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Bioavailability prediction of phytochemicals present in *Calotropis procera* (Aiton) R. Br. by using Swiss-ADME tool

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ABSTRACT

The medicinal plant, *Calotropis procera* (Aiton) R. Br. is a common shrub and this plant has several phytochemicals that act as analgesic and anti-inflammatory agents. The aim of the present study was to detect bioavailability potential through absorption, distribution, metabolism and excretion (ADME) of phytocompounds established in *C. procera* plant parts. *In silico* study, especially pharmacokinetics, bioavailability, drug-likeness and medicinal chemistry friendliness prediction was performed by using the SwissADME online tool to know the lead phytocompound for the drug candidate for the prevention of pain and inflammation. The common established eleven phytocompounds such as Methyl myrisate, Methyl behenate, Anthocyanin, Uzarigenin, Lupeol, β-amyrin, α-amyrin, Uscharin, Calotropin, β-sitosterol and Quercetin-3-rutinoside as well as 2 synthetic anti-inflammatory medicines were selected for the present computational prediction. The predictions of pharmacokinetics, bioavailability, drug-likeness and medicinal chemistry friendliness obtained a suitable phytocompound Uzarigenin of *C. procera,* which showed resemblance with several parameters of Ibuprofen and the synthetic drug Ibuprofen is well-established analgesic and anti-inflammatory agent. In conclusion, the small molecule, Uzarigenin can be suitable drug candidate. Further study should be done by *in vitro* and *in vivo* assay for toxicology, pharmacology and experimental bioavailability for pain and inflammation reliving phytomedicine to confirm the present predictions.

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Keywords: Pharmacokinetics, Bioavailability, Drug-likeness, Medicinal chemistry, *Calotropis procera*, Phytocompounds, Synthetic compounds

1. INTRODUCTION

Among Indian medicinal plants, *C. procera* (Aiton) R. Br., belongs to milkweed family and the parts of the plant extract are used traditionally for the relief of pain and inflammation (Sangraula et al., 2002; Kumar and Roy, 2007; Saba et al., 2011; Murti et al., 2015; Shukla et al., 2018). The inflammatory disease leads to internal and external inflammation in tissues, organs, etc. There are well established anti-inflammatory synthetic drugs, which help in pain relief as well as recovery of swelling in various tissues, however, synthetic compounds may cause side effect like ulceration in the gastrointestinal tract (Brodie et al., 1970; Bjarnason et al., 1993; Higuchi et al., 2009a; b; Matsui et al., 2011). The experimental study has been reported that aqueous flower and latex extracts of *C. procera* relief pain, fever and inflammation (Mascolo et al., 1998; Dewan et al., 2000) while ethanolic extract of root bark and leaf showed anti-inflammatory properties without any side effect (Winter et al., 1962; Parihar et al., 2011; Saba et al., 2011).

The term pharmacokinetics describes the fate of compound in the organism during therapeutic purpose. In other words, the pharmacokinetics depend upon absorption, distribution, metabolism and excretion (ADME) parameters. According to Hay et al. (2014), an early measure of ADME in the discovery phase reduced drastically the fraction of pharmacokinetics-related failure in the clinical phases. For drug discovery, ADME is an important parameter. Bioavailability term describes the extent and rate in which the active moiety (drug or metabolite) entered systemic circulation, ultimately accessed the site of action (Le, 1989).

Generally, bioavailability is estimated as per Lipinski's 'rule of five' in which it was known that better bioavailable of a compound depends upon <5 hydrogen bond donors, <10 hydrogen bond acceptors, <500 daltons molecular mass, <5 a partition co-efficient log P-value and <10 rotatable bonds (Lipinski et al., 2001).

Beside these, several other factors could also play a role in limiting bioavailability and these are solubility of the compound, stability due to gastric and colonic pH, metabolism by gut microflora, absorption across the intestinal wall, active efflux mechanism and first-pass metabolic effects (Aqil et al., 2013). However, it may difficult to assess bioavailability of compounds based solely on their physicochemical properties. The drug-likeness is based on experiments that orally active compound with highly probable range of physico-chemical properties and can be used as an oral drug (Lipinski et al., 2001). According to Holbrook et al. (2017), the term medicinal chemistry is defined as "synthesizing bioactive molecules" as well as "the design and synthesis of biologically active molecules to discuss unmet medical needs".

An *in silico* approach, especially computational prediction through ADME software is a suitable method for faster screening, less time consuming, no animal testing, etc. Among several tools, SwissADME online tool is a valid alternative of an experimental drug design from natural products or synthetic compounds (Daina et al., 2014; Daina and Zoete, 2016; Daina et al., 2017a; b). This tool helps to find narrow range of compound(s) for future experimental work on pharmacokinetics, bioavailability, etc. lead to new drug development.

The aim of the present study was to detect bioavailability potential through absorption, distribution, metabolism and excretion (ADME) of phytocompounds established in *C. procera* plant parts. The computational prediction of pharmacokinetics, bioavailability, drug-likeness and medicinal chemistry friendliness was performed by using the SwissADME online tool to know the lead phytocompound for the prevention of pain and inflammation.

2. MATERIALS AND METHODS

2. 1. Brief description of plant species

Two members of the plant species under family Asclipiadaceae and Indian *Calotropis* sp. are known as *Calotropis procera* and *Calotropis gigantea*, commonly called as "Akanda" in Bengali language. Generally, the plant species attain a height of 14-16 feet. The plant is grown on course, sandy, etc. soil. The plant contains latex, which are toxic to grazers (Mahmoud et al., 1979). However, the plant species are used to treat various diseases as traditional system of medicine (Murti et al., 2015; Shukla et al., 2018). The plant species is exhibited in Fig 1.

Fig. 1. Twig of *Calotropis* sp.

2. 2. Selection of ligands

Two synthetic medicines used as common anti-inflammatory drugs viz. ibuprofen and indomethacin were selected from the previous study by Edwards (2014). There were eleven established common phytocompounds such as Methyl myrisate, Methyl behenate, Anthocyanin, Uzari-genin, Lupeol, β-amyrin, α-amyrin, Uscharin, Calotropin, β-sitosterol and Quercetin-3-rutinoside selected from literature as bioactive phytochemicals found in *C. procera*

(Quazi et al., 2013). The canonical SMILES (simplified molecular input line entry system) string for these eleven phyto-compounds as well as two drugs of synthetic origin were obtained from PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/ compound). Each SMILES string was used for ADME prediction by using a computer tool.

2. 3. Pharmacokinetics, bioavailability drug-likeness and medicinal chemistry friendliness prediction of ligands

The predictive study of pharmacokinetics especially ADME, bioavailability, drug-likeness and medicinal chemistry of ligands were carried out by using the SwissADME online tool developed by Daina et al. (2017a; b). The canonical SMILES string for each chemical was incorporated in this tool for the computational simulation. The tool predicts bioavailability radar as per six physicochemical properties such as lipophilicity, size, polarity, solubility, flexibility and saturation to detect drug-likeness. The ADME properties viz. passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation as well as substrate or non-substrate of the permeability glycoprotein (P-gp) as detected positive or negative in the BOILED-Egg model within the tool developed by Daina, and Zoete, (2016) and Daina et al. (2017a). The estimation of lipophilicity (Log p/w) parameters such as iLOGP was calculated for n-octanol and water on free energies of solvation as per the generalized-born and solvent accessible surface area (GB/SA) model developed by Daina et al. (2014), XLOGP3 is an atomistic method including corrective factors and knowledge-based library developed by Cheng et al. (2007), WLOGP has been implemented for a purely atomistic method based on the fragment system of Wildman and Crippen (1999), M-LOGP is an archetype of topological method relying on a linear relationship with 13 molecular descriptors implemented as per researchers (Moriguchi et al., 1992; 1994) and SILICOS-IT is an hybrid method, relying on 27 fragments and 7 topological descriptors (Daina et al., 2017a).

The Lipinski (Pfizer) filter is the pioneer rule-of-five has been incorporated in this tool from Lipinski et al. (2001) and this tool has also been inbuilt for the prediction of drug-likeness (Daina et al., 2017a). The bioavailability radar for oral bioavailability prediction as per different physico-chemical parameters has been developed by SwissADME tool (Daina et al., 2017a; b). The medicinal chemistry techniques prediction has based on the root of structural alert (Brenk et al., 2008), the pan assay interference compounds or PAINS structural alert (Baell and Holloway, 2010) or the Lilly MedChem (Bruns and Watson, 2012) filters applied to cleanse chemical libraries of compounds most likely unstable, reactive, toxic, or prone to interfere with biological assays because unspecific frequent hitters, dyes or aggregators (Irwin et al., 2015). The synthetic accessibility (SA) score has based primarily on the assumption that the frequency of molecular fragments in ‘really’ obtainable molecules correlates with the ease of synthesis. The developed and validated method has been characterized through the molecule synthetic accessibility score, which observed between 1 and 10 (easy and very difficult to make) has been described by Ertl and Schuffenhauer (2009).

3. RESULTS AND DISCUSSION

The results on predictive data for pharmacokinetics, bioavailability, drug-likeness and medicinal chemistry friendliness of established 11 phytoligands such as Methyl myristate, Methyl behenate, Anthocyanin, Uzarigenin, β-sitosterol, Quercetin-3-rutinoside, Lupeol,

β-amyrin, α-amyrin, Uscharin and Calotropin, of *C. procera* and 2 synthetic ligands viz. Indomethacin and Ibuprofen (Table 1 – 4).

In Table 1, for pharmacokinetics prediction, the gastrointestinal (GI) absorption rate was obtained higher for phytoligands viz. Methyl myristate, Anthocyanin, Uzarigenin and Calotropin and both the synthetic ligands such as Indomethacin and Ibuprofen while lower for phytoligands viz. Methyl behenate, β-sitosterol, Quercetin-3-rutinoside, Lupeol, β- and α-amyrin and Uscharin respectively. The blood-brain permeability was observed for Methyl myristate, Anthocyanin, Uzarigenin, Indomethacin and Ibuprofen while Methyl behenate, β-sitosterol, Quercetin-3-rutinoside, Lupeol, β- and α-amyrin, Uscharin and Calotropin were observed permeability negative. In case of skin permeation (log Kp, cm/s), higher negative value was obtained for Quercetin-3-rutinoside (-10.26) followed by Uscharin (-8.92) and Calotropin (-8.89), Uzarigenin (-6.71), Anthocyanin (-5.16), Indomethacin (-5.45) and Ibuprofen (-5.07) and lower for Methyl behenate (-1.22) followed by Lupeol (-1.90), β-sitosterol (-2.20), β-amyrin (-2.41), α-amyrin (-2.51) and Methyl myristate (-3.23) respectively. The phyto and synthetic ligands viz. Methyl myristate, Methyl behenate, β-sitosterol, Lupeol, β-amyrin, α-amyrin, Indomethacin and Ibuprofen did not show p-glycoprotein substrate activity while Anthocyanin, Uzarigenin, Quercetin-3-rutinoside, Uscharin and Calotropin showed p-gp substrate activity. To detect inhibitory activity for cytochrome p450 as CYP1A2, all ligands were showed non-inhibitors except Methyl myristate, Methyl behenate, Anthocyanin and Indomethacin; for CYP2C19 and CYP2C9, all ligands were showed non-inhibitors except Indomethacin; for CYP2D6 all ligands were showed non-inhibitors except Anthocyanin and for CYP3A4 all ligands were observed non-inhibitors.

Table 1. Pharmacokinetics prediction of phytoligands established in *C. procera* compared to synthetic ligands

Sl. No.	Ligands	Gastro- intestinal absorption	Blood-brain permeant	P- glycoprotein substrate	CYP450 1A2 inhibitor	CYP450 2C19 inhibitor	CYP450 2C9 inhibitor	CYP450 2D6 inhibitor	CYP450 3A4 inhibitor	Skin permeation as log Kp (cm/s)
1.	Methyl myristate	High	Yes	No	Yes	No	No	No	No	-3.23
2.	Methyl behenate	Low	No	No	Yes	No	No	No	No	-1.22
3.	Anthocyanin	High	Yes	Yes	Yes	No	No	Yes	No	-5.16
4.	Uzarigenin	High	Yes	Yes	No	No	No	No	No	-6.71
5.	β-sitosterol	Low	No	No	No	No	No	No	No	-2.20
6.	Quercetin-3-rutinoside	Low	No	Yes	No	No	No	No	No	-10.26

7.	Lupeol	Low	No	No	No	No	No	No	No	-1.90
8.	β-amyrin	Low	No	No	No	No	No	No	No	-2.41
9.	α-amyrin	Low	No	No	No	No	No	No	No	-2.51
10.	Uscharin	Low	No	Yes	No	No	No	No	No	-8.92
11.	Calotropin	High	No	Yes	No	No	No	No	No	-8.89
12.	Indomethacin	High	Yes	No	Yes	Yes	Yes	No	No	-5.45
13.	Ibuprofen	High	Yes	No	No	No	No	No	No	-5.07

The prediction of bioavailability (Table 2) revealed that same bioavailability scores were obtained for all studied small molecules (0.55) such as Methyl myristate, Methyl behenate, Anthocyanin, Uzarigenin, β-sitosterol, β-amyrin, α-amyrin, Uscharin and Calotropin but Quercetin-3-rutinoside (0.17) and Indomethacin and Ibuprofen were obtained 0.56. The water solubility data obtained for soluble compounds viz. Anthocyanin (-3.34), Uzarigenin (-3.69), Quercetin-3-rutinoside (-4.87), Calotropin (-3.28) and Ibuprofen (-3.97) and moderately soluble compounds viz. Methyl myristate (-6.76), Uscharin (-4.10) and Indomethacin (-5.42) and poorly soluble ligands viz. Methyl behenate (-10.69), β-sitosterol (-9.67), Lupeol (-10.22), β-amyrin (-9.47) and α-amyrin (-9.33) respectively.

Table 2. Bioavailability prediction of phytoligands established in *C. procera* compared to synthetic ligands

Sl. No.	**Ligands**	**Bioavailability score**	**Water solubility as logS**	**iLOGP**	**XLOGP3**	**WLOGP**	**MLOGP**	**SILICOS-IT**
1.	Methyl myristate	0.55	Moderately soluble as -6.76	3.88	6.41	4.86	3.94	4.96
2.	Methyl behenate	0.55	Poorly soluble as -10.69	6.13	10.20	7.98	5.79	8.48
3.	Anthocyanin	0.55	Soluble as -3.34	-0.68	3.39	4.38	3.28	2.79
4.	Uzarigenin	0.55	Soluble as -3.69	3.09	2.64	3.60	3.56	3.45
5.	β-sitosterol	0.55	Poorly soluble as -9.67	4.79	9.34	8.02	6.73	7.04
6.	Quercetin-3-rutinoside	0.17	Soluble as -4.87	2.43	-0.33	-1.69	-3.89	-2.11

7.	Lupeol	0.55	Poorly soluble as -10.22	4.89	9.87	8.02	6.92	6.82
8.	β-amyrin	0.55	Poorly soluble as -9.47	4.75	9.15	8.17	6.92	6.92
9.	α-amyrin	0.55	Poorly soluble as -9.33	4.77	9.01	8.02	6.92	6.52
10.	Uscharin	0.55	Moderately soluble as -4.10	3.38	1.36	2.77	1.78	3.30
11.	Calotropin	0.55	Soluble as -3.28	2.86	0.93	2.00	1.49	1.88
12.	Indomethacin	0.56	Moderately soluble as -5.42	2.76	4.27	3.93	3.30	3.91
13.	Ibuprofen	0.56	Soluble as -3.97	2.36	3.50	3.07	3.13	3.15

In case of bioavailability prediction, five other parameters such as iLOGP, XLOGP3, WLOGP, MLOGP and SILCOS-ST were also obtained. For iLOGP, Methyl behenate (6.13), Lupeol (4.89), β-sitosterol (4.79), α-amyrin (4.77), β-amyrin (4.75) observed higher value followed by Methyl myristate (3.88), Uscharin (3.38), Uzarigenin (3.09), Calotropin (2.86), Indomethacin (2.76), Quercetin-3-rutinoside (2.43), Ibuprofen (2.36) while Anthocyanin (-0.68) showed lower value. For XLOGP3, Methyl behenate (10.2), Lupeol (9.87), β-sitosterol (9.34), β-amyrin (9.15), α-amyrin (9.01) and Methyl myristate (6.41) observed higher value followed by Indomethacin (4.27), Ibuprofen (3.50), Anthocyanin (3.39) and Uzarigenin (2.64) while Quercetin-3-rutinoside (-0.33) showed lower value followed by Calotropin (0.93) and Uscharin (1.36). For WLOGP, β-amyrin (8.17), β-sitosterol, α-amyrin and Lupeol (8.02), Methyl behenate (7.98), Methyl myristate (4.86) and Anthocyanin (4.38) observed higher value followed by Indomethacin (3.93), Uzarigenin (3.60) and Ibuprofen (3.07) while Quercetin-3-rutinoside (-1.69) showed lower value followed by Calotropin (2.00) and Uscharin (2.77). For MLOGP, Lupeol, β-amyrin and α-amyrin (6.92), β-sitosterol (6.73), and Methyl behenate (5.79) observed higher value followed by Methyl myristate (3.94), Uzarigenin (3.56), Indomethacin (3.30), Anthocyanin (3.28) and Ibuprofen (3.13) while Quercetin-3-rutinoside (-3.89) showed lower value followed by Uscharin (1.78) and Calotropin (1.49). For SILCOS-IT, Methyl behenate (8.48), β-sitosterol (7.04), β-amyrin (6.92), Lupeol (6.82), α-amyrin (6.52) and Methyl myristate (4.96) observed higher value followed by Indomethacin (3.91), Uzarigenin (3.45), Uscharin (3.30) Ibuprofen (3.15) and Anthocyanin (2.79) while Quercetin-3-rutinoside (-2.11) showed lower value followed by Calotropin (1.88).

For drug-likeness prediction (Table 3), Methyl myristate, Anthocyanin, Uzarigenin, Indomethacin and Ibuprofen were obtained suitable for Lipinski rule as 0 violation while Methyl behenate, β-sitosterol, Lupeol, β-amyrin, α-amyrin, Uscharin and Calotropin were showed Lipinski rule as 1 violation except Lipinski rule as 3 violation for Quercetin-3-rutinoside. For Ghose filter, Methyl myristate, Anthocyanin, Uzarigenin, Indomethacin and Ibuprofen were obtained suitable as 0 violation while Methyl behenate violation as 2 and rest ligands viz. β-sitosterol, Lupeol, β-amyrin, α-amyrin, Uscharin and Calotropin were obtained violation as 3 except Quercetin-3-rutinoside violation as 4. For Veber filter, 0 violation was observed for ligands such as Methyl myristate, Anthocyanin, Uzarigenin, Indomethacin and Ibuprofen while 1 violation was obtained for Methyl myristate, Methyl behenate, Quercetin-3-

rutinoside and Uscharin. For Egan filter, 0 violation was also observed for ligands such as Methyl myristate, Anthocyanin, Uzarigenin, Indomethacin and Ibuprofen while 1 violation was obtained for Methyl behenate, β-sitosterol Quercetin-3-rutinoside, Lupeol, β-amyrin, α-amyrin, Uscharin and Calotropin. For Muegge filter, Uzarigenin, Calotroin, Indomethacin and Ibuprofen were obtained 0 violation while Methyl myristate, Anthocyanin and Uscharin obtained 1 violation, Methyl behenate, β-sitosterol, Lupeol, β-amyrin and α-amyrin obtained 2 violation and Quercetin-3-rutinoside was 4 violation respectively.

Table 3. Druglikeness prediction of phytoligands established in *C. procera* compared to synthetic ligands

Sl. No.	Ligands	Lipinski rule	Ghose filter	Veber filter	Egan filter	Muegge filter
1.	Methyl myristate	0	0	1	0	1
2.	Methyl behenate	1	2	1	1	2
3.	Anthocyanin	0	0	0	0	1
4.	Uzarigenin	0	0	0	0	0
5.	β-sitosterol	1	3	0	1	2
6.	Quercetin-3-rutinoside	3	4	1	1	4
7.	Lupeol	1	3	0	1	2
8.	β-amyrin	1	3	0	1	2
9.	α-amyrin	1	3	0	1	2
10.	Uscharin	1	3	1	1	1
11.	Calotropin	1	3	0	1	0
12.	Indomethacin	0	0	0	0	0
13.	Ibuprofen	0	0	0	0	0

In case of medicinal chemistry friendliness prediction (Table 4), the leadlikeness had showed 3 violation for Methyl myristate and Methyl behenate, 2 violation for β-sitosterol, Lupeol, β-amyrin, α-amyrin and Indomethacin while 1 violation for Anthocyanin, Uzarigenin, Quercetin-3-rutinoside, Uscharin, Calotropin and Ibuprofen. The PAINS structural alert obtained 0 violation for Methyl myristate, Methyl behenate, Anthocyanin, Uzarigenin, β-

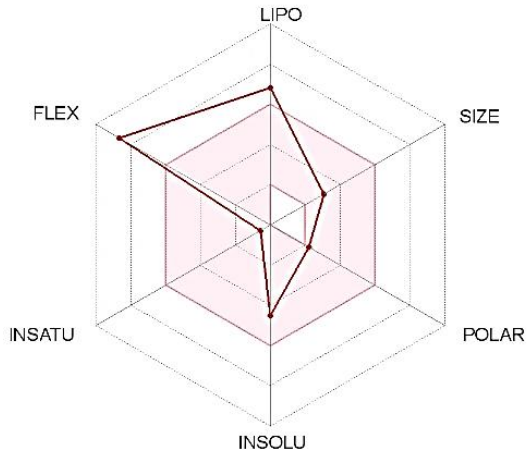
sitosterol, Lupeol, β-amyrin, α-amyrin, Uscharin, Calotropin, Indomethacin and Ibuprofen while 1 violation for Quercetin-3-rutinoside. The Brenk structural alert as 0 violation for Methyl myristate, Methyl behenate, Uzarigenin, Indomethacin and Ibuprofen while 1 violation for Anthocyanin, β-sitosterol, Quercetin-3-rutinoside, Lupeol, β-amyrin and α-amyrin and 2 violation for Uscharin and Calotropin were obtained. The synthetic accessibility score showed in a following manner as Uscharin (7.58), Calotropin (6.78), Quercetin-3-rutinoside (6.52), β-sitosterol (6.30), α-amyrin (6.17), β-amyrin (6.04), Uzarigenin (5.40), Methyl behenate (3.24), Anthocyanin (2.78), Indomethacin (2.51) and Ibuprofen (1.92) respectively.

Table 4. Medicinal chemistry prediction of phytoligands established in *C. procera* compared to synthetic ligands

Sl. No.	Ligands	Lead-likeness	PAINS structural alert	Brenk structural alert	Synthetic accessibility score
1.	Methyl myristate	3	0	0	2.31
2.	Methyl behenate	3	0	0	3.24
3.	Anthocyanin	1	0	1	2.78
4.	Uzarigenin	1	0	0	5.40
5.	β-sitosterol	2	0	1	6.30
6.	Quercetin-3-rutinoside	1	1	1	6.52
7.	Lupeol	2	0	1	5.49
8.	β-amyrin	2	0	1	6.04
9.	α-amyrin	2	0	1	6.17
10.	Uscharin	1	0	2	7.58
11.	Calotropin	1	0	2	6.78
12.	Indomethacin	2	0	0	2.51
13.	Ibuprofen	1	0	0	1.92

The bioavailability radar (Fig. 2) for oral bioavailability prediction for two ligands viz. Uzarigenin and Ibuprofen showed with the range of >-0.7 and <+5 for LIPO as XLOGP3 (2.64

and 3.50). The SIZE as molecular weight (gm/mol) was showed 374.51 for Uzarigenin and 206.28 for Ibuprofen. The POLAR as TPSA (Å²) 66.76 and 37.30 for Uzarigenin and Ibuprofen within a range of >20 and <130 Å². The INSOLU Logs (ESOL) values were showed negative value for both ligands (-3.69 and -3.97) as water soluble, the insolubility range of >0 and <6. The INSATU (insaturation) as per Csp3 data range >0.25 and <1.0, 0.87 and 0.46 for Uzarigenin and Ibuprofen. The data for FLEX as per no. of rotatable bonds range >0 and <9, 1 no. for Uzarigenin and 4 nos. for Ibuprofen. Among all compounds, these two compounds were found within the data range and coloured part of radar in which Uzarigenin phytoligand (phytosteroid) of *C. procera* can be suitable as lead molecule like Ibuprofen, which is an established analgesic and anti-inflammatory drug.



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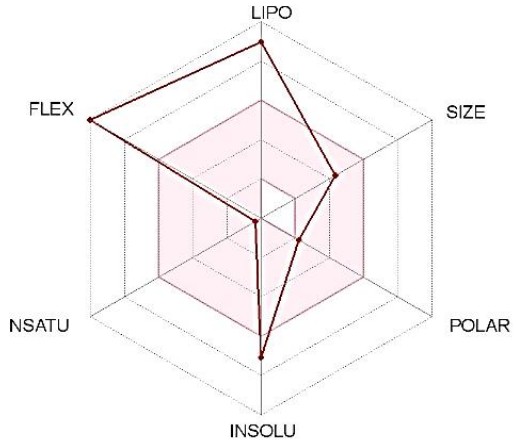

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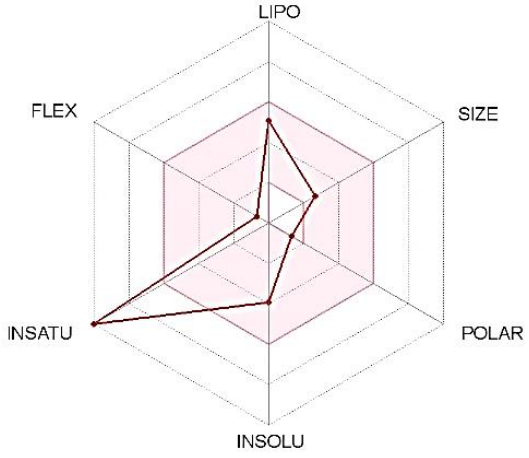

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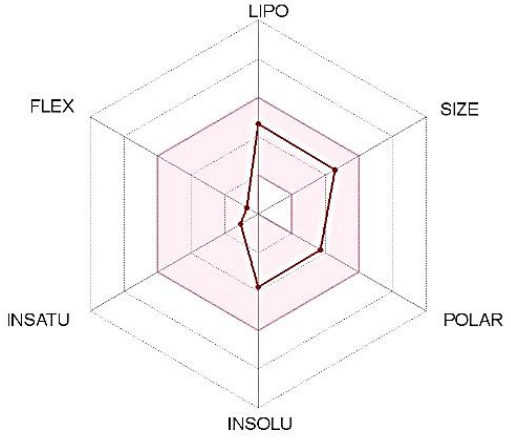

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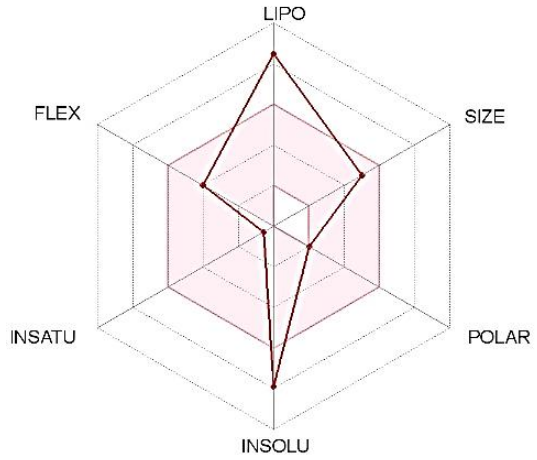
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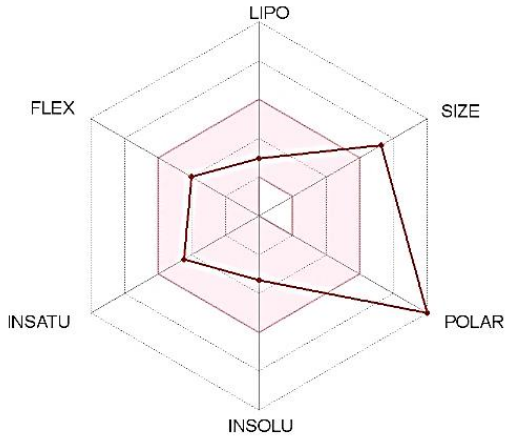
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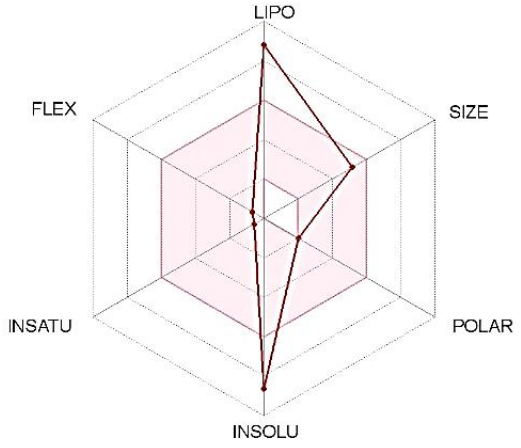
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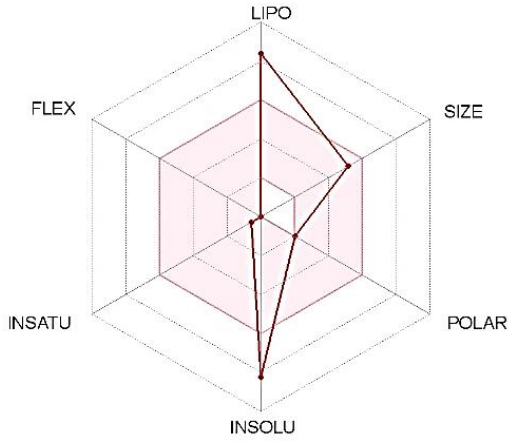
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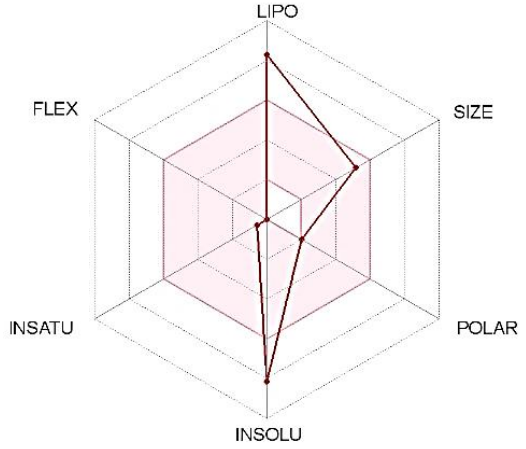
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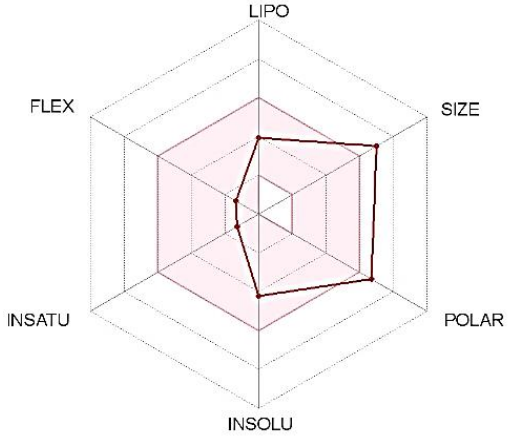
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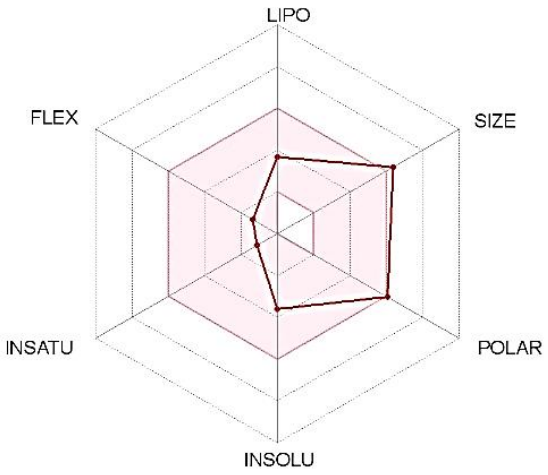

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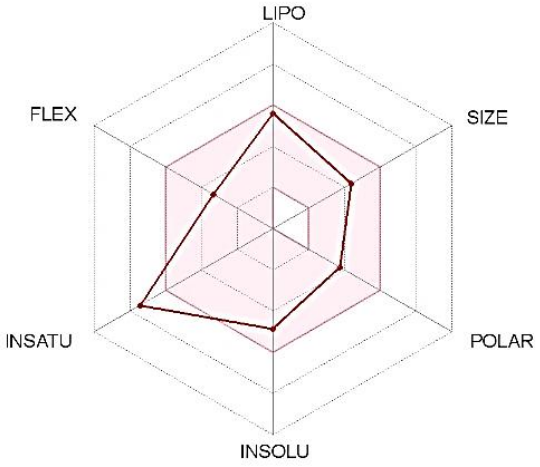

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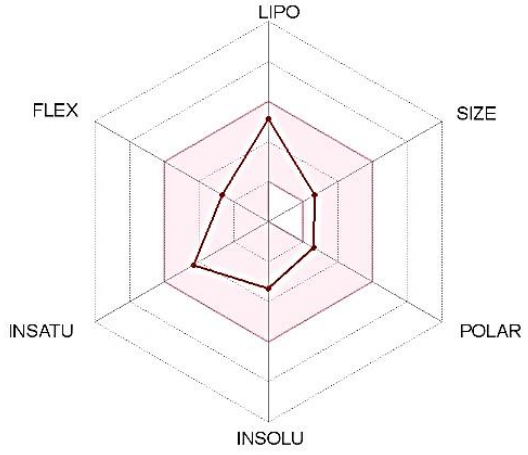

M

Fig. 2. Bioavailability radar (pink area exhibits optimal range of particular property) for studied small molecules [A = Methyl myristate; B = Methyl behenate; C = Anthocyanin; D = Uzarigenin; E = β-sitosterol; F = Quercetin-3-rutinoside; G = Lupeol; H = β-amyrin; I = α-amyrin; J = Uscharin; K = Calotropin; L = Indomethacin and M = Ibuprofen (LIPO = lipophilicity as XLOGP3; SIZE = size as molecular weight; POLAR = polarity as TPSA (topological polar surface area); INSOLU = insolubility in water by log S scale; INSATU = insaturation as per fraction of carbons in the sp3 hybridization and FLEX = flexibility as per rotatable bonds]

The inbuilt BOILED-Egg model represented that Uzarigenin and Ibuprofen showed the capability of GI absorption as well as blood brain barrier penetration. The phytocompound Uzarigenin was found P-gp positive as substrate while Ibuprofen was obtained P-gp negative

as non-substrate in the present predictive model (Fig 3). There is a possibility that Uzarigenin may not hamper glycoprotein activity while Ibuprofen may inhibit glycoprotein activity.

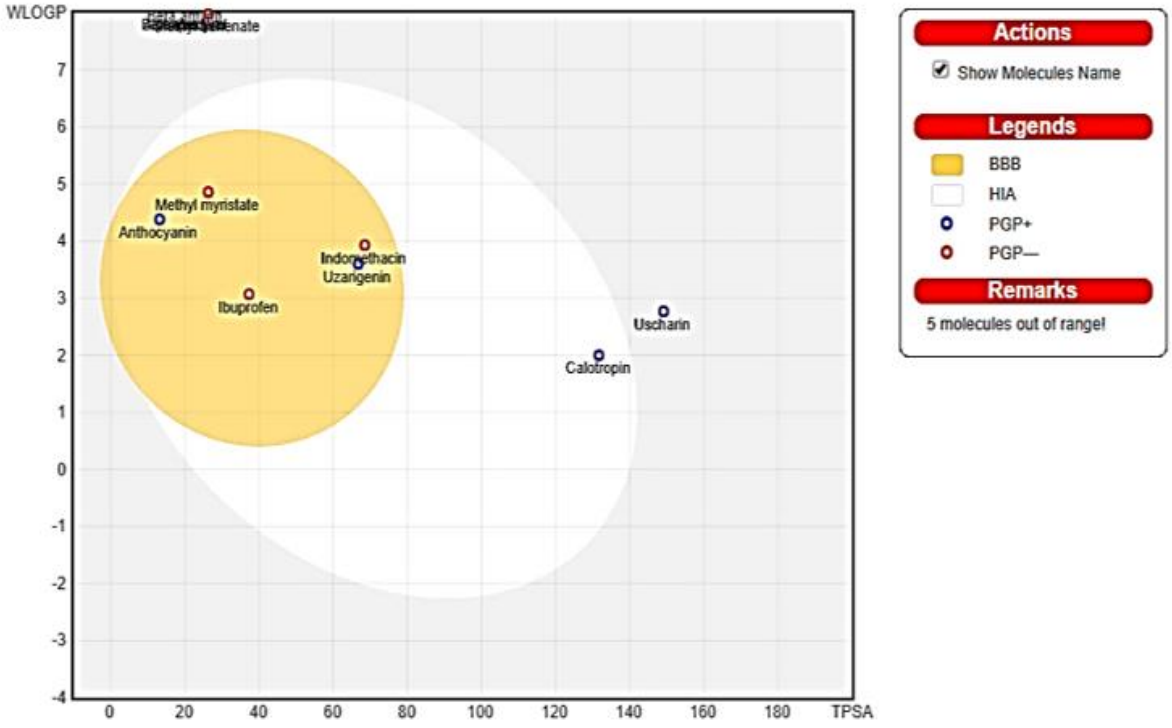

Fig. 3. The BOILED-Egg represents for intuitive evaluation of passive gastrointestinal absorption (HIA) white part and brain penetration (BBB) yellow part as well as blue and red points PGP positive and negative in function of the position of the small molecules in the WLOGP-versus-TPSA graph

The prediction of small molecules may be from natural products or synthetic origin through the computational study of pharmacokinetics, bioavailability, drug-likeness and medicinal chemistry friendliness are the potent research arena for new drug development from natural product by using the SwissADME online tool (Daina et al., 2014; Daina and Zoete, 2016; Daina et al., 2017a; b; Karmakar et al., 2019; Chakravarty et al., 2019). The present predictive study was done on phytocompounds of *C. procera* and compared the same effect as known synthetic drug (Ibuprofen) by using the SwissADME online tool. It was well-known that the physicochemical properties such as solubility and lipophilicity prediction are also detected the small molecule whether progressing a successful drug candidate (Daina et al., 2017a; b). The graphical representation of Brain Or IntestinaL EstimateD permeation method (BOILED-Egg) has already been proposed as an accurate predictive model, which supports the computational prediction of the lipophilicity and polarity of studied small molecules (Daina et al., 2014; Daina and Zoete, 2016; Daina et al., 2017a; b; Karmakar et al., 2019; Chakravarty et al., 2019). Moreover, the crude leaf extract of *C. procera* has been used for the prevention of pain and inflammation in experimental study done by researchers (Saba et al., 2011; Murti et al., 2015; Shukla et al., 2018) but it is unknown about exact phytocompound(s) to prevent pain

and inflammation. The present study is supported by an earlier work that leaf crude extract of *C. gygantea* (other family member) was affecting better as synthetic drug namely Ibuprofen (Bulani et al., 2011) and herein, present prediction revealed Uzarigenin of the leaf may be more suitable like Ibuprofen. The overall predictive results, phytosteroid Uzarigenin of *C. procera* can be suitable drug candidate, which showed resemblance with several parameters of ADME, bioavailability radar and BOILED-Egg representation of Ibuprofen. Furthermore, these predictive results should be validated by *in vitro* and *in vivo* toxicological, pharmacological assay and experimental bioavailability test for this lead compound in relation to the prevention of pain and inflammation.

4. CONCLUSIONS

The prediction of pharmacokinetics, bioavailability, drug-likeness and medicinal chemistry friendliness revealed that the small molecule, Uzarigenin can be a lead compound for new drug candidate for analgesic and anti-inflammatory phytomedicine. However, it is suggested further *in vitro* and *in vivo* assay for toxicology, pharmacology and experimental bioavailability study for pain and inflammation reliving phytocompound to validate the present predictions.

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