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High Throughput Virtual Screening for Pharmacokinetics and Molecular Docking for the Phyto Constituents as Antidiabetic Agents in *Boswellia scara* Using SWISS ADME and mcule

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ABSTRACT

An objective of a current project had been to analyze cellular docking studies for anti-diabetic activity and pharmacokinetics studies of phytocompounds reported in *Boswellia scara* (commonly known as Luban Plant in Oman) using SWISS ADME and mcule software. Peroxisomes proliferator-activated receptor gama (PPAR-γ) agonists were also advantageous within management of diabetes through trying to stimulate sensitivity to insulin as well as antagonizing hepatocyte glycogen synthesis. In the current research work aims to research a PPAR- γ agonist property like phytocompounds from *the Boswellia scara*(BS) use of a kind in-silico strategy. Docking studies like BSon human PPAR-γ protein database has been resolute by whilst online available free softwares SWISS ADME and mcule but also comparison as for glibenclamide an identified agonist like PPAR-γ. PK of all the drugs reveals that, they were not well absorbed through GI tract, however, due to their high lipophilic character all the phytochemicals cross Blood brain barrier (BBB) except β-caryophyllene. Docking studies recommended that, Limonene had enough better fitness start scoring like -6.3 kcal/mole, however it was less compared to standard drug glibenclamide, -9.4. It was satisfied Swiss ADME and mcule features and displayed encouraging 'simulation results. Advanced plots obtained by docking studies analyze predicted stability like proposed protein-ligand complex. However, as the docking scores are less for BS compared with standard drug glibenclamide, we propose that BS may have a mild anti-diabetic activity. Hands on wet laboratory validation is warranted.

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INTRODUCTION

Target-based computational screening finds compounds that may serve as protein inhibitors (or putative drugs). This would be executed through scanning an enormous librarian like 3-D ligand structure. All this recognizes substances a certain 'best suit' a target's binding site. A potential lead molecule needs good pharmacokinetics [1].

Diabetes mellitus (DM) develops from defective insulin secretion and action. Peroxisome proliferator-activated receptors are essential regulatory bodies like glycogen but also lipid accumulation even though those that trigger protein synthesis. PPARG upregulates adipocyte glycerol

kinase, which increases glycerol incorporation into triglyceride. PPAR-γ enhances glucose transporter 1 and 4 expression, which increases glucose elimination in peripheral tissue [2].

Frankincense is a resin from Boswellia plants (Burseraceae family). Oman and Yemen's *Boswellia sacra* is among them. Boswellia sp. resins have therapeutic qualities, too. Boswellia resins are used to treat rheumatoid arthritis and Crohn's disease.

Anti-inflammatory, anti-bacterial, anti-fungal, anti-carcinogenic, and anti-neoplastic actions were also identified (breast cancer) [3, 4]. Some modest studies suggest that frankincense may help reduce blood sugar levels in patients with diabetes. More research is needed because other studies have revealed no impact.

The current research investigates molecular docking for anti-diabetic efficacy and pharmacokinetics of *Boswellia scara* phytocompounds utilising SWISS ADME and mcule software [5, 6].

MATERIALS AND METHODS

Pharmacokinetics Prediction

Swiss ADME predicts pharmacokinetics and drug-likeness. This platform analyses submitted compounds using molecular similarity and predictive regression [7].

Molecular Docking

Docking studies is also crucial method in structural biology as well as computer-aided drug design. Free internet programme called 'mcule' did molecular docking. mcule calculates PPAR gamma ligand binding using -pinene, Limonene, p-cymene, Myrcene, sabinene, -caryophyllene, and -thujene [8]. Mcule findings were used to examine binding energy and docked structure interactions.

Ligand Preparation

Pubchem provided the 2D structures and Canonical SMILES molecules of the BS ligands (https://pubchem.ncbi.nlm.nih.gov/).

Pharmacokinetics Prediction Using Swiss ADME

Analyzing phytochemical substances on the swiss ADME website predicted ADME pharmacokinetic parameters (http://www.swissadme.ch/index.php).

Protein Preparation

A 3D structure like PPAR gamma (PDB ID: 4EM9) has been uploaded first from protein data bank (PDB) (http://www.pdb.org/pdb/home/home.do) already when instituting docking simulation studies.

Docking Reassurance Utilising mcule

Mcule enhances early-phase drug development by it's own integrated molecular dynamics devices, computing capability but also high-quality composite dataset (https://mcule.com/dashboard/). Docking studies utilising mcule has been executed within structure-based virtual monitor-process flow contractor. A ligand has been submitted such as 2D. A nutrient which would be the focus has been submitted through 3D with such a binding site top centre X: 19.92, Y: 7.12, Z: 15.48.

RESULTS AND DISCUSSION

From the literature, it was evident that, BS consists of the following major chemical constituents whose structure and canonical SMILES (A summarized molecular-input line-entry system) were shown in Table 1. The chemical profiles and canonical SMILES of the Phyto constituents were searched on PubChem web.

Pharmacokinetic Profile

Table 2 demonstrates pharmacokinetic profile parametric but also bioavailability of phytochemical constituents like *B. scara*. All the seven compounds (76%) of the BS had shown low virtues such as GI permeation. This would be direct proportion to a permeant blood-brain barrier (BBB), in which six phytoconstituents out of 7 shows good BBB penetration except Beta-caryophyllene. Which means that plenty of the phytoconstituents within *B. scara* extract have some very low absorption. An Egan egg, which has been used to evaluate a predictive ability of a concept such as GI passive permeation but also predictive model as nervous system access through passive diffusion to put its BOILED-Egg eventually, is just an elliptical continent populated through low-absorbed particles (Brain but rather intestinal L approximate value Dpermeability prediction model). Figure 1 shows the Predicted BOILED-Egg plot from swiss ADME online web tool for BS phytochemicals. A BOILED-Egg concept actually creates a fast, spontaneous, effective, yet boisterous method to predict passive GI permeation, which would be beneficial such as development and research [9, 10]. A white province consists of substances which are more likely to be acquired by the digestive tract, whereas the yellow region (yolk) contains substances which are more likely to influent the neocortex [11].

Lipophilic Characteristics

Table 3 demonstrates lipophilicity characteristic features of phytochemical constituents like *B. scara*. SwissADME would provide 5 freely accessible

Table 1: Molecular Structures of Chemical Constituents of BS with their SMILES

S. No	Name	Canonical SMILES
1	Alpha-pinene	CC1=CCC2CC1C2(C)C
2	Limonene	CC1=CCC(CC1)C(=C)C
3	p-cymene	CC1=CC=C(C=C1)C(C)C
4	Myrcene	CC(=CCCC(=C)C=C)C
5	Sabinene	CC(C)C12CCC(=C)C1C2
6	Beta-caryophyllene	CC1=CCCC(=C)C2CC(C2CC1)(C)C
7	Alpha-thujene	CC1=CCC2(C1C2)C(C)C

Table 2: Pharmacokinetic Prediction of Chemical Constituents of BS

Molecule	GI Absorption	Perme-ant	P-gp Subst-rate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Log Kp (Skin Permeation) (cm/s)
Alpha-pinene	Low	yes	No	No	No	yes	No	No	-3.95
Limonene	Low	yes	No	No	No	yes	No	No	-3.89
p-cymene	Low	yes	No	No	No	No	yes	No	-4.21
Myrcene	Low	Yes	No	No	No	No	No	No	-4.17
Sabinene	Low	Yes	No	No	No	No	No	No	-4.94
Beta-caryophyllene	Low	No	No	No	yes	yes	No	No	-4.44
Alpha-thujene	Low	Yes	No	No	No	No	No	No	-5.11

GI Absorption - Gastrointestinal Absorption; BBB Permeant – Blood Brain Barrier Permeation; p-glycoprotein Substrate; CYP-Cytochrome Enzymes

Table 3: Lipophilic Characteristics of Chemical Constituents of BS

Molecule	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log $P_{o/w}$
Alpha-pinene	2.63	4.48	3.00	4.29	2.79	3.44
Limonene	2.72	4.57	3.31	3.27	2.97	3.37
p-cymene	2.51	4.10	3.12	4.47	3.29	3.50
Myrcene	2.89	4.17	3.48	3.56	3.05	3.43
Sabinene	2.65	3.09	3.00	4.29	3.23	3.25
Beta-caryophyllene	3.25	4.38	4.73	4.63	4.19	4.24
Alpha-thujene	2.67	2.85	3.00	4.29	2.95	3.15

Table 4: Drug Likeness Rule and Bioavailability Score of Chemical Constituents of BS

Molecule	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
Alpha-pinene	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MW<160	Yes	yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Limonene	Yes; 0 violation	No; 1 violation: MW<160	Yes	yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
p-cymene	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MW<160	Yes	yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Myrcene	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Sabinene	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Beta-caryophyllene	Yes; 1 violation: MLOGP>4.15	yes	Yes	Yes	No; 1 violation: Heteroatoms<2	0.55
Alpha-thujene	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55

Table 5: Medicinal Chemistry Properties of Chemical Constituents of BS

Molecule	Pains	Brenk	Leadlikeness	Synthetic accessibility
Alpha-pinene	0	1 alert: isolated alkene	No; 2 violations: MW<250, XLOGP3>3.5	4.44
Limonene	0	1 alert: isolated alkene	No; 2 violations: MW<250, XLOGP3>3.5	3.46
p-cymene	0	0	No; 2 violations: MW<250, XLOGP3>3.5	1.00
Myrcene	0	2 alerts: isolated_alkene, polyene	No; 2 violations: MW<250, XLOGP3>3.5	2.85
Sabinene	0	1 alert: isolated_alkene	No; 1 violation: MW<250	2.87
Beta-caryophyllene	0	1 alert: isolated_alkene	No; 2 violations: MW<250, XLOGP3>3.5	4.51
Alpha-thujene	0	1 alert: isolated_alkene	No; 1 violation: MW<250	3.99

Table 6: Docking Scores of Chemical Constituents of BS

Molecule	Docking scores (kcal/mol)
Alpha-pinene	-5.8
Limonene	-6.3
p-cymene	-6.2
Myrcene	-5.7
Sabinene	-6.1
Beta-caryophyllene	-5.2
Alpha-thujene	-6.1
Glibenclamide - Standard	-9.4

designs to evaluate a lipophilicity personality of such a composite, particularly XLOGP3, WLOGP, MLOGP, SILICOS-IT, but also iLOGP [12].

XLOGP3, a kind atomic level strategy with suitable remedial considerations or a knowledge-based library. WLOGP [13] is just an exclusively atomistic technique which is implemented to such a fragmental system.

MLOGP [14, 15], an archetype of a topological technique, is based on such a linear relation as for 13 cellular descriptors executed.

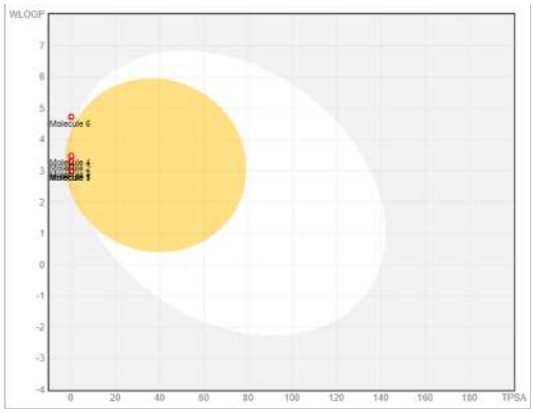
SILICOS-IT seems to be a hybrid algorithm a certain reliant through 27 fragments and 7 topological descriptors.

iLOGP has been a physics-based method which uses a generalized born but also solutes accessible surface region (GB/SA) model for calculating solubilisation of unlimited forms of energy through n-octanol as well as water.

An arithmetic mean of virtues predicted even by 5 proposed methodology [16] has been the consensus log P o/w.

Drug Likeness Rule and Bioavailability Score

Table 4 demonstrates drug-likeness principle start scoring of phytochemical constituents like *B. scara*. The whole substances within extricate like *B. s*acrament drug-likeness as according to Lipinski's regulations. A Lipinski filter (Pfizer) will be the first of 5 regulations and it categorize small-molecule predicated through physio-chemical property profiles such like molecular mass (MW) below than 500, MLOGP $\leq$ 4.15, N but rather O $\leq$ 10, NH but rather OH $\leq$ 5. The whole nitrogens as well as oxygens including at lesser one hydrogen have been regarded H-bond acceptors through Lipinski. The whole nitrogens as well as oxygens from at lesser one hydride have been regarded H-bond donors. Moreover, aliphatic fluorines have been acceptors, whilst the alanine nitrogen does neither a recipient neither an acceptor [17].



Molecule- 1: Alpha-pinene; 2: Limonene; 3: p-cymene; 4: Myrcene; 5: Sabinene; 6: Beta-caryophyllene; 7: Alpha-thujene

Figure 1: Predicted Boiled-Egg Plot from swiss ADME Online Web Tool for BS Phytochemicals

Medicinal Chemistry Properties

Table 5 shows the medicinal chemistry properties of Phytoconstituents of BS. All 7 chemicals show poorLeadlikeness. The scores for Synthetic accessibility for the chemical constituents were good (from 1 (very easy) to 10 (very difficult)). Out of 7 chemicals studied, p-cymene was very easy to prepare chemically with synthetic accessibility score of 1.00 and Beta-caryophyllene was difficult to prepare amount the chemicals of BS with synthetic accessibility score of 4.51.

Antidiabetic Property of Chemical Constituents of BS

In the present investigation, to screen out the potential compounds responsible for antidiabetic activity, docking score was used to validate the potential binding energy. The molecules were also subjected to docking studies using web-based tool, mcule to characterize their binding ability to human PPAR

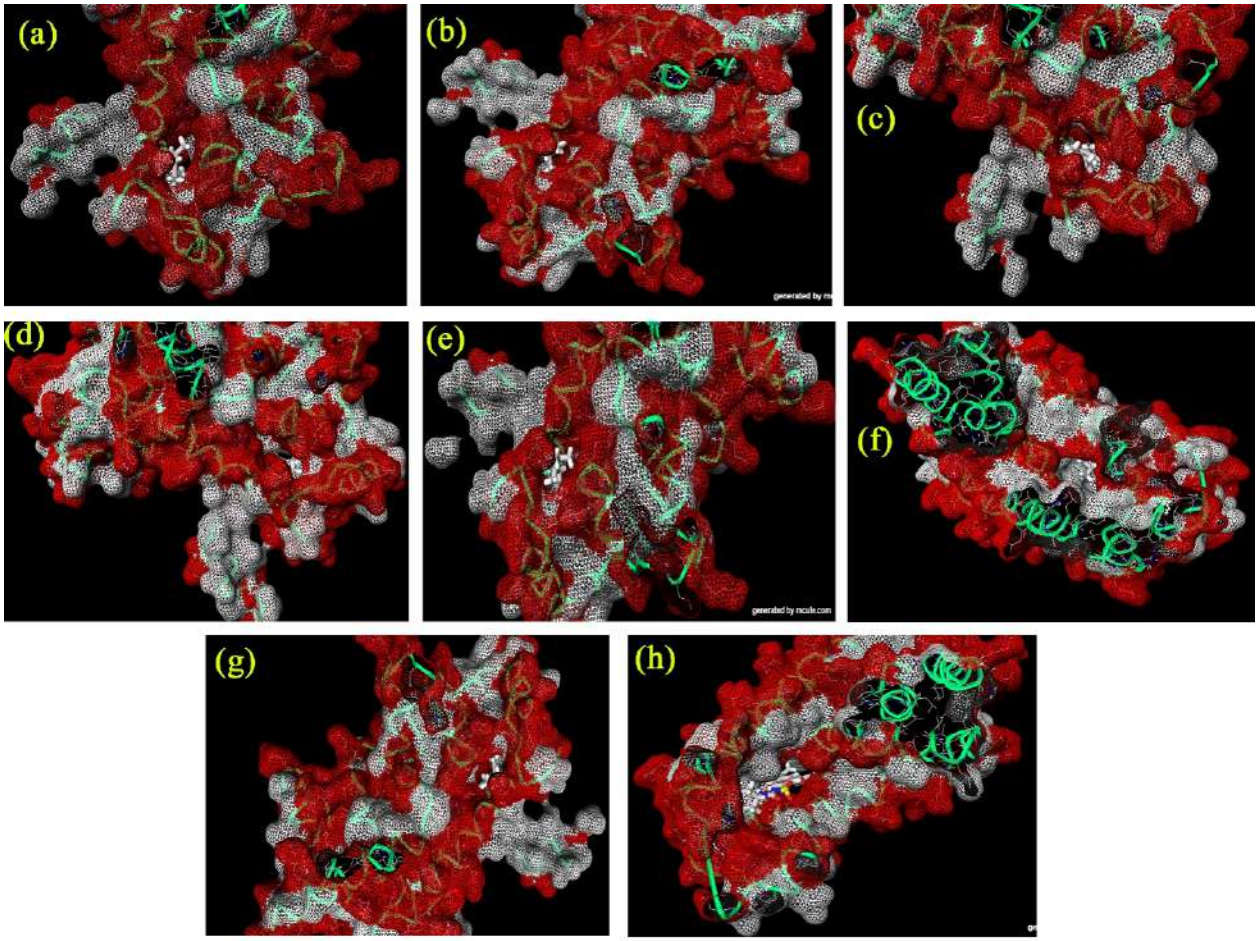


Figure 2: Protein-Ligands Interaction of Ligands into PPAR Gamma: (a) Alpha-Pinene; (b) Limonene; (c) p-cymene; (d) Myrcene; (e) Sabinene; (f) Beta-Caryophyllene; (g) Alpha-Thujene; (h) Glibenclamide (Standard)

gamma receptor. Docking studies showed that out of the seven compounds included in the study, Limonenehad the best docking score of −6.3, compared with standard Glibenclamide with its score -9.4. Table 6 shows the docking scores of chemical constituents of BS and Figure 2 shows the docking of Chemical constituents of BS with PPAR gamma.

CONCLUSION

Through structural drug design, a receptor (protein) but also ligand were also crucial. Within present study, phytochemical constituents through *Boswellia scara* have been anticipated for their pharmacokinetic profile, but also we deducted PPAR-γ only with phytochemical constituents. Based on the molecular docking evaluation, Limonene did find pledging like the main targeted against mellitus (minimum hydrogen -bonding length but also highest docked score). However, compared to the standard drug, glibenclamide, it's less efficient. Handful structure-based variations as well as *in-vivo* but also *in-vitro* have been recommended of about elucidate this compound effectiveness in the treatment of type 2 diabetes.

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Conflict of Interest

The authors declare that there is no conflict of interest for this study.

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