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RESEARCH PAPER

Insilico ADME and drug likeness evaluation of Anti-inflammatory compounds isolated from *Cymbopogon flexuosus*

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ABSTRACT

Two anti inflammatory compounds such as Phytol and Bornyl acetate, identified by GC-MS analysis of methanolic extract of *Cymbopogon flexuosus* were subjected to computational ADME, pharmacokinetics and drug likeness evaluation, using the web tool swiss ADME. The physicochemical parameter shows significant lipophilicity and low water solubility. These two compounds are expected to have good oral Bioavailability and bornyl acetate are not considered to be P-glycoprotein substrates. On contrast with Phytol ,Bornyl acetate has higher solubility, GI tract absorption and it passes Blood Brain Barrier (BBB). The evaluation of their inhibitory profiles in several cytochrome P450 isoforms indicates that all of them as CYP2C9 inhibitors, whereas the expected modulatory effects on CYP's varied among the compounds. The drug likeness evaluation employed five alternative rules based filters and Bornyl acetate compiled with the lipinski's "rule of five. Taken together the calculated ADME and pharmacokinetics parameters, gives us reason to consider the Bornyl acetate from *cymbopogonflexuosus* as a perspective inflammatory lead compounds for further more detailed inflammopharmacology and toxicological evaluation.

Keywords: - Anti-inflammatory, ADME, Bioavailability, Drug likeness, Pharmacokinetics.

INTRODUCTIO

Cymbopogonflexuosus has been customarily utilized as a solution for an assortment of wellbeing condition. Ongoing logical investigations have given proof supporting its antimicrobial, cancer prevention agent, antifungal and calming properties in a few infected models.[1,2,3]. Taking into account that irritation may prompt different ailments, for example, rheumatoid joint pain, fiery inside ailment or psoriasis and current steroidal and non-steroidal provocative medications used to treat incendiary issue can create numerous antagonistic impacts. The revelation of new and more secure calming specialists keep on being an issue of high intrigue. Right now, utilized in people medication become fantastic research contender for their latent capacity content in mixes lead to compelling home grown details from institutionalized dynamic concentrates.

The promising pharmacological movement anyway is anything but a lone essential of a fruitful pharmaceutical commercialization of a concoction substance, since it ought to be joined

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by appropriate physicochemical and biopharmaceutical properties, making an interpretation of thus into the ideal pharmacokinetic parameters.[4]

As a high throughput pre-screen help in tranquilize disclosure various *insilico* approaches have been created for guess and estimation of Absorption, Distribution, Metabolism and Excretion [ADME] profiles and for appraisal of the alleged medication resemblance, characterized as a subjective expectation of plausibility for worthy bioavailability and pharmacokinetics after oral intake.[5-8]

The precursor work of Lipinski et.al, investigated an exhaustive number of orally dynamic mixes and instituted the infamous principle - of-five as a value of ideal scope of the medication's physicochemical reaches to bear the cost of ideal pharmacokinetic conduct after oral intake.[9-11]

So as to clarify the capability of the Phytol and Bornyl acetate for additional improvement as calming specialists, we in this portray the computational examination of their pharmacokinetic profile and medication resemblance utilizing a board of channels, routinely used in the prescreen phase of medication advancement in the pharmaceutical organizations.

MATERIALS AND METHODS

Collection of plant material

Cymbopogon flexuosus was gathered from in and around the regions of yerkaud ,salem area, Tamilnadu, India. New entire plant material was washed under running faucet water, air dried and powdered. The plant was verified by Prof.P.Jayaraman, plant Anatomy Research Center (PARC), west Tambaram, Chennai, Tamilnadu, India.

Preparation of Extract

In reflux technique, 50g of shade dried leaf of *C.flexuosus* was powdered and thoroughly refluxed with methanol (150ml ×3) for 4 hrs. The concentrate was sifted through, concentrated and dried over a turning evaporator in a preweighed flagon. The got buildup was 2.6g.

GC-MS Analysis

The creation of the methanolic remove was set up by GC-MS investigation. The investigation was performed on a JEOL GCMATE II GC-MS framework in EI/CI mode furnished with a split/splitless injector (220°C), at a split proportion of 1/10, utilizing a VF-IMS melded silica hair-like column. The stove temperature was customized from 60°C (5mins) to 280°C at a pace of 4°C/mins and held at the temperature for 10 mins. Helium was utilized as a bearer gas at a stream pace of 0.8ml/min. mass spectra were taken at 70eV; a sweep interim of 0.5 seconds and sections from 40 to 55oDa. The ranges of the segments were contrasted and the database of known range parts put away in the NIST library.[12]

Target Compounds and Computational Tools

The broke down mixes were detached from the leaves of C.flexuosus . The Insilico ADMET screening and drug likeness evaluation was performed utilizing the free webtool swiss ADME, created by the Swiss Institute of Bioinformatics, and openly accessible at http:www.swissadme.ch.[7] Phytol 1 is a non-cyclic diterpene liquor and Bornyl acetate 2 is an ester of borneol.

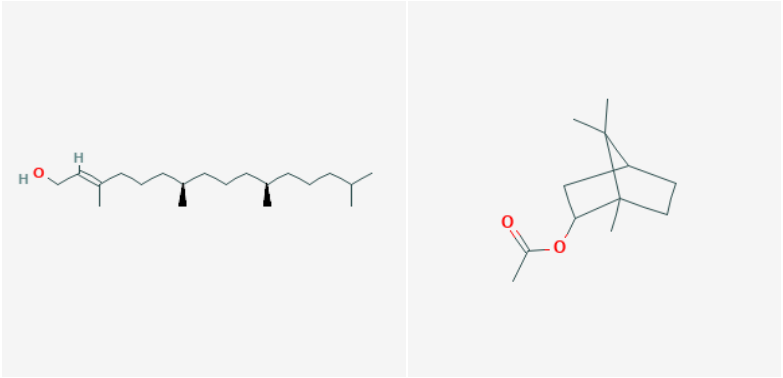

Figure 1: Chemical structures of the target phytol and Bornyl Acetate from *Cymbopogon flexuosus*

Table 1. Designation of the target compounds

Compound designation	Structure/nomenclature
1	(E,7R,11R) – 3,7,11,15- tetramethylhexadec-2-en-1-ol
2	(1,7,7 – trimethyl – 2-bicyclo[2.2.1] heptanyl) acetate

Physicochemical Properties and general Computational Methodology

The SMILES for every structure were produced by the structure document generator, accessible at the free online device swiss ADME website page. Utilizing the web apparatus we determined various basic sub-atomic and physicochemical descriptors, for example, molecular weight (MW), molecular refractivity (MR), tally of explicit particles types and the topological polar surface region (TPSA), the later demonstrated as a helpful descriptor in numerous models for estimation of film dissemination, ADME and pharmacokinetic conduct. The lipophilicity was surveyed by methods for five option prescient models, i.e.XLOGP ;WLOGP;SILICOS-IT ; iLOGP, together with an accord logp estimation, in light of the normal estimation of the diverse computational parameters [13]. On the other hand, the fluid dissolvability was set up, too utilizing three elective models.

ADME

The ADME/pharmacokinetic investigation focused on estimation of center parameters, for example, gastro-intestinal ingestion, P-glycoprotein intervened efflux, capacity to infiltrate the Blood Brain Barrier (BBB). In addition , we examined whether the objective

mixes are substrates of a battery of basic isoforms of the cytochrome p450 (cyp) family, to be specific CYP1A2, CYP2D6, CYP2C9, CYP2C19 and CYP3A4.

To meet this target the swiss adme instrument is depending on a vigorous vector machine calculation (SVM) with unequivocally cleaned exhaustive datasets of set up inhibitors/non-inhibitors and substrates/non-substrates. The theoretic foundation, improvement and approval of these computational methodologies have been portrayed in detail elsewhere.[14]

Drug LikenessEstimation

The Drug likeness investigation was done utilizing the approved standards utilized a high throughput screens channel in a portion of the main pharmaceutical organizations, as follows: Lipinsiki (Pfizer), Ghose (Amgen), Veber(GSK), Egan (Pharmacia) andMugge (Bayer). The abott Bioavailability score was determined to anticipate the likelihood for a 10% oral bioavailability or caco-2 diffusion.

These channels have been created to asses sedate resemblance, for example to foresee whether a substance element is probably going to have a valuable pharmacokinetic properties, utilizing estimations, in view of parameters, for example, sub-atomic weight, Logp, number of HPA and HBD.[4-8]

Besides the possibility to investigate the introduced structures is beginning platforms or lead mixes in a future manufactured medication revelation program was examined utilizing explicit restorative science and lead resemblance filter.[7]

Results and Discussions

GC-MS Analysis

The GC-MS results demonstrated the nearness of nine bioactive mixes in methanolic leaf concentrate of *C.flexuosus*. the Identification of the compounds was confirmed based on the peak area, retention time (RT) and molecular formula.The dynamic rule with their RT, molecular formula, MW, peak area in percentage as presented in Fig 1 and table 2.

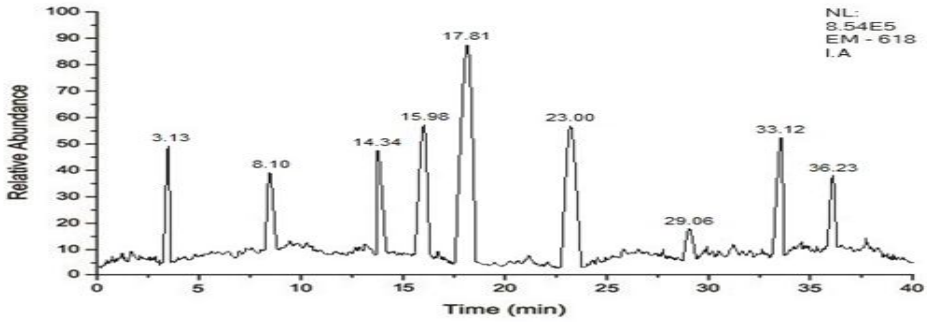

Figure 2: GC-MS analysis of methanolic ectract of *C.flexuosus*

Table 2: GC-MS interpretation of methanolic extract of *C.flexuosus*

RT	Name of the compound	Molecular Formula (MF)	Molecular weight (MW)	Peak area (%)
3.13	Carbetapentane	$C_{20}H_{31}NO_3$	333.5	0.45
8.10	Propenoic acid	$C_3H_4O_2$	72.06	0.83
14.34	Bornyl acetate	$C_{12}H_{20}O_2$	196.29	0.89
15.98	Heptadecanoic Acid	$C_{17}H_{34}O_2$	270.5	3.42
17.81	Phytol	$C_{20}H_{40}O$	128.17	24.90
23.00	1(3H)-Isobenzofuranone, 3-ethoxy-	$C_{10}H_{10}O_3$	178.18	7.79
29.06	Quinhydrone	$C_{12}H_{10}O_4$	218.2	0.62
33.12	9,12,15-Octadecatrienoic acid ethyl ester	$C_{20}H_{34}O_2$	306.5	2.00
36.23	15-Methylhexadecanoicacid	$C_{17}H_{34}O_2$	270.5	0.77

ADME and Drug similarity assessment of Anti-inflammatory compounds

The essential physicochemical parameters are depicted in Table 3. Though the lipophilicity and water solubility estimations are introduced in Table 4 and 5 separately. In view of the determined Logp values every tried compound end up being lipophilic with accord esteems running from 3 to 6.22 (Table 4). These are considered as limit an incentive for the greater part of the medication resemblance channels utilized by the pharmaceutical business. Alternately, these discoveries were reflected by the estimation of the water solubility demonstrated that the target compounds are moderately to poorly soluble, depending on the logs estimation model and the tested compound (Table 5).

Table 3: Basic physicochemical properties and computational descriptors of the tested compounds

Properties	1	2
Formula	C20H40O	C12H20O2
Molecular weight	296.53 g/mol	196.29 g/mol
Num. heavy atoms	21	14
Num. arom. heavy atoms	0	0
Fraction Csp3	0.90	0.92
Num. rotatable bonds	13	2
Num. H-bond acceptors	1	2
Num. H-bond donors	1	0
Molar Refractivity	98.94	56.33
TPSA	20.23A	26.30A

Table 4: Lipophilicity of the tested compounds

Properties	1	2
Log *P*o/w (iLOGP)	4.71	2.50
Log *P*o/w (XLOGP3)	8.19	4.30
Log *P*o/w (WLOGP)	6.36	2.76
Log *P*o/w (MLOGP)	5.25	2.76
Log *P*o/w (SILICOS-IT)	6.57	2.66
Consensus Log *P*o/w	6.22	3.00

Table 5: Water solubility prediction values, based on three alternative models

Properties	1	2
Log *S* (ESOL)	–5.98	–3.63
Solubility	3.10.10–4 mg/ml; 1.05.10–6 mol/l	4.56.10–2 mg/ml; 2.32.10–4 mol/l
Class	Moderately soluble	Soluble
Log *S* (Ali)	–8.47	–4.57
Solubility	9.94.10–7 mg/ml; 3.35.10–9 mol/l	5.34.10–3 mg/ml; 2.72.10–5 mol/l
Class	Poorly soluble	Moderately soluble
Log *S* (SILICOS-IT)	–5.51	–2.58
Solubility	9.06.10–4 mg/ml; 3.05.10–6 mol/l	5.20.10–1 mg/ml; 2.65.10–3 mol/l
Class	Moderately soluble	Soluble

Table 6: Calculated ADME and pharmacokinetic parameters

Properties	1	2
GI absorption	low	High
BBB permeant	No	Yes
P-gp substrate	Yes	No
CYP1A2 inhibitor	No	No
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	Yes	Yes
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Log *K*p (skin permeation)	–2.29 cm/s	–4.44 cm/s

The fundamental ADME parameters of the pharmacokinetics conduct of the tried phytol and Bornyl acetate are depicted in Table 6 with the main special case of phytol compound, bornyl acetate are evaluated to have high assimilation in the gastrointestinal tract which is a profoundly ideal component of a medication applicant, thinking about the undisputable points of interest of the oral courses of organization.

With not many exemptions the phytol and Bornyl acetate are not expected to go about as inhibitor of CYP1A2, CYP2D6 which intervenes

at the biotransformation of various significant classes of medications [15]. Both Bornyl acetate and phytol are expected to act as CYP2C9 inhibitor also.

The computational information demonstrates that the Bornyl acetate has equipped for intersection the Blood Brain Barrier with exemption of phytol . Another valuable issue for phytol and Bornylacetae is that the computational screening shows them as non-p-gb substrates. Therefore the discoveries showing the Bornyl acetate as non-p-gb substrates in essential for movement against multi-drug resistance inflammatory cells, over-communicating this medication transporters. Despite what might be expected, the computational information for the Phytol demonstrates it as p-gbsubstrates.Nevertheless, our pharmacological information from going before examines shows that this compound is fit for killing multi-drug resistance ,which indirectly indicates that it is actually an inhibitor of the ATP-binding cassette transporters such as p-gb.

The skin permeability of the tested compounds is expected to be very low, based on the calculated log$K_p$values.

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Table 7. Drug likeness, medicinal chemistry and lead-likeness parameters for the tested compounds

Properties	1	2
Lipinski	Yes; 1violations: MLOGP>4.15	Yes; 0 violations
Ghose	No; 1 violation: WLOGP>5.6	Yes
Veber	NO;1 violation: Rotors>10	Yes
Egan	No;1 violation: WLOGP>5.88	Yes
Muegge	No; 2 violation: XLOGP3>5, Heteroatoms<2	No; 1 violation: MW<200
Bioavailability Score	0.55	0.55
Brenk	1 alerts: Isolated_alkene	0

The drug likeness evaluation is summarized in Table 7, except for phytol, Bornyl acetate demonstrated to follow the lipinski'srule, which involves the spearheading drug competitor channel, actualized in the medication revelation screens of Pfizer and are viewed as a definitive archeotypte of all drug likeness tools..

Then again the tried Bornyl acetate has no infringement of the principles, actualized in Veber, ghose, veggie lover channel, yet had variable achievement rates in muge channels. The phytol shows variable rates in all channels.

We additionally determined the Abott bioavailability score which gauges the likelihood

of a compound to have at any rate 10% oral bioavailability in rodent or quantifiable caco2 permeability.[7] Based on the semi quantitative score, determined based on all out charge, TPSA and infringement of lipinski'schannel . The tried mixes ar orders to four classes of mixes with likelihood of 11%, 17%, 56% or 85%.

In accordance with GI tract assimilation information from Table 3, the tried phytol and Bornyl acetic acid derivation were delegated having 55% likelihood of accomplishing previously mentioned Bioavailability end points.Due to the chemical complexity high molecular mass and lipophilicity, the tested compounds generally failed to comply to mugge and brent lead likeness filter,[7] which indicates that of they are to employed as starting scaffolds for a drug discovery programs. The synthetic strategies should be focused on structure simplification, elimination of troublesome functionalities and decreased lipophilicity.

CONCLUSION

The gobal ADME and PK features of the Bornyl acetate generally indicates the main issue of concern is their significant lipophilicity and low water solubility, otherwise the analysedbornyl acetate have a suitable amalgam of physicochemical and biopharmaceutical properties, to afford plausible pharmacokinetic properties. This together with the promising anti-inflammatory effects gives us reason to consider the bornyl acetate from *Cymbopogon flexuosus* as a perspective set of lead compounds for further more detailed pharmacological and toxicological evaluation.

Conflict of Interest

No conflict of Interest.

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