In Silico Study of Bioavailability, ADME, Pharmacokinetics, Drug-likeness, Medicinal Chemistry of Selected Phytochemicals of the Fruit (*Musa* sp. Linn.)

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Abstract: *The banana fruit of Musa sp. contains several phytocompounds and it is well known to prevent gastric ulcer. Moreover, the fruit is used raw or cooked and people intake beneficial phytocompounds, which may prevent gastritis. The present predictive study was attempted to know pharmacokinetics of selected phytochemicals present in Musa sp. Compared to synthetic medicine by using online tool (Swiss-ADME). The pharmacological attributes of small molecules were predicted. In this tool, simplified molecular-input line-entry system (SMILES) of each compound was taken from PubChem database and incorporated in the appropriate place followed by clicking run button within the web interface. The prediction of different druggability parameters of selected phytocompounds, Quercetin can be a suitable drug candidate, which may prevent gastric ulcer related to Ranitidine. It is concluded that in silico data indicated flavonoid Quercetin can be a suitable drug candidate after extraction from the fruits of Musa sp. It is suggested that present predictive results should be validated by in vitro and in vivo toxicological and pharmacological assay for the prevention of gastric ulcer.*

Keywords: **In silico, ADME profiling, Gastric ulcer prevention, Phytocompounds, Musa sp.**

1. INTRODUCTION

The fruit is commonly known as banana (*Musa* sp.) belonging to family Musaceae and has high medicinal and nutritive value due to the presence of several phytochemicals estimated by many authors [1-2], as well as for the gastroprotective potential [3]. In earlier study, it was identified that three phytoligands viz. Quercetin, Myricetin and Kaempferol showed favourable binding energy and binding interaction compared to a synthetic medicine namely Ranitidine on matrix metalloproteinases-9 or MMP-9 [4], but the prediction of bioavailability, absorption, distribution, metabolism, and excretion (ADME), pharmacokinetics, drug-likeness is lacking for the effectiveness of new drug to prevent gastric-ulcer.

An *in-silico* evaluation of bioavailability, ADME, pharmacokinetics, drug-likeness along with toxicological pathways are useful to know the pharmacological properties of any organic compound. In recent days, the prediction of above-mentioned profiles for organic compounds is suitable as per faster screening, without laboratory expanse and animal harming [5-10].

Among several predictive tools, Swiss-ADME online tool developed by Daina et al. helps to easily determine several parameters viz. pharmacokinetics, bioavailability, drug-likeness, and medicinal chemistry of small molecules [11,12].

Major studies have been observed that natural products of banana fruit in combination, potential to prevent gastric ulcer and it is a tedious work to extract each phytochemical and perform pharmacological assay. In this context, the specific phytochemicals of earlier studies and previous virtual screening of receptor-ligand binding potential [1,4], the present study was attempted an *in-silico* study of pharmacokinetics to predict the druggable compound(s) by using online tool (Swiss-ADME).

2. MATERIALS AND METHODS

2.1. Selection of phytochemicals

As per earlier study by Sreejith et al. [2], the phytochemicals were selected and also from earlier study on molecular docking [4], three compounds viz. Quercetin, Myricetin, Kaempferol along with other selected phytochemicals such as Glycerol, 5-(hydroxymethyl)-2-Furaldehyde, Diphenyl sulfone, Methyl palmitate, Palmitic acid, 1-Heptatriacotanol, Cycloartanyl acetate, Butyl crotonate, n-Propyl linolenat, Trilinolein and 1 synthetic drug (Ranitidine) were taken for the present predictive study.

2.2. Pharmacokinetics, bioavailability, drug-likeness, and medicinal chemistry prediction of ligands

The predictive study of pharmacokinetics especially ADME, bioavailability, drug-likeness and medicinal chemistry of ligands were done through SwissADME online tool developed by Daina et al [11,12]. The tool predicted to detect drug-likeness compound. Herein, the ADME properties mainly studied as gastrointestinal absorption (GI) and blood-brain barrier (BBB) penetration and substrate or non-substrate of the permeability glycoprotein (PGP) as detected positive or negative in the Brain Or IntestinaL EstimateD permeation method (BOILED-Egg) model within the tool developed by Daina, and Zoete [11] and Daina et al [12]. All the studied inbuilt parameters such as iLOGP, GB/SA, XLOGP3, WLOGP, MLOGP, SILICOS-IT, Lipinski rule, etc. were studied and developed by researchers in this tool [12-19].

3. RESULT

The results on predictive values for pharmacokinetics, bioavailability, drug-likeness, and medicinal chemistry data on studied small molecules were obtained (Table 1-4). For pharmacokinetics prediction, the GI absorption rate was obtained higher for Glycerol, 5-(hydroxymethyl)-2-Furaldehyde, Diphenyl sulfone, Methyl palmitate, Palmitic acid, Butyl crotonate, n-Propyl linolenat, Quercetin and Kaempferol and Ranitidine and lower for 1-Heptatriacotanol, Cycloartanyl acetate, Trilinolein and Myricetin. The blood-brain permeability did not obtain for studied compounds except five phytocompounds. In case of skin permeation (log Kp, cm/s), higher negative value was obtained for Glycerol (-8.11) and Ranitidine (-8.03) followed by 5-(hydroxymethyl)-2-Furaldehyde (-7.48), Myricetin (-7.40), Quercetin (-7.05) and Kaempferol (-6.70). All phytoligands did not show p-glycoprotein substrate activity except 1-Heptatriacotanol, Trilinolein and Ranitidine. To detect inhibitory activity for cytochrome p450 as CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 inhibitors, Ranitidine did not show inhibition for all of these CYP while few phytoligands showed inhibition for CYP1A2, CYP2C9, CYP2D6, and CYP4503A4 (Table 1).

Table 1. Prediction of pharmacokinetics of phyto and synthetic ligands

Sl. No.	Ligands	GI absorption	BB permeant	PGP substrate	CYP450 1A2 inhibitor	CYP450 2C19 inhibitor	CYP450 2C9 inhibitor	CYP450 2D6 inhibitor	CYP450 3A4 inhibitor	Skin permeation as log Kp (cm/s)
1.	Glycerol	High	No	No	No	No	No	No	No	-8.11
2.	5-(hydroxymethyl)-2-Furaldehyde	High	No	No	No	No	No	No	No	-7.48
3.	Diphenyl sulfone	High	Yes	No	No	No	No	No	No	-5.93
4.	Methyl palmitate	High	Yes	No	Yes	No	No	No	No	-2.71
5.	Palmitic acid	High	Yes	No	Yes	No	Yes	No	No	-2.77
6.	1-Heptatriacotanol	Low	No	Yes	No	No	No	No	No	3.55
7.	Cycloartanyl acetate	Low	No	No	No	No	No	No	No	-1.50
8.	Butyl crotonate	High	Yes	No	Yes	No	No	No	No	-6.16
9.	n-Propyl linolenat	High	Yes	No	Yes	No	No	No	No	-6.16
10.	Trilinolein	Low	No	Yes	No	No	No	No	No	2.78
11.	Quercetin	High	No	No	Yes	No	No	Yes	Yes	-7.05
12.	Myricetin	Low	No	No	Yes	No	No	No	Yes	-7.40
13.	Kaempferol	High	No	No	Yes	No	No	Yes	Yes	-6.70
14.	Ranitidine	High	No	Yes	No	No	No	No	No	-8.03

GI = Gastro-intestinal; BB = Blood-brain; PGP = p-Glycoprotein

In case of bioavailability prediction, the parameters such as iLOGP, XLOGP3, WLOGP, MLOGP and SILCOS-ST data were obtained higher for Trilinolein and 1-Heptatriacotanol, but bioavailability score was found lower (Table 2).

Table 2. Prediction of pharmacokinetics of phyto and synthetic ligands

Sl. No.	Ligands	Bioavailability score	Water solubility as log S & SILICOS-IT	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT
1.	Glycerol	0.55	0.83	0.45	-1.76	-1.67	-1.51	-0.96
2.	5-(hydroxymethyl)-2-Furaldehyde	0.55	-0.54	0.91	-0.58	0.43	-1.06	1.24
3.	Diphenyl sulfone	0.55	-3.17	2.01	2.40	3.60	3.07	2.32
4.	Methyl palmitate	0.55	-5.18	4.41	7.38	5.64	4.44	5.84
5.	Palmitic acid	0.85	-5.02	3.85	7.17	5.55	4.19	5.25
6.	1-Heptatriacotanol	0.17	-12.51	9.27	18.49	13.65	8.75	14.94
7.	Cycloartanyl acetate	0.55	-9.10	5.67	10.80	8.82	7.19	8.21
8.	Butyl crotonate	0.55	-2.56	2.82	2.25	1.98	1.21	2.91
9.	n-Propyl linolenat	0.55	-2.56	2.82	2.25	6.53	1.21	2.91
10.	Trilinolein	0.17	-14.81	12.82	20.34	17.43	9.25	20.55
11.	Quercetin	0.55	-3.16	1.63	1.54	1.99	-0.56	1.54
12.	Myricetin	0.55	-3.01	1.08	1.18	1.69	-1.08	1.06
13.	Kaempferol	0.55	-3.31	1.70	1.90	2.28	-0.03	2.03
14.	Ranitidine	0.55	-1.48	2.82	0.27	1.00	-0.60	-0.46

For drug-likeness prediction, Glycerol, 5-(hydroxymethyl)-2-Furaldehyde, Quercetin, Kaempferol and Ranitidine obtained suitable for Lipinski rule and Ghose filter in which all compounds obtained 0 violation except Methyl palmitate, Palmitic acid, 1-Heptatriacotanol, Trilinolein and Myricetin for Lipinski rule while for Veber filter, Egan filter and Muegge filter, all compounds obtained suitable except these phytoligands (Table 3).

Table 3. Prediction of drug-likeness of phyto and synthetic ligands

Sl. No.	Ligands	Lipinski rule	Ghose filter	Veber filter	Egan filter	Muegge filter
1.	Glycerol	Yes; 0 violation	No; 4 violations	Yes; 0 violation	Yes; 0 violation	No; 2 violations
2.	5-(hydroxymethyl)-2-Furaldehyde	Yes; 0 violation	No; 3 violations	0 violation	0 violation	1 violation
3.	Diphenyl sulfone	0 violation	0 violation	0 violation	0 violation	0 violation
4.	Methyl palmitate	1 violation	1 violation	1 violation	0 violation	1 violation
5.	Palmitic acid	1 violation	0 violation	1 violation	0 violation	1 violation
6.	1-Heptatriacotanol	2 violations	4 violations	1 violation	1 violation	3 violations
7.	Cycloartanyl acetate	1 violation	3 violations	0 violation	1 violation	1 violation
8.	Butyl crotonate	0 violation	0 violation	0 violation	0 violation	0 violation
9.	n-Propyl linolenat	0 violation	0 violation	0 violation	0 violation	0 violation
10.	Trilinolein	2 violations	4 violations	1 violation	1 violation	3 violations
11.	Quercetin	Yes; 0 violation	Yes	Yes violation	Yes	Yes
12.	Myricetin	Yes; 1 violation	Yes	No; 1 violation	No; 1 violation	No; 2 violations
13.	Kaempferol	Yes; 0 violation	Yes	Yes	Yes	Yes
14.	Ranitidine	Yes; 0 violation	Yes	Yes	Yes	Yes

In case of medicinal chemistry friendliness prediction, three phytoligands obtained lead-likeness but not synthetic ligand as 1 violation. For Pan assay interface structure and Brenk structural alert four compounds viz. 1H-Pyrrole-2,4-dicarboxylic acid, 3,5-dimethyl-, diethyl ester, n-Propyl 9,12,15-octadecatrienoate or n-Propyl linolenat, Quercetin and Myricetin showed 1 alert, and 2 alert observed for Trilinolein while rest compounds did not show any alert. The synthetic accessibility score obtained higher Ranitidine (3.58) followed by Myricetin (3.27), Quercetin (3.23) and Kaempferol (3.14), respectively and rest compounds were observed lower value (Table 4).

Table 4. Prediction of medicinal chemistry of phyto and synthetic ligands

Sl. No.	Ligands	Lead-likeness	Pan assay interface structure	Brenk structural alert	Synthetic accessibility score
1.	Glycerol	1	0 alert	0 alert	1.31
2.	5-(hydroxymethyl)-2-Furaldehyde	1	0 alert	1 alert	2.25
3.	Diphenyl sulfone	1	0 alert	0 alert	1.90
4.	Methyl palmitate	2	0 alert	0 alert	2.53
5.	n-Hexadecanoic acid or Palmitic acid	2	0 alert	0 alert	2.31
6.	1-Heptatriacotanol	3	0 alert	0 alert	4.87
7.	9,19-Cyclolanostan-3-ol, acetate, (3.beta.)	2	0 alert	0 alert	6.39
8.	Butyl crotonate	1	0 alert	1 alert	2.59
9.	n-Propyl linolenat	1	0 alert	1 alert	2.59
10.	Trilinolein	3	0 alert	2 alert	8.46
11.	Quercetin	Yes	1 alert: catechol_A	1 alert: catechol	3.23
12.	Myricetin	Yes	1 alert: catechol_A	1 alert: catechol	3.27
13.	Kaempferol	Yes	0 alert	0 alert	3.14
14.	Ranitidine	No; 1 violation	0 alert	1 alert: oxygen-nitrogen_single bond	3.58

The inbuilt BOILED-Egg model represented Quercetin, Kaempferol and Ranitidine showed the capability of GI absorption and two phytocompounds were observed within a range of

Ranitidine. All phytoligands were found PGP negative as non-substrate while Ranitidine showed PGP positive as substrate in the present predictive model (Figure 1).

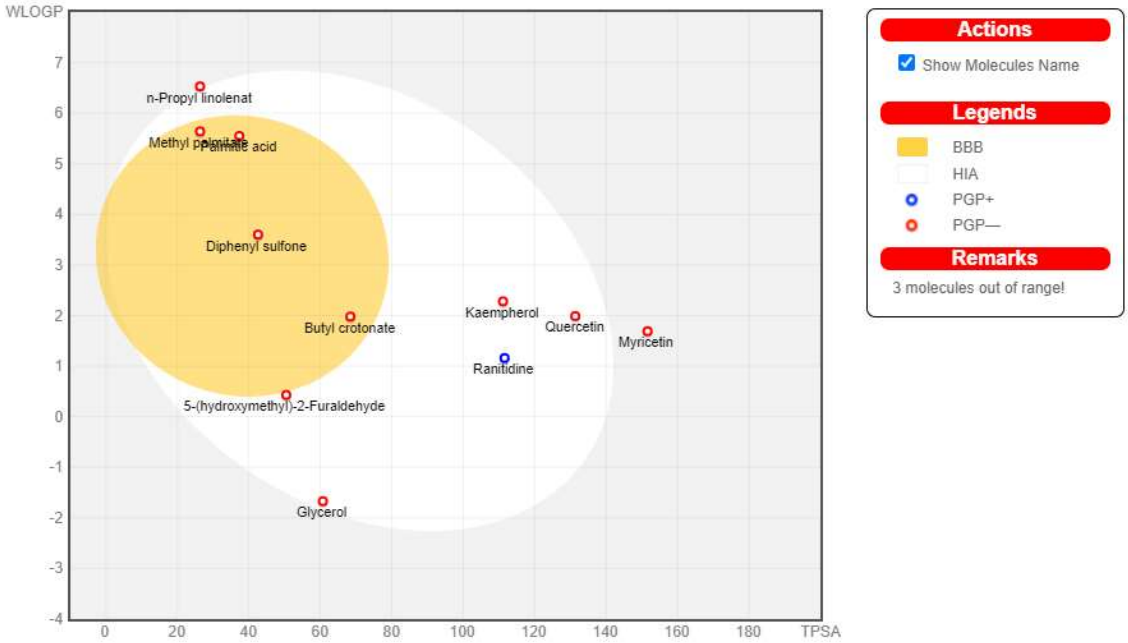

Figure 1. The BOILED-Egg representation for intuitive evaluation of passive gastrointestinal absorption (HIA) white part and brain penetration (BBB) yellow part as well as blue and red points PGP positive and negative in function of the position of the small molecules in the WLOGP-versus-TPSA graph

4. DISCUSSION

As per earlier virtual screening by Roy Choudhury and Talapatra [4], it was obtained Quercetin had favourable binding energy (-8.2 Kcal/mol) followed by Kaempferol (-8.0 Kcal/mol) compared to Ranitidine (-5.6 Kcal/mol) on MMP-9 as suitable lead small molecules of *Musa* sp. for gastric ulcer prevention, which had similar finding [3]. In the present study, it was attempted to predict ADME profiles in relation to pharmacokinetics, bioavailability, drug-likeness, and medicinal chemistry of these selected phytocompounds compared to well-established synthetic medicine namely Ranitidine. An *in-silico* approach through SwissADME online tool is supported by several researchers [5-10], because this toll helps faster screening, no costing involved and animal harming. The BOILED-Egg representation has already been evaluated for the accuracy of predictive model, which determines by *in silico* approach for the prediction of lipophilicity and polarity of small molecules [11,12].

5. CONCLUSION

It is concluded from *in silico* study, the predictive data obtained flavonoid Quercetin can be a suitable drug candidate after isolation from the fruits of *Musa* sp. Based on BOILED-Egg representation and different druggability parameters studied through SwissADME online tool. In future, it is suggested the experimental assay with dose dependent manner because higher dose (40,000ppm) of Quercetin was obtained potentially carcinogenic [20]. Moreover, present *in silico* data should be validated by *in vitro* and *in vivo* toxicological and pharmacological assay for the prevention of gastric ulcer.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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