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An *In Silico* Approach to Identify Lead Molecules among GC-MS Analyzed Compounds of *Mimusops Elengi* against Glycosyl Transferase of *Streptococcus Mutans*

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Abstract

Streptococcus mutans is reported to be the major causative organism in the development of dental caries as it is primarily responsible for biofilm formation. The adhesive polysaccharide which initiates biofilm formation on the tooth surface is due to the activity of glucansucrase produced by *S. mutans*. The objective was to identify a lead like compounds among 28 molecules identified by GC-MS analysis of the leaf extracts of *Mimusops elengi* through *in silico* approach with the potential to inhibit glucansucrase. Molecular docking of all the phytocompounds against glucansucrase (3AIE) of *S. mutans* resulted in the identification of two compounds namely 2-Isopropyl-5-methylcyclohexyl-3-(1-(4-chlorophenyl)-3-oxobutyl)-coumarin-4-yl-carbonate (ME19) and Pseduosarsasapogenin-5,20-dien (ME21) with binding energies -8.3 Kcal/mol and -9.6 Kcal/mol, respectively. They also showed better Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties when compared to the standard drug chlorhexidine available as anti-plaque agent. These lead compounds can further be tested for *in vitro* enzyme inhibition studies to come up with a potential drug molecule in the future.

Keywords: Glucansucrase; Mimusops elengi; Streptococcus mutans; biofilm; dental caries

1. Introduction

Streptococcus mutans is a gram positive spherical bacteria which is well known for its role in dental caries by inhabiting the human oral cavity on surface of teeth [1]. *S mutans* is reported to be more virulent species among 34 *Streptococcus species* [2]. The strong adherence to the tooth surface is due to extracellular enzyme produced by them called glucansucrases. Glucansucrases belongs to glycoside hydrolase family which are classified as mutansucrase, dextransucrase, alternansucrase and levansucrase based on the glycosidic linkage they catalyze. Three types of glucantransferases are produced by *S. mutans* which are genetically different, i.e., GTF-I, GTF-SI, GTF-S which are encoded by the genes gtf B, gtf C and gtf D respectively. GTF-S is a dextransucrase that synthesis mainly soluble glucan with alpha (1-6) glycosidic linkage, GTF-SI and GTF-I is a mutansucrase that synthesizes predominantly insoluble glucan with alpha (1-3) linkage. Glucan will form a sticky surface to which bacteria and food substances gets attached around the tooth leading to the plaque formation and the acid produced subsequently leads to the demineralization of the tooth and dental diseases like periodontitis [3,4].

Plants form the major source for chemical compounds having various effects on human body. Some are considered as medicinal plants due to their presence of phytocompounds that have disease healing properties [5]. *Mimusops elengi* widely known as Bakula is a tree from the family Sapotaceae, mainly cultivated in North India,

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Peninsular India and in Andaman Islands. They are large glabrous evergreen trees measuring 12 to 15 metres high, with a compact leafy head and a short, erect trunk, and grayish-smooth bark. White, fragrant, nearly 2.5 cm across, solitary, buds ovoid, acute; pedicels 6.20 mm long; leaves 6.3-10 by 3.2-5 cm, elliptic shortly acuminate, glabrous, base acute or rounded; petioles 1.3-2.5 cm long. 8 stamens opposite the inner lobe's circle, 1 cm long calyx. When ripe, the fruit is about 2.5 cm long, ovoid, yellow, and the seed is solitary, ovoid, compressed, brown, and shining [6]. It is considered as one of the prime medicinal plants due to presence of medicinal properties in all its parts which helps in curing many diseases. Pharmacological properties exhibited by *M. elengi* includes antibacterial, antifungal, antiviral, anti-helminthic, antioxidant, anticarcinogenic, free radical scavenging activities, gastro protective and cytotoxic activities [7,8]. The parts of *M. elengi* is said to have a significant role in oral health and has its mention in Ayurveda wherein the roots have been reported to strengthen the gums, bark to cure gum diseases and seeds to fix the loose tooth. It is the main ingredient in "Mahakhadiradivati," a natural remedy for pharyngeal problems, halitosis, spongy gums, and stomatitis, and a key component of several herbal tooth powders [9]. The teeth have benefited from the use of twigs and flowers [10]. *Mimusops elengi*, one of the ingredients in polyherbal dentifrice, was shown in a study to improve plaque, gingivitis, and bleeding indices. In further studies, silver nanoparticles synthesized using extracts of *M. elengi* showed anti-bacterial, anti-biofilm and anti-cancerous activity [11,12].

Drug discovery using *in- silico* techniques utilize bioinformatics tools which are advantageous over *in-vivo* approaches in saving time and money. *In-silico* approaches help in the identification of drug targets, studying the structure of the targets, prediction of binding sites with binding energies and lead optimization [13]. Hence, molecular docking plays a key role in binding the ligand molecule into active site of a receptor with more specificity and potential efficacy [14]. The computational docking programmes PyRx, iGemDock, and Discovery Studio, which are known to be speedy, user-friendly, and compatible with most systems, were employed [15].

The nature of ADME (absorption, distribution, metabolism, excretion) and PK (pharmacokinetics) inquiries during drug discovery and development has evolved in recent years from being largely descriptive to seeking a more quantitative and mechanistic understanding of the fate of drug candidates in biological systems [16].

The current study aimed to identify a lead molecule for inhibition of the enzyme glucansucrase, which is responsible for many dental infections and oral diseases. Different solvent extracts (Petroleum ether, Chloroform and Methanol) of *M. elengi* leaf extracts were obtained by sequential soxhlet extraction based on the polarity and phytocompounds identified by GC MS analysis. The lead molecules were identified using molecular docking approaches by considering the binding affinities to glucansucrases and its potential role as therapeutics for dental diseases. This study taken in force to understand the underlying mechanism using *in-silico* approaches.

2. Methodology

2.1 Preparation of plant extract and GC-MS analysis

The shade-dried leaves of *M. elengi* were collected from the field area of the Indian Institute of Horticultural Research (13.0336° N, 77.5339° E), Karnataka, India and employed for successive solvent extraction using different solvents petroleum ether, chloroform, and methanol. The Clarus 680 GC instrument was used for the GC-MS analysis of the solvent leaf extracts, and the GC-MS NIST (2008) library was used to match the spectra to known spectra [17].

2.2 Protein preparation

Crystallographic structure of glucansucrase from *S. mutans* was used as a target protein. The 3D structure of the protein (Fig:1) was downloaded from Protein Data Bank (https://www.rcsb.org) with the PDB ID 3AIE which had a resolution of 2.10Å. The Protein was modified by retaining only the A chain (Fig:1), deleting heteroatoms (HETATM) using Notepad++v8.4.8. The modified protein was then loaded to AutoDock PyRx Vina version 0.8 [18].

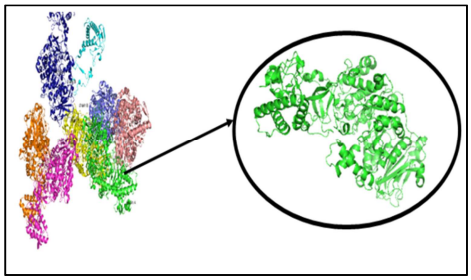


Fig. 1: 3D structure of protein 3AIE with chain A separated from the protein

2.3 Ligand preparation:

The 28 compounds obtained from the GC-MS analysis of *M. elengi* extracts obtained using three solvents namely methanol, chloroform and petroleum ether were used as ligands for docking studies. The standard drug chlorhexidine was used for the comparative study. The 3D structures of the same were downloaded from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and converted to .pdb file format using OpenBabel 2.4.1 software.

2.4 Molecular docking:

Docking of all 28 compounds and chlorhexidine with the target protein was carried out using AutoDock PyRx Vina Version 0.8 as described by Trott and Olson [19] to analyze the binding affinity of the ligands with the target protein. AutoDock runs are based on the Lamarckian genetic algorithm (LGA), which is a combination of a genetic algorithm (GA) with an adaptive local search (LS) [20]. The modified protein and all the ligand molecules were loaded in the PDB format. The grid box was set and the docking was carried out. Results were validated using another docking software iGemDock [21], A Graphical Environment for Recognizing Pharmacological Interactions and Virtual Screening.

2.5 Post docking analysis

2.5.1 Drug likeliness prediction

The drug likeliness of the compounds was predicted on the basis of the Lipinski rule [22], where the compounds have to fulfill certain criteria to be accepted as possible drug candidates. The criteria include molecular weight <500 Da, Hydrogen bond acceptor count should be <10, Hydrogen bond donor count should be <5 and logP value should be <5 [23].

2.5.2 Absorption, Distribution, Metabolism, Excretion/ Toxicity (ADME/T) predictions:

The 2D structures of the best compounds obtained after docking analysis were subject to ADMET analyses for solubility, intestinal absorption, hepatotoxicity, plasma protein binding ability, blood-brain barrier (BBB) penetration, the likeliness of compound to be metabolic substrate or inhibitor, Pgp inhibition using ADMETlab 2.0. All the above said parameters predict the pharmacokinetic and pharmacological effects of drugs [24].

3 Result and Discussion

3.1 GC-MS analysis and Molecular docking studies:

The GC-MS analysis of various solvent leaf extracts of *M. elengi* revealed about 28 compounds. Alkanes, fatty acids, and a small number of terpenoids were among the major compounds that were detected (Table 1, Fig 2). Some of these compounds have a strong potential for pharmacological use and have previously been described as having bioactive properties in plants. In a previous work, the methanol leaf extract of *M. elengi* demonstrated strong levels of free radical scavenging activity using the DPPH assay at low concentrations, with a percentage inhibition of more than 98% [17].

3.2 Molecular docking:

The molecular docking studies of 28 compounds with the protein glucansucrase (PDB ID:3AIE) resulted in screening of two best ligands based on their binding energies tabulated in Table1. The protein structure (PDB ID 3AIE) was selected on the basis of resolution (2.10A), Domain completeness, nature of the structure (wild type) and side chain completeness. ME19 showed the binding energy of -8.3 Kcal/ml and the residues involved in the interaction were TYRA:430, and GLNA:592 in forming conventional hydrogen bond, PHEA:907, SERA:589, TYRA:610, ASPA:593, ASNA:481, ARGA:540, GLYA:429, LYSA:977 in van der waals force of attraction, TRPA:517 in carbon hydrogen bond, GLUA:515 and ASPA:588 in Pi-Anion interaction, ALAA:478, LEUA:433 and LEUA:382 in Pi-Sigma interaction as shown in Fig3(a). Pseduosarsasapogenin-5,20-dien showed binding energy of -9.6 Kcal/mol and the residues involved in interaction were GLNA:592 and ASPA:424 in conventional hydrogen bond, GLYA:428, SERA:518, THRA:426, GLYA:429, ASPA:480, ASNA:481, GLUA:515, ASPA:477, ASPA:909, HISA:587, LEUA:908, PHEA:907, ASPA:588 and ASNA:862 in Van der Waals force of attraction. TYRA:430, ALAA:478, LEUA:434, LEUA:382, LEUA433 and TRPA517 in Alkyl interaction as shown in Fig3(b). The standard drug chlorhexidine used as anti-plaque in mouth rinses showed a binding energy of -8.1Kcal/mol and the

residues involved in interaction were ILEA:912, PHEA:621, THRA:664, ASNA:625, LYSA:626,GLYA:667 and ALAA:865 in van der waals force of attraction, ILEA:617 and META:614 in alkyl interaction, LYSA:618 in Pi-Alkyl interaction, ASPA:666 and GLUA:612 in Pi-Anion interaction, HISA:672 in unfavorable positive-positive interaction as shown in Fig2(c).

The findings were verified using iGemDock docking programme. It revealed comparable trends with our PyRx results. This programme employs rigorous docking and determines the binding side in accordance with the ligand that is present inside the receptor. Autodock, however, functions by exploiting adaptable binding sites. Therefore, we looked at the top two molecules and noticed a similar pattern (M19, ME21) (Supplementary data).

Mohanthy et al., 2015 reported quercetin and rutin for their anti- inflammatory, analgesic and anti-oxidant activity [25]. The anti-inflammatory effect of flavonoids was also demonstrated by Usha et al., 2014[18], Previously, 2-Isopropyl-5-methylcyclohexyl-3-(1-(4-chlorophenyl)-3-oxobutyl)-coumarin-4-yl-carbonate is a known Benzopryrone that has been reported for anti-inflammatory, anti-oxidant and antimicrobial activity [26]. In their study Thirumalaisamy et al., 2018, indicated in their molecular docking studies that this molecule exhibited lowest binding energies with TNF α and IL- 1β. Their study suggested they can possibly play an important role in reducing inflammation in gingivitis associated with dental caries and needs further investigation [26].

Previously, Steroidal saponins are effective therapeutic options to combat inflammatory diseases because they are able to act directly on pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin–6 (IL-6) [27]. In our study, sapogenin, pseduosarsasapogenin-5, 20-dien showed the lowest inhibition against glucansucrase which is remarkably high when compared to Chlorhexidine and is quite promising.

It was previously stated by Khaldan et al (2019) that 3AIE inhibitors should interact with Tyr residue. and further contact will strengthen the ligand-protein interface, which may prevent the *Streptococcus mutans* glucansucrase (GSase) from causing an antimicrobial reaction [28].

The amino acid sites that are found to be crucial for GTF-SI activity is TRPA: 517 which is the acceptor site for glycosyl moiety and ASPA: 593 that catalyses transglycosylation with α (1-3) glycosidic linkages and α (1–6) linkages resulting in insoluble glucan and soluble glucan respectively. The type of glycosidic linkage is based on the acceptor sugar orientation influenced by ASPA: 593 (Ito et al., 2011). In the present study, the two best ligands apart from their lower binding energy were also involved in the interaction with the above-mentioned amino acid sites. The ligand 2-Isopropyl-5-methylcyclohexyl-3-(1-(4-chlorophenyl)-3-oxobutyl)-coumarin-4-yl-carbonate interacted with both TRPA: 517 and ASPA: 593 while Pseduosarsasapogenin-5, 20-dien interacted to TRPA: 517. The standard drug did not show interaction with either of the sites. Hence the two ligands can be a novel inhibitor of GTF –SI. (Table 1)

Table 1

Molecular docking results of compounds obtained from *M. elengi* leaf extracts against Glucansucrase of *S. mutans*

Sl.NO	Compound Name	Retention time (Rt)	M.W	Formula	CAS	CID	Binding energy Kcal/mol
	Petroleum ether solvent						
1	2R-Acetoxymethyl-1,3,3-trimethyl-4t-(3-methyl-2-buten-1-yl)-1t-cyclohexanol	28.559	282	$C_{17}H_{30}O_3$	900144-12-4	550401	-5.9
2	Dotriacontane	22.992	450	$C_{32}H_{66}$	544-85-4	11008	-5.0
3	Heptacosane, 1-chloro-	23.957 27.503	414	$C_{27}H_{55}Cl$	62016-79-9	545593	-4.6

4	Hexadecanoic acid, 2-oxo-, methyl ester	28.964	284	$C_{17}H_{32}O_3$	55836-30-1	545549	-5.0
5	Hexatriacontane	24.592 25.673 26.308	506	$C_{36}H_{74}$	630-06-8	12412	-4.2
6	Octacosane	25.198	394	$C_{28}H_{58}$	630-02-4	12408	-4.4
7	Octadecane, 1-chloro-	28.179	288	$C_{18}H_{37}Cl$	3386-33-2	18815	-4.3
8	Squalene	24.082	410	$C_{30}H_{50}$	7683-64-9	638072	-4.2
9	Tetratetracontane	23.477	618	$C_{44}H_{90}$	7098-22-8	23494	-3.7
	Chloroform solvent						
10	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	18.875	296	$C_{20}H_{40}O$	102608-53-7	5366244	-8.0
11	1-Octadecanesulphonyl chloride	24.217	352	$C_{18}H_{37}O_2Cl$	900342-70-4	66281	-4.2
12	Octadecane, 1-chloro-	24.772	288	$C_{18}H_{37}Cl$	3386-33-2	18815	-4.3
13	Behenyl chloride	25.323	344	$C_{22}H_{45}Cl$	42217-03-8	545602	-5.4
14	Heptacosane, 1-chloro-	25.848	414	$C_{27}H_{55}Cl$	62016-79-9	545593	-4.6
15	Heptacosane	26.393 26.913	380	$C_{27}H_{56}$	593-49-7	11636	-4.6
16	1-Methylene-2B-hydroxymethyl-3,3-dimethyl-4B-(3-methylbut-2-enyl)-cyclohexane	26.698	222	C15H26O	900144-10-6	550196	-6.9
17	Hexadecane, 1-chloro-	27.493 27.754 28.909 30.010	260	$C_{16}H_{33}Cl$	4860-03-1	20993	-3.9
18	Tetradecane, 1-chloro-	28.149	232	$C_{14}H_{29}Cl$	2425-54-9	17043	-5.0
19	1-Heptatriacotanol	29.434	536	$C_{37}H_{76}O$	105794-58-9	537071	-4.8
20	2-Isopropyl-5-methylcyclohexyl 3-(1-(4-chlorophenyl)-3-oxobutyl)-coumarin-4-yl carbonate	29.824	524	$C_{30}H_{33}O_6Cl$	900143-59-5	537118	-8.3
21	Pseduosarsasapogenin-5,20-dien	32.090	414	$C_{27}H_{42}O_3$	900214-84-5	261799	-9.6
	Methanol solvent						
22	2R-Acetoxymethyl-1,3,3-trimethyl-4t-(3-methyl-2-buten-1-yl)-1t-cyclohexanol	26.658	282	$C_{17}H_{30}O_3$	900144-12-4	550401	-5.9
23	Dotriacontane	24.177	450	$C_{32}H_{66}$	544-85-4	11008	-5.0
24	Eicosanoic acid, 2-ethyl-2-methyl-, methyl ester	23.587	368	$C_{24}H_{48}O_2$	55282-04-7	575666	-4.2
25	1-Monooleoylglycerol trimethylsilyl ether	21.801	500	$C_{27}H_{56}O_4Si_2$	54284-47-8	5366386	-6.2
26	Pyrrole-2-carboxylic acid, 4-(1-chlorodec-1-enyl)-3,5-dimethyl-, ethyl ester	19.970	339	$C_{19}H_{30}O_2NCl$	900295-53-6	5362859	-5.4
27	Pyruvic acid, trimethylsilyl ester	20.921	160	$C_6H_{12}O_3Si$	900353-24-2	445639	-5.1
28	Tetracosanoic acid, trimethylsilyl ester	21.886	440	$C_{27}H_{56}O_2Si$	74367-37-6	522540	-6.2

Table 2

Drug likeliness prediction of screened compounds in comparison with standard drug

Compound	Molecular weight	H-bond donor count	H-bond acceptor count	LogP	Lipinski rule
ME19	524	0	6	6.488	Rejected
ME21	414	2	3	-5.799	Accepted
Chlorhexidine	504.2	10	10	2.683	Rejected

2a)

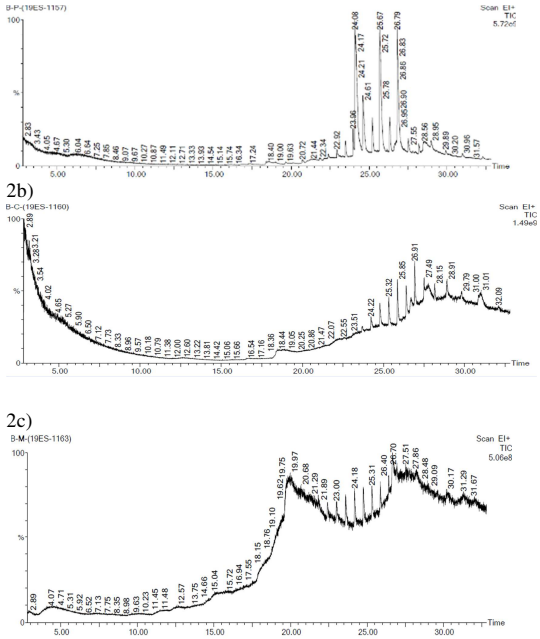
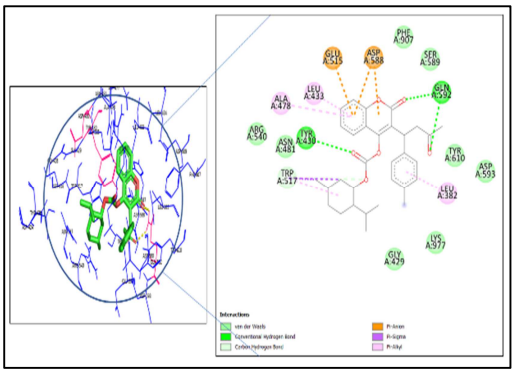


Fig. 2: (a), (b) and (c) represents the chromatogram of GC- MS analysis of the petroleum ether, chloroform and methanol leaf extracts of *M. elengi* respectively

3a)



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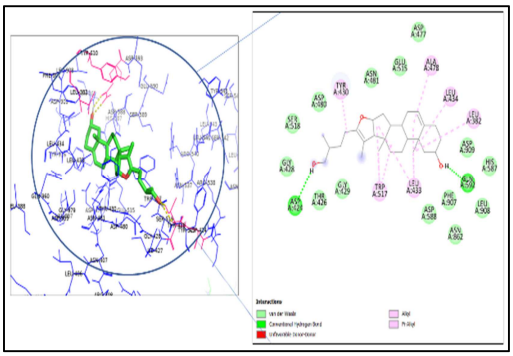

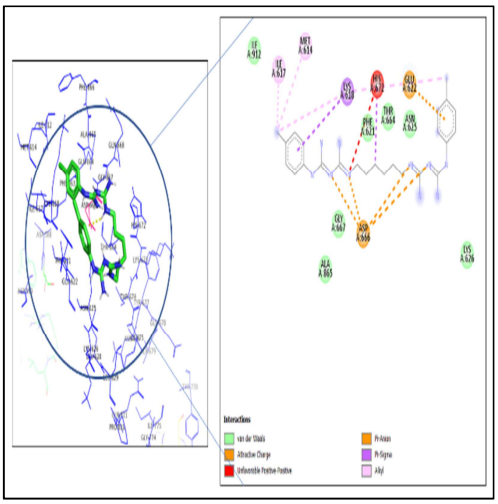

3c)

Fig 3: (a), (b) and (c) represents the interaction of M19, ME21, and Chlorhexidine (standard drug) with 3AIE respectively

3.3 Absorption, Distribution, Metabolism, Excretion/ Toxicity (ADMET) prediction:

Toxicological prediction yields result such as a compound's ability to cause cancer, hepatotoxicity, mutagenicity, and cytotoxicity. The extract plant samples' compounds are predicted to be carcinogenic, noncarcinogenic, and nonirritant. Certain plant bioactive compounds can be confirmed as a good or bad drug candidate based on ADMET assessment and empirical decision available at ADMET prediction software [29]. ADMET analysis of the two best compounds obtained after molecular docking was done using ADMETlab 2.0 and compared with the standard drug. The results as tabulated in Table 3 shows that the Caco-2 permeability and Human intestinal absorption of the ligands were excellent when compared to the standard drug. Pgp-inhibition showed a good value when compared to the standard drug. Plasma protein binding of the compounds including standard drug showed poor value. BBB penetration value standard drug is excellent whereas lead compounds showed moderate values. ME21 was estimated to be carcinogenic. In their review work, Tian et al., 2017 also indicated the role of saponins in inflammation [30].

Table 3: ADME/T predictions of screened compounds and stand standard drug

Properties	2-Isopropyl-5-methylcyclohexyl 3-(1-(4-chlorophenyl)-3-oxobutyl)-coumarin-4-yl carbonate (ME19)	Pseduosarsasapogenin-5,20-dien (ME21)	Chlorhexidine (Standard drug)	Empirical decision
Caco-2	-4.806	-4.737	-5.457	> -5.15: excellent
HIA	0.003	0.012	0.833	0-0.3: excellent 0.3-0.7: medium 0.7-1.0: poor
MDCK	1.66e-05	1.66e-05	2.77e-05	>2 x 10^{-6}cm/s: excellent
Pgp inhibitor	0.995	0.753	0.995	0-0.3: excellent 0.3-0.7: medium 0.7-1.0: poor
Plasma protein binding	100.72%	95.94%	96.26%	≤ 90%: excellent
BBB	0.636	0.72	0.14	0-0.3: excellent 0.3-0.7: medium 0.7-1.0: poor
CYP1A2 inhibitor	0.06	0.031	0.101	Probability of being substrate/inhibitor is within the range 0-1
CYP1A2-sub	0.746	0.384	0.957	
CYP2C19-inhibitor	0.668	0.071	0.067	
CYP2C19-substrate	0.941	0.798	0.069	
CYP2C9-inhibitor	0.685	0.128	0.002	
CYP2C9-substrate	0.976	0.183	0.039	
CL	2.62	19.894	12.56	≥ 5: excellent < 5: poor
$T_{1/2}$	0.028	0.043	0.237	0-0.3: excellent 0.3-0.7: medium 0.7-1.0: poor
hERG blockers	0.006	0.016	0.677	
AMES toxicity	0.011	0.018	0.55	
Carcinogenicity	0.059	0.149	0.094	
Skin sensitization	0.447	0.157	0.293	
H-HT	0.34	0.243	0.4	

4 Conclusions

After a thorough analysis, we sought out the strongest medication that could be obtained from natural sources. Discovering natural remedies with anti-inflammatory action against glucansucrase, which plays a vital role in biofilm formation by *S. mutans* has become an important research target to obtain good oral health. Therefore, using an in-silico technique, molecular docking, characteristics, and toxicity have been examined. The present *in silico* studies shows that two phytocompounds namely ME19 and ME21 obtained from GC-MS analysis of *M. elengi* extracts can inhibit glucansucrases. The drug likeliness and ADME/T predictions of the compounds showed better values than that of the standard drug, chlorhexidine. These versatile natural substances could therefore have an inhibitory effect and work as a brand-new glucansucrase inhibitor and therapy. Authors feel that all of this drug-like compounds has the ability to be used against glucansucrase and should be further researched using other approaches such as *in vivo, in vitro* as prophylactic treatments. Hence the screened compound can be efficient in treating dental caries and can be used in toothpaste, mouthwash.

5. Conflicts of interest

"There are no conflicts to declare".

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