxidoreductase	0.639333184	50/7
	Xanthophylls	Vitamin D receptor	Nuclear receptor	0.082221517	0/57
		Androgen receptor	Nuclear receptor	0.082221517	0/52
		Protein-tyrosine phosphatase 1B	Phosphatase	0.082221517	0/16

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 prevent to have an effective antiulcer property [2]. Anticancer activity of *M. longifolia* was reported in Ayurvedic literature and some *in vitro* cell line studies also confirmed its 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 its site of administration into the body. Small molecules diffuse easily than large molecules. Lipid soluble drugs are absorbed faster. Acidic drugs get well absorbed in the stomach (ph-2) and basic drugs get well absorbed in the small intestine (ph-8.0). Most of the drugs get absorbed in the intestine than in the stomach because the surface area of the stomach is smaller than that of the intestine. LogP tells us about the hydrophilic and hydrophobic balance. More the value of logP is hydrophobic and its less soluble. Lower the value of logP, the compound is hydrophilic and it

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 it is 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 filing 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]. Transporters 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 0 and N atoms), (3) number of H-bond donors <5 (N-H or 0-H groups), (4) LogP >5 then it is hydrophobic, and (5) LogP id 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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AUTHORS' CONTRIBUTIONS

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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