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Research Article

ADMET informatics of Tetradecanoic acid (Myristic Acid) from ethyl acetate fraction of *Moringa oleifera* leaves

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Abstract

In-silico Computer-Aided Drug Design (CADD) often comprehends virtual screening (VS) of datasets of natural pharmaco-active compounds for drug discovery protocols. Plant Based Natural Products (PBNPs) still, remains to be a prime source of pharmaco-active compounds due to their unique chemical structural scaffolds and functionalities with distinct chemical characteristic feature from natural source that are much acquiescent to drug metabolism and kinetics. In the Post-COVID-Era number of publications pertaining to PBNPs and publicly accessible plant based natural product databases (PBNPDBs) has significantly increased. Moreover, PBNPs are important sources of inspiration or starting points to develop novel therapeutic agents. However, a well-structured, in-depth ADME/Tox profile of PBNPs has been limited or lacking for many of such compounds, this hampers the successful exploitation of PBNPs by pharma industries. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties play key roles in the discovery/ development of drugs, pesticides, food additives, consumer products, and industrial chemicals. In the present study, ADMET-informatics of Tetradecanoic Acid (Myristic Acid) from ethyl acetate fraction of *Moringa oleifera* leaves to predict drug metabolism and pharmacokinetics (DMPK) outcomes has been taken up. This work contributes to the deeper understanding of Myristic acid as major source of drug from commonly available medicinal plant - *Moringa oleifera* with immense therapeutic potential. The data generated herein could be useful for NP based lead generation programs.

Keywords: *Moringa oleifera*; Secondary Metabolites; Bioactive Substances; Myristic acid (MA); DMPK; ADME/Tox; Natural Products (NPs); PBNPs; PBNPDBs

INTRODUCTION

Myristic Acid (MA) (IUPAC: Tetradecanoic acid) is a common saturated fatty acid with the molecular formula $CH_3(CH_2)_{12}COOH$. Its salts and esters are referred to as myristates or tetradecanoates. Named after *Myristica fragrans*, from which MA was first isolated in 1841 by Lyon Playfair[1], is a long-chain saturated fatty acid (C:D ratio of 14:0). MA is one of the most abundant fatty acids in milk fat (10%), alternatively obtained from plant sources such as palm oil, coconut oil. MA occurs as hard, faintly yellow or white, glossy crystalline solid or as yellow-white or white powder. People with allergic reactions to MA end-up with blockage in digestive system, undiagnosed abdominal pain and children under the age of 6 years should not use it. Studies depict that diet rich in MA significantly increase concentrations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the liver and blood plasma[2]; it enhances ALA tissue storage and increases DHA and Arachidonic acid (AA) concentrations in brain tissues. Further, it has been demonstrated that MA significantly increases activity of delta 6-desaturase in a dose dependent manner indicating that MA could be a possible activator of ALA conversion to DHA[3]. Embryonic neural stem cells (eNSCs) are immature precursors of central nervous system (CNS), with self-renewal and multi-potential differentiation capacities. These are regulated by endogenous

and exogenous factors such as α-linolenic acid (ALA), stearic acid (SA), myristic acid (MA), and β-sitosterol on proliferation and differentiation of eNSCs[3]. MA is commonly added via a covalent linkage to the N-terminal glycine of many eukaryotic and viral proteins, a process called myristoylation. Myristoylation enables proteins to bind to cell membranes and facilitates protein-protein interactions. Myristolyation of proteins affect many cellular functions and thus has implications in health and disease[4]. Commercially, MA esters and salts are used in soaps, eye makeup, detergents, nail care products, hair care products, shaving products and others[5]. MA may cause side effects such as skin irritation, eye irritation, cough, urge to vomit, abdominal cramps, diarrhea, rash, allergic reaction and glycerin laxative-anal.

So far 13 species have been reported in the genus *Moringa*, of all *M. oleifera* is the most widely distributed species[6]. *M. oleifera* is native to India, however, cultivated all over the world[7,8]. It is a deciduous tree with brittle stem, whitish-gray corky bark with branches; leaves pale green, bipinnate/ tri-pinnate with opposite, ovate leaflets[7,9]. *M. oleifera* has versatile nutraceutical uses[10,11], all parts including leaves, roots, flowers, pods, seeds, and gum are endowed with nutraceutical and pharmaceutical properties[7-11]. *M. oleifera* has been traditionally used in folk remedies across various indigenous systems of medicine[12]. Pharmacological studies indicate that extracts obtained from the plant have antioxidants[13], anti-carcinogenic[14], anti-diabetic[15], anti-bacterial[16], and anti-fungal[17] properties. Interestingly, no adverse effects have been reported yet[8]. Though, significant variation in composition of different species exists versatile nature of phytochemicals remains the key aspect of nutrient content.

Due to overwhelming nutritive and medicinal use of the plant, it is indicated that *Moringa* can be widely exploited for its nutritionally important phytoconstituents in the development of functional foods, nutraceuticals and therapeutic agents[18]. Further, GCMS analysis revealed the presence of 41 compounds of which Dihydroxyacetone; Monomethyl malonate; 4H-Pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl; 1,3-Propanediol, 2-ethyl-2-(hydroxymethyl); Propanoic acid, 2-methyl-, octyl ester; 3-Deoxy-d-mannoic lactone; Sorbitol; Inositol; Cyclohexanemethanol, alpha-methyl-4-(1-methylethyl), Hexadecanoic acid, Methyl palmitate; n-Hexadecanoic acid (Palmitic acid); 9-Octadecenoic acid, methyl ester; Phytol; 9,12,15-Octadecatrienoic acid[19] However, summative information on toxic effects of MA is not available/ lacking, therefore, in the present study ADMETox profile of MA from *Moringa oleifera* has been carried out and its DMPK properties are "fine-tuned" in order to expand the chances of making MA fit for clinical trials prospecting biomedical applications. Aim of this study is to bioprospect MA from the leaves of MO towards molecular and biological properties.

MATERIALS AND METHODS

In silico Drug-Likeliness and Bioactivity Prediction

Drug likeliness and bioactivity of MA was analyzed using Molinspiration server (http://www.molinspiration.com)[20]. In Molinspiration-based drug-likeness analysis, includes lipophilicity level (logP) and polar surface area (PSA) directly associated with pharmacokinetic properties (PK) of the compounds[21]. In Molinspiration-based bioactivity analysis, calculation of the bioactivity score of compounds toward GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors, and enzyme targets were analyzed by Bayesian statistics[20]. This was carried out for G protein-coupled receptors (GPCR), ion channels, kinases, nuclear hormone receptors, proteases, and other enzymes (RdRp)[22].

In silico ADMET Analysis

SwissADME: a Web tool that gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, druglikeness and medicinal chemistry friendliness, among which *in-house* proficient methods such as iLOGP (a physics-based model for lipophilicity)[23] or BOILED-Egg (an intuitive graphical classification model for gastrointestinal absorption and brain access)[23]. It supports ADME-related calculation for multiple molecules, allowing chemical library analysis and efficient lead optimization[23]. PK properties were predicted using admerSAR v2.0 server (http://lmmd.ecust.edu.cn/admetsar2), an open-source computational tool for prediction of ADMET properties of compounds[24]. In ADMET analysis, absorption (A) has been attributed to membrane permeability (Caco-2)[25] human intestinal absorption (HIA)[26], p-glycoprotein substrate or inhibitor[27], distribution (D) depends on the ability to cross blood-brain barrier (BBB)[28], metabolism (M) is calculated by CYP, MATE1 and OATP1B1-OATP1B3 models, excretion (E) is estimated based on renal OCT substrate and toxicity (T) of drugs is predicted on Human Ether-A-Go-Go related gene inhibition, carcinogenic status, mutagenic status, and acute oral toxicity[29,30].

vNN model building and analysis

vNN method was used to calculate the similarity distance between molecules in terms of their structure, and distance threshold to define a domain of applicability to ensures that the predictions generated are reliable. vNN models can be built keeping quantitative structure–activity relationship (**QSAR**) up-to-date to maintain their performance levels. Performance characteristics of the models are comparable, and often superior to those of other more elaborate model.[31-34] One of the most widely used measures of similarity distance between two small molecules is Tanimoto distance, d, which is defined as:

$$d = 1 - \frac{n(\mathrm{P} \cap \mathrm{Q})}{n(P) + n(Q) - (\mathrm{P} \cap \mathrm{Q})}$$

where n(P∩Q) is number of features common to molecules p and q, and n(P) and n(Q) are the total numbers of features for molecules p and q, respectively. The predicted biological activity y is given by a weighted across structurally similar neighbours:

$$y = \frac{\sum_{i=1yie}^{v} -(di/h)^2}{\sum_{i=1e}^{v} -(di/h)^2} \; di \leq d0$$

where d_i denotes Tanimoto distance between a query molecule for which a prediction is made and a molecule i of the training set; d_0 is a Tanimoto-distance threshold, beyond which two molecules are no longer considered to be sufficiently similar to be included in the average; y_i is the experimentally measured activity of molecule i; v denotes the total number of molecules in the training set that satisfies the condition $d_i \leq d_0$; and h is a smoothing factor, which dampens the distance penalty. Values of h and d_0 are determined from cross-validation studies. To identify structurally similar compounds, Accelrys extended-connectivity fingerprints with a diameter of four chemical bonds (ECFP4) was used.[35-38]

Model Validation

A 10-fold cross-validation (CV) procedure was used to validate new models and to determine the values of smoothing factor h and Tanimoto distance d_0. In this procedure, data was

randomly divided into 10 sets, and used 9 to develop the model and 10th to validate it, this process was repeated 10 times, leaving each set of molecules out once.

Performance Measures

Following metrics were used to assess model performance. (1) sensitivity measures a model's ability to correctly detect true positives, (2) specificity measures a model's ability to detect true negatives, (3) accuracy measures a model's ability to make correct predictions and (4) kappa compares the probability of correct predictions to the probability of correct predictions by chance (its value ranges from +1 (perfect agreement between model prediction and experiment) to –1 (complete disagreement), with 0 indicating no agreement beyond that expected by chance).

$$sensitivity = \frac{TP}{TP + FN}$$

$$specificity = \frac{TN}{FP + TN}$$

$$accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

$$kappa = \frac{accuracy - Pr(e)}{1 - Pr(e)}$$

where TP, TN, FP, and FN denote the numbers of true positives, true negatives, false positives, and false negatives, respectively. Kappa is a metric for assessing the quality of binary classifiers. Pr (e) is an estimate of the probability of a correct prediction by chance. It is calculated as:

$$Pr(e) = \frac{(TP + FN)(TP + FP) + (TP + FN)(TP + FP)}{(TP + FN + FP + TN)^2}$$

The coverage is the proportion of test molecules with at least one nearest neighbour that meets the similarity criterion. The coverage is a measure of how many test compounds are within the applicability domain of a prediction model.

RESULTS AND DISCUSSION

Chemical Kingdom	:	Organic Compounds
Super Class	:	Lipids and Lipid-like Molecules
Class	:	Fatty Acyls
Subclass	:	Fatty Acids and Conjugates
IUPAC Name	:	Tetradecanoic Acid
Common Name	:	Myristic Acid
Synonym		12-Methyltetradecanoic acid
Compound CID	:	11005
PubChem Identifier	:	11005
ChEBI Identifier	:	28875
CAS Identifier	:	544-63-8
Molecular Formula	:	$C_{14}H_{28}O_2$
Molecular Weight	:	228.37g/mol
Canonical SMILES	:	CCCCCCCCCCCCCC(=O)O
InChIKey	:	TUNFSRHWOTWDNC-UHFFFAOYSA-N

Physicochemical, Druggability, ADMET Properties of MA

Physicochemical Properties

Physicochemical properties of MA has been reviewed by Golshan Tafti et al.[39] accordingly, in the present study, molecular weight (228.38 g/mol); LogP (4.77); LogD (2.95); LogSw (-4.31); Number of stereocenters (0); Stereochemical complexity (0.000); Fsp3 (0.929); Topological polar surface area (37.30 Å2); Number of hydrogen bond donors (1); Number of hydrogen bond acceptors (1); Number of smallest set of smallest rings (SSSR) (0); Size of the biggest system ring (0); Number of rotatable bonds (12); Number of rigid bonds (1); Number of charged groups (1); Total charge of the compound (-1); Number of carbon atoms (14); Number of heteroatoms (2); Number of heavy atoms (16); Ratio between the number of non-carbon atoms and the number of carbon atoms (0.14) respectively (Table 1).

Druggability Properties

Lipinski's rule of 5 violations (1); Veber rule (Good); Egan rule (Good); Oral PhysChem score (Traffic Lights) (4); GSK's 4/400 score (Good); Pfizer's 3/75 score (Bad); Weighted quantitative estimate of drug-likeness (QEDw) score (0.409); Solubility (3058.03); Solubility Forecast Index (Good) respectively (Table 1).

ADMET Properties

Human Intestinal Absorption (HIA+ - 0.989); Blood Brain Barrier (BBB+ - 0.949); Caco-2 permeable (Caco2+ - 0.833); P-glycoprotein substrate (Non-substrate - 0.632); P-glycoprotein inhibitor I (Non-inhibitor - 0.960); P-glycoprotein inhibitor II (Non-inhibitor - 0.928); CYP450 2C9 substrate (Non-substrate - 0.789); CYP450 2D6 substrate (Non-substrate - 0.896); CYP450 3A4 substrate (Non-substrate - 0.698); CYP450 1A2 inhibitor (Inhibitor - 0.833); CYP450 2C9 inhibitor (Non-inhibitor - 0.881); CYP450 2D6 inhibitor (Non-inhibitor - 0.955); CYP450 2C19 inhibitor (Non-inhibitor - 0.958); CYP450 3A4 inhibitor (Non-inhibitor - 0.948); CYP450 inhibitory promiscuity (Low CYP Inhibitory Promiscuity - 0.965); Ames test (Non AMES toxic - 0.987); Carcinogenicity (Non-carcinogens - 0.645); Biodegradation (Ready biodegradable - 0.880); Rat acute toxicity (1.328 LD50, mol/kg - NA); hERG inhibition (predictor I) (Weak inhibitor - 0.932); hERG inhibition (predictor II) (Non-inhibitor - 0.887) Table 1.

In silico Drug-Likeliness and Biomolecular activity Prediction

Molecular properties with their Calculated Values in parenthesis were miLogP (6.05); TPSA (37.30); Natoms (16); MW (228.38); nON (2); nOHNH (1); Nviolations (1); Nrotb (12); volume (257.82) respectively (Table 1). Likewise, the calculated Bioactivity Scores for the molecule provided in parenthesis were GPCR ligand (-0.11); ion channel modulator (0.03); kinase inhibitor (-0.51); nuclear receptor ligand (-0.06); protease inhibitor (-0.19); enzyme inhibitor (0.13) respectively (Table 1). Details of physicochemical, lipophilicity, water solubility, pharmacokinetics, and druglikeness properties of MA is provided in Table 2

The implemented Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) prediction models, including their performance measures, are available in the paper online. The 15 models cover a diverse set of ADMET endpoints. Some of the models have already been published, including those for Maximum Recommended Therapeutic Dose (MRTD), chemical mutagenicity, human liver microsomal (HLM), Pgp inhibitor/substrates.

Liver Toxicity

DILI: Drug-induced liver injury (DILI) has been one of the most commonly cited reasons for drug withdrawals from the market[40]. This application predicts whether a compound could cause DILI. The dataset of 1,431 compounds was obtained from four sources used by Xu et al.[38] This dataset contains both pharmaceuticals and non-pharmaceuticals; a compound was classified as causing DILI if it was associated with a high risk of DILI and not if there was no such risk (Table 3).

Cytotoxicity (HepG2): Cytotoxicity is the degree to which a chemical causes damage to cells[41]. A cytotoxicity prediction model was developed using in vitro data on toxicity against HepG2 cells for 6,000 structurally diverse compounds, which was collected from ChEMBL. In developing the model, the compounds with an $IC_{50} \leq 10$ μM were considered in the in vitro assay as cytotoxic (Table 3).

Metabolism

HLM: The human liver microsomal (HLM) stability assay is commonly used to identify and exclude compounds that are too rapidly metabolized[42]. For a drug to achieve effective therapeutic concentrations in the body, it cannot be metabolized too rapidly by the liver. Compounds with a half-life of 30 min or longer in an HLM assay are considered as stable; otherwise they are considered unstable. HLM data was retrieved from the ChEMBL database, manually curated the data, and classified compounds as stable or unstable based on the reported half-life (T1/2 > 30 min was considered stable, and T1/2 < 30 min unstable. The final dataset contained 3,654 compounds. Of these, as much as 2,313 were classified as stable and 1,341 as unstable (Table 3).

Cytochrome P450 enzyme (CYP) inhibition: CYPs constitute a superfamily of proteins that play an important role in the metabolism and detoxification of xenobiotics[43]. In vitro data derived from five main drug-metabolizing CYPs-1A2, 3A4, 2D6, 2C9, and 2C19 were used to develop CYP inhibition models. CYP inhibitors were retrieved from PubChem and classified a compound with an $IC_{50} \leq 10$ μM for an enzyme as an inhibitor of the enzyme. Predictions for the following enzymes: CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2C19 have been provided (Table 3).

Membrane Transporters

BBB: The blood-brain barrier (BBB) is a highly selective barrier that separates the circulating blood from the central nervous system. VNN-based BBB model has been developed, using 352 compounds whose BBB permeability values (logBB) were obtained from the literature respectively. Compounds with logBB values of less than –0.3 and greater than +0.3 were classified as BBB non-permeable and permeable (Table 3).

Pgp Substrates and Inhibitors: P-glycoprotein (Pgp) is an essential cell membrane protein that extracts many foreign substances from the cell. Cancer cells often overexpress Pgp, which increases the efflux of chemotherapeutic agents from the cell and prevents treatment by reducing the effective intracellular concentrations of such agents—a phenomenon known as multidrug resistance. For this reason, identifying compounds that can either be transported out of the cell by Pgp (substrates) or impair Pgp function (inhibitors) is of great interest. Models to predict both Pgp substrates and Pgp inhibitors were developed. Pgp substrate dataset was collected by Hou and co-workers. This dataset consists of measurements of 422 substrates and 400 non-substrates. To generate a large Pgp inhibitor dataset, and both the datasets were combined, and removed duplicates to form a combined dataset consisting of a training set of 1,319 inhibitors and 937 non-inhibitors (Table 3).

hERG (Cardiotoxicity): The human ether-à-go-go-related gene (hERG) codes for a potassium ion channel involved in the normal cardiac repolarization activity of the heart. Drug-induced blockade of hERG function can cause long QT syndrome, which may result in arrhythmia and death. As much as 282 known hERG blockers from the literature were retrieved known hERG blockers from the literature and classified compounds with an IC_{50} cut-off value of 10 μM or less as blockers.[9] A set of 404 compounds with IC_{50} values greater than 10 μM were collected from ChEMBL and classified them as non-blockers (Table 3).

MMP (Mitochondrial Toxicity): Given the fundamental role of mitochondria in cellular energetics and oxidative stress, mitochondrial dysfunction has been implicated in cancer, diabetes, neurodegenerative disorders, and cardiovascular diseases. A largest dataset of chemical-induced changes in mitochondrial membrane potential (MMP), was used based on the assumption that a compound that causes mitochondrial dysfunction is also likely to reduce the MMP. A vNN-based MMP prediction model was developed using 6,261 compounds collected from a previous study that screened a library of 10,000 compounds (~8,300 unique chemicals) at 15 concentrations, each in triplicate, to measure changes in the MMP in HepG2 cells.[10] The present study found that nearly 913 compounds decreased the MMP, whereas 5,395 compounds had no effect (Table 3).

Mutagenicity (Ames test): Mutagens are chemicals that cause abnormal genetic mutations leading to cancer. A common way to assess a chemical's mutagenicity is the Ames test. A prediction model was developed using a literature dataset of 6,512 compounds, of which 3,503 were Ames-positive (Table 3).

MRTD: The Maximum Recommended Therapeutic Dose (MRTD) is an estimated upper daily dose that is safe. A prediction model was developed based on a dataset of MRTD values publically disclosed by the FDA, mostly of single-day oral doses for an average adult with a body weight of 60 kg, for 1,220 compounds (most of which are small organic drugs). Organometallics, high-molecular weight polymers were excluded (>5,000 Da), nonorganic chemicals, mixtures of chemicals, and very small molecules (<100 Da). An external test set of 160 compounds collected by the FDA was used for validation (Table 3). The total dataset for the model contained 1,185 compounds. Predicted MRTD value is reported in mg/day unit based upon an average adult weighing 60 kg.

Probable Target, Class of Proteins/ Enzymes for MA

TARGET Class of Proteins/ Enzymes for MA with respective probability in parenthesis include Peroxisome proliferator-receptor α (0.8589); Fatty acid binding protein muscle (0.5549); Free fatty acid receptor 1 (0.5549); Peroxisome proliferator- receptor delta (0.5376); Fatty acid binding protein adipocyte (0.5199); Fatty acid binding protein epidermal (0.5199); Fatty acid binding protein intestinal (0.5199); 11-beta-hydroxysteroid dehydrogenase 1 (0.1818); Solute carrier family 22 member 6 (0.1644); Dual specificity phosphatase Cdc25A (0.1471); DNA polymerase beta (0.1125); Aldo-keto reductase family 1 B10 (0.1038); Histone lysine demethylase PHF8 (0.0951); Protein farnesyltransferase (0.0951); Corticosteroid binding globulin (0.0951); Testis-specific androgen-binding protein (0.0951); Estradiol 17-beta-dehydrogenase 3 (0.0951); Glucose-6-phosphate 1-dehydrogenase (0.0951); GABA-B receptor (0.0951); Prostanoid EP2 receptor (0.0951); G-protein

coupled bile acid receptor 1 (0.0864); Bile acid receptor FXR (0.0864); Androgen Receptor (0.0864); Lysine-specific demethylase 2A (0.0778); Lysine-specific demethylase 5C (0.0778); Niemann-Pick C1-like protein 1 (0.0778); GABA A receptor α-2/beta-2/gamma-2 (0.0778); Vitamin D receptor (0.0778); Protein-tyrosine phosphatase 1B (0.0691); UDP-glucuronosyltransferase 2B7 (0.0691); Hydroxyacid oxidase 1 (0.0691); Cytochrome P450 19A1 (0.0691); Prostanoid FP receptor (0.0604); Carbonic anhydrase II (0.0604); Retinoid X receptor α (0.0604); Glutathione S-transferase kappa 1 (0.0604); 11-beta-hydroxysteroid dehydrogenase 2 (0.0604); Carbonic anhydrase I (0.0604); Plasminogen (0.0604); Serotonin 2b (5-HT2b) receptor (0.0604); Retinoid X receptor beta (0.0604); Retinoic acid receptor gamma (0.0604); Retinoid X receptor gamma (0.0604); Retinoic acid receptor beta (0.0604); Retinoic acid receptor α (0.0604); Nuclear receptor ROR-beta (0.0604); MAP kinase ERK2 (0.0604); Nuclear receptor ROR-α (0.0604); Solute carrier family 22 member 12 (0.0604); Monocarboxylate transporter 1 (0.0604); Inosine-5'-monoP dehydrogenase 2 (0.0604); Transient receptor potential ion channel (0.0604); GPCR 44 (0.0604); Thromboxane A2 receptor (0.0604); Peroxisome proliferator-act receptor γ (0.0604); Voltage-gated cA channel α2/δ subunit 1 (0.0604); Prostanoid EP4 receptor (0.0604); Plasma retinol-binding protein (0.0604); G-protein coupled receptor 120 (0.0604); Squalene synthetase (0.0604); Neuronal acetylcholine receptor protein α-7 (0.0604); p53-binding protein Mdm-2 (0.0604); Prostaglandin E synthase 2 (0.0604); A-2b adrenergic receptor (0.0604); MAP kinase p38 α (0.0604); Prostaglandin E synthase (0.0604); Arachidonate 15-lipoxygenase (0.0604); Arachidonate 12-lipoxygenase (0.0604); Cytochrome P450 26B1 (0.0604); Prostanoid DP receptor (0.0604); Cytochrome P450 26A1 (0.0604); Aldo-keto-reductase family 1 member C3 (0.0604); Cytosolic phospholipase A2 (0.0604); Type-1 angiotensin II receptor (0.0604); Epoxide hydratase (0.0604); Metabotropic glutamate receptor 5 (0.0604); Endothelin receptor ET-A (0.0604) respectively is provided in Table 4.

CONCLUSION

Revitalization of local health traditions (RLHT) has become an inevitable aspect of human wellbeing in the post COVID era[44]. In the present study MA from *M. oleifera* was ADMET predicted for functional properties. It has been well established that in the human system that MA is converted to EPA/ DHA. Further, EPA/ DHA is endowed with cardioprotective potentials lowers blood cholesterol level and reduces the risk of heart disease. With limited data, it is not obvious to conclude that MA of MO is safe as a dietary ingredient as evidence on risks associated with MA remains inadequate as of now. *In-silico* ADMET prediction data presented in the paper is expected to assist the process of drug discovery by rapid design, evaluation, and prioritization of MA as novel lead.

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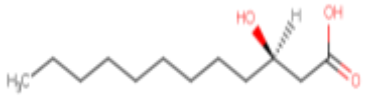
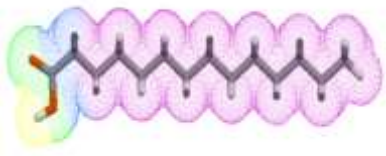
Table 1: 2D, 3D structures, molecular properties and bioactivity scores of MA





MOLECULAR PROPERTIES	CALCULATED VALUES
miLogP	6.05
TPSA	37.30
Natoms	16
MW	228.38
nON	2
nOHNH	1
Nviolations	1
Nrotb	12
volume	257.82
BIOLOGICAL PROPERTIES	**BIOACTIVITY SCORES**
GPCR ligand	-0.11
Ion channel modulator	0.03
Kinase inhibitor	-0.51
Nuclear receptor ligand	-0.06
Protease inhibitor	-0.19
Enzyme inhibitor	0.13

Table 2: Physicochemical, Lipophilicity, Water Solubility, Pharmacokinetics, and Druglikeness Properties of MA

PHYSICOCHEMICAL PROPERTIES	
Formula	C14H28O2
Molecular weight	228.37 g/mol
Num. heavy atoms	16
Num. arom. heavy atoms	0
Fraction Csp3	0.93
Num. rotatable bonds	12
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	71.18
TPSA	37.30 Å^2
LIPOPHILICITY	
Log $P_{o/w}$ (iLOGP)	3.32
Log $P_{o/w}$ (XLOGP3)	6.11
Log $P_{o/w}$ (WLOGP)	4.77
Log $P_{o/w}$ (MLOGP)	3.69
Log $P_{o/w}$ (SILICOS-IT)	4.37
Consensus Log $P_{o/w}$	4.45
WATER SOLUBILITY	
Log *S* (ESOL)	-4.31
Solubility	1.11e-02 mg/ml ; 4.86e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-6.67

Solubility	4.83e-05 mg/ml ; 2.11e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-4.51
Solubility	7.12e-03 mg/ml ; 3.12e-05 mol/l
Class	Moderately soluble
PHARMACOKINETICS	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-3.35 cm/s
DRUGLIKENESS	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	No; 1 violation: Rotors>10
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.85
MEDICINAL CHEMISTRY	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 3 violations: MW<250, Rotors>7, XLOGP3>3.5
Synthetic accessibility	2.09

Query	Liver Toxicity		Metabolism						Membrane Transporters			Others			
			Cyp Inhibitors for												
	DILI	Cyto-toxicity	HLM	1A2	3A4	2D6	2C9	2C19	BBB	P-gp Inhibitor	P-gp Substrate	hERG Blocker	MMP	AMES	MRTD (mg/day)
	Yes	⊘	⊘	No	No	No	No	No	⊘	No	No	Yes	No	No	20

Table 3: Performance measures of vNN models in 10-fold cross validation using a restricted or unrestricted applicability domain

Model	Data[a]	d_0[b]	h[c]	Accuracy	Sensitivity	Specificity	kappa	R[d]	Coverage
DILI	1427	0.60	0.50	0.71	0.70	0.73	0.42		0.66
		1.00	0.20	0.67	0.62	0.72	0.34		1.00
Cytotox (hep2g)	6097	0.40	0.20	0.84	0.88	0.76	0.64		0.89
		1.00	0.20	0.84	0.73	0.89	0.62		1.00
HLM	3219	0.40	0.20	0.81	0.72	0.87	0.59		0.91
		1.00	0.20	0.81	0.70	0.87	0.57		1.00
CYP1A2	7558	0.50	0.20	0.90	0.70	0.95	0.66		0.75

		1.00	0.20	0.89	0.61	0.95	0.60		1.00
CYP2C9	8072	0.50	0.20	0.91	0.55	0.96	0.54		0.76
		1.00	0.20	0.90	0.44	0.96	0.46		1.00
CYP2C19	8155	0.55	0.20	0.87	0.64	0.93	0.58		0.76
		1.00	0.20	0.86	0.52	0.94	0.50		1.00
CYP2D6	7805	0.50	0.20	0.89	0.61	0.94	0.57		0.75
		1.00	0.20	0.88	0.52	0.95	0.51		1.00
CYP3A4	10373	0.50	0.20	0.88	0.76	0.92	0.68		0.78
		1.00	0.20	0.88	0.69	0.93	0.64		1.00
BBB	353	0.60	0.20	0.90	0.94	0.86	0.80		0.61
		1.00	0.10	0.82	0.88	0.75	0.64		1.00
Pgp Substrate	822	0.60	0.20	0.79	0.80	0.79	0.58		0.66
		1.00	0.20	0.73	0.73	0.74	0.47		1.00
Pgp Inhibitor	2304	0.50	0.20	0.85	0.91	0.73	0.66		0.76
		1.00	0.10	0.81	0.86	0.74	0.61		1.00
hERG	685	0.70	0.70	0.84	0.84	0.83	0.68		0.80
		1.00	0.20	0.82	0.82	0.83	0.64		1.00
MMP	6261	0.50	0.40	0.89	0.64	0.94	0.61		0.69
		1.00	0.20	0.87	0.52	0.94	0.50		1.00
AMES	6512	0.50	0.40	0.82	0.86	0.75	0.62		0.79
		1.00	0.20	0.79	0.82	0.75	0.57		1.00
MRTD[e]	1184	0.60	0.20					0.79	0.69
		1.00	0.20					0.74	1.00

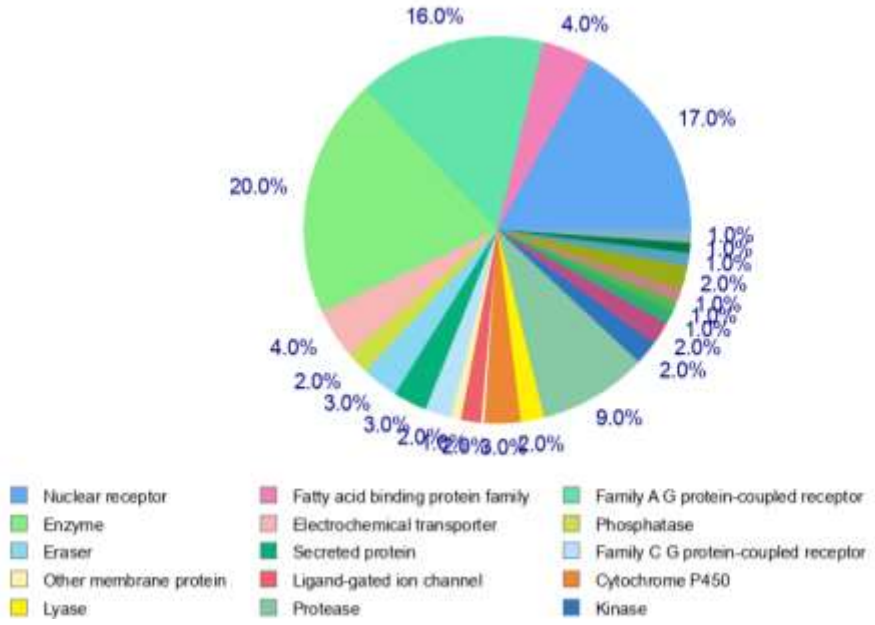


Figure 1: Probable target, class proteins for MA with predicted percentage

Table 4: List of probable target, class for MA with predicted probability values

TARGET	COMMON CODE	UNIPROT ID	TARGET CLASS	PROBABILITY*
Peroxisome proliferator- receptor α	PPARA	Q07869	Nuclear receptor	0.858940178705
Fatty acid binding protein muscle	FABP3	P05413	Fatty acid BPF	0.554904781379
Free fatty acid receptor 1	FFAR1	O14842	Family A GPCR	0.554904781379
Peroxisome proliferator- receptor delta	PPARD	Q03181	Nuclear receptor	0.537563862121
Fatty acid binding protein adipocyte	FABP4	P15090	Fatty acid BPF	0.519923086957
Fatty acid binding protein epidermal	FABP5	Q01469	Fatty acid BPF	0.519923086957
Fatty acid binding protein intestinal	FABP2	P12104	Fatty acid BPF	0.519923086957
11-beta-hydroxysteroid dehydrogenase 1	HSD11B1	P28845	Enzyme	0.181786517225
Solute carrier family 22 member 6	SLC22A6	Q4U2R8	Electrochemical transporter	0.164442067635
Dual specificity phosphatase Cdc25A	CDC25A	P30304	Phosphatase	0.147106563998
DNA polymerase beta	POLB	P06746	Enzyme	0.112450964818
Aldo-keto reductase family 1 B10	AKR1B10	O60218	Enzyme	0.103761755413
Histone lysine demethylase PHF8	PHF8	Q9UPP1	Eraser	0.0951255886644
Protein farnesyltransferase	FNTA	P49354	Enzyme	0.0951255886644
Corticosteroid binding globulin	SERPINA6	P08185	Secreted protein	0.0951255886644
Testis-specific androgen-binding protein	SHBG	P04278	Secreted protein	0.0951255886644
Estradiol 17-beta-dehydrogenase 3	HSD17B3	P37058	Enzyme	0.0951255886644
Glucose-6-phosphate 1-dehydrogenase	G6PD	P11413	Enzyme	0.0951255886644
GABA-B receptor	GABBR1	Q9UBS5	Family C GPCR	0.0951255886644
Prostanoid EP2 receptor	PTGER2	P43116	Family A GPCR	0.0951255886644
G-protein coupled bile acid receptor 1	GPBAR1	Q8TDU6	Family A GPCR	0.0864426933852
Bile acid receptor FXR	NR1H4	Q96RI1	Nuclear receptor	0.0864426933852
Androgen Receptor	AR	P10275	Nuclear receptor	0.0864426933852
Lysine-specific demethylase 2A	KDM2A	Q9Y2K7	Eraser	0.0777583259988
Lysine-specific demethylase 5C	KDM5C	P41229	Eraser	0.0777583259988
Niemann-Pick C1-like protein 1	NPC1L1	Q9UHC9	Other membrane protein	0.0777583259988
GABA A receptor α-2/beta-2/gamma-2	GABRA2	P47869	Ligand-gated ion channel	0.0777583259988
Vitamin D receptor	VDR	P11473	Nuclear receptor	0.0777583259988
Protein-tyrosine phosphatase 1B	PTPN1	P18031	Phosphatase	0.0690974435253
UDP-glucuronosyltransferase 2B7	UGT2B7	P16662	Enzyme	0.0690974435253
Hydroxyacid oxidase 1	HAO1	Q9UJM8	Enzyme	0.0690974435253
Cytochrome P450 19A1	CYP19A1	P11511	Cytochrome P450	0.0690974435253
Prostanoid FP receptor	PTGFR	P43088	Family A GPCR	0.0604245879294
Carbonic anhydrase II	CA2	P00918	Lyase	0.0604245879294
Retinoid X receptor α	RXRA	P19793	Nuclear receptor	0.0604245879294
Glutathione S-transferase kappa 1	GSTK1	Q9Y2Q3	Enzyme	0.0604245879294
11-beta-hydroxysteroid dehydrogenase 2	HSD11B2	P80365	Enzyme	0.0604245879294
Carbonic anhydrase I	CA1	P00915	Lyase	0.0604245879294

Plasminogen	PLG	P00747	Protease	0.0604245879294
Serotonin 2b (5-HT2b) receptor	HTR2B	P41595	Family A GPCR	0.0604245879294
Retinoid X receptor beta	RXRB	P28702	Nuclear receptor	0.0604245879294
Retinoic acid receptor gamma	RARG	P13631	Nuclear receptor	0.0604245879294
Retinoid X receptor gamma	RXRG	P48443	Nuclear receptor	0.0604245879294
Retinoic acid receptor beta	RARB	P10826	Nuclear receptor	0.0604245879294
Retinoic acid receptor α	RARA	P10276	Nuclear receptor	0.0604245879294
Nuclear receptor ROR-beta	RORB	Q92753	Nuclear receptor	0.0604245879294
MAP kinase ERK2	MAPK1	P28482	Kinase	0.0604245879294
Nuclear receptor ROR-α	RORA	P35398	Nuclear receptor	0.0604245879294
Solute carrier family 22 member 12	SLC22A12	Q96S37	Electrochemical transporter	0.0604245879294
Monocarboxylate transporter 1	SLC16A1	P53985	Electrochemical transporter	0.0604245879294
Inosine-5'-monoP dehydrogenase 2	IMPDH2	P12268	Oxidoreductase	0.0604245879294
Transient receptor potential ion channel	TRPA1	O75762	Voltage-gated ion channel	0.0604245879294
GPCR 44	PTGDR2	Q9Y5Y4	Family A GPCR	0.0604245879294
Thromboxane A2 receptor	TBXA2R	P21731	Family A GPCR	0.0604245879294
Peroxisome proliferator-act receptor γ	PPARG	P37231	Nuclear receptor	0.0604245879294
Voltage-gated cA channel α2/δ subunit 1	CACNA2D1	P54289	Calcium channel	0.0604245879294
Prostanoid EP4 receptor	PTGER4	P35408	Family A GPCR	0.0604245879294
Plasma retinol-binding protein	RBP4	P02753	Secreted protein	0.0604245879294
G-protein coupled receptor 120	FFAR4	Q5NUL3	Family A GPCR	0.0604245879294
Squalene synthetase	FDFT1	P37268	Enzyme	0.0604245879294
Neuronal acetylcholine receptor protein α-7	CHRNA7	P36544	Ligand-gated ion channel	0.0604245879294
p53-binding protein Mdm-2	MDM2	Q00987	Other nuclear protein	0.0604245879294
Prostaglandin E synthase 2	PTGES2	Q9H7Z7	Enzyme	0.0604245879294
A-2b adrenergic receptor	ADRA2B	P18089	Family A GPCR	0.0604245879294
MAP kinase p38 α	MAPK14	Q16539	Kinase	0.0604245879294
Prostaglandin E synthase	PTGES	O14684	Enzyme	0.0604245879294
Arachidonate 15-lipoxygenase	ALOX15	P16050	Enzyme	0.0604245879294
Arachidonate 12-lipoxygenase	ALOX12	P18054	Enzyme	0.0604245879294
Cytochrome P450 26B1	CYP26B1	Q9NR63	Cytochrome P450	0.0604245879294
Prostanoid DP receptor	PTGDR	Q13258	Family A GPCR	0.0604245879294
Cytochrome P450 26A1	CYP26A1	O43174	Cytochrome P450	0.0604245879294
Aldo-keto-reductase family 1 member C3	AKR1C3	P42330	Enzyme	0.0604245879294
Cytosolic phospholipase A2	PLA2G4A	P47712	Enzyme	0.0604245879294
Type-1 angiotensin II receptor	AGTR1	P30556	Family A GPCR	0.0604245879294
Epoxide hydratase	EPHX2	P34913	Protease	0.0604245879294
Metabotropic glutamate receptor 5	GRM5	P41594	Family C GPCR	0.0604245879294
Endothelin receptor ET-A	EDNRA	P25101	Family A GPCR	0.0604245879294