In Silico study of Pharmacokinetic and Target Prediction of Chemical Composition from Kaedhatuphikar Recipe

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Abstract

Since King Rama V of Siam reign, Thai traditional cannabis medicine has been used to treat several diseases such as relief of pain, sleep problems, and loss of appetite, in particular, Kaedhatuphikar recipe was used for longevity. In this study, the chemical composition of Kaedhatuphikar recipe was analyzed by GCMS technique. Also, the pharmacokinetic and target prediction were studied. The result showed the 34 identified compounds which is piperine (20.49%) as a major compound. The 11 compounds (>1% peak area) demonstrated good pharmacokinetic properties and target prediction demonstrated the cannabinoid receptor as a major target. In conclusion, the Kaedhatuphikar recipe showed the possibility of treating diseases that are relevant to cannabinoid receptors. Therefore, Kaedhatuphikar recipe can be developed for pharmaceutical products.

Keywords: Pharmacokinetic, Target prediction, Kaedhatuphikar recipe, GCMS, Chemical composition

1. Introduction

In traditional medicine and ethnomedicine, medicinal plants have long been recognized as the basis for materials in therapeutic applications worldwide (Zhang & Wang, 2023). Various parts of medicinal plants such as seeds, leaves, flowers, fruits, stems, and roots are rich sources of bioactive compounds (Sun & Shahrajabian, 2023). The bioactive compounds in medicinal plants contain hydrocarbons, organic acids, polysaccharides, starch, protein, fatty and fatty acids, essential oils, alkaloids, tannins, saponins, glycosides, bitter substances, phytoncides, trace elements, vitamins, mineral salts and others (Tuyg'unovna, 2023).

There are many medicinal plants used to treat several diseases in Thailand. The mixture of several medicinal plants used to make the formulation in Thai Traditional Medicine (TTM), which can be divided into Royal TTM and Folk Medicine (FM) (Chotchoungchatchai et al., 2012). *Cannabis sativa* is herbaceous plant belonging to the Cannabaceae family. *C. sativa* have been reported the many biological activity such as antioxidant, anti-inflammatory, antidiabetic,

antiepileptic and anticancer activities (Hourfaneet al., 2023). Moreover, cannabis has been used as one of the ingredients in TTM since King Rama V of Siam reign, it has more than 90 recipes of Thai medicine containing cannabis (Laohavanich, 2022). In the literature review, the Kae Mussakaya Thatu Atisan recipe was used to treat diarrhea, these showed a high content of several compounds such as phenolics, flavonoids and cannabinoids contents (Chimpalee et al., 2024). In addition, the Inthajaworn, Mahawattana, and Kaedhatuphikar recipe were a Thai traditional cannabis medicine for longevity. These recipes showed good antioxidant activity (Sripan et al., 2022). However, there are less reported of *in silico* studies of chemical composition in TTM.

In silico study is scientific discoveries that are made using computer simulation instead of biological studies (Beyleveld et al., 2013). The Pharmacokinetics study was used to how pharmaceuticals are handled in the body, consists of four stages which are absorption, distribution, metabolism, and excretion (ADME). It plays a very important role in drug research and development because any drug candidate must be checked for pharmacokinetics and toxicity (ADMET) properties to ensure efficacy and safety (Tran et al., 2023). Target prediction is a crucial step in drug discovery and the study of disease mechanisms (Shaikh et al., 2021). The experimental methods that identify these relationships based on clinical remedies are time-taking, costly, laborious, and complex introducing a lot of challenges. The development of new computational methods which are more accurate can be preferable to experimental methods, in terms of total cost and time (Abbasi Mesrabadi et al., 2023).

1.1 Research Objective

This research aimed to analyze the chemical composition by GCMS technique of Kaedhatuphikar recipe. In addition, the pharmacokinetics and target of action were predicted.

2. Material and methods

2.1 Sample preparation

The composition of Kaedhatuphikar recipe was described in National Thai traditional remedies with cannabis in 2021. The medicinal plants were purchased from Healthy Hills Farm Company Limited, Bangkok, Thailand. The cannabis leaves were provided from Taratera Corporation Company Limited, Bangkok, Thailand. The Kaedhatuphikar recipe consists of *Piper sarmentosum* root 1.86 g, *Piper longum* fruit 35.70 g *Iresine herbstii* leaves 9.60 *Piper nigrum* fruit 1.80 g and *Cannabis sativa* leaves 1.80 g. Kaedhatuphikar recipe 20 g was extracted with 95% ethanol 100 ml. After that, the extract was filtrated. Then, ethanol was removed by a rotary evaporator to obtain Kaedhatuphikar crude ethanol extract 7.05% (Sripan et al., 2022).

2.2 GCMS analysis

GCMS analysis of extract was performed by using a SHIMADZU QP-2010 instrument (Kyoto, Japan). The sample was injected in a volume of 1 µL into Agilent J&W DB-5MS column (30 m×0.25 mm, 0.25 µm, Santa Clara, CA, USA) with a flow rate was 1 mL/min and helium 5.5 was a carrier gas. The split ratio was set to 1:20. The oven temperature program was set as follows: starting temperature 70°C (hold time 2 min), with gradual increases in temperature from 70 to 200°C (5.0°C /min, hold 10 min), from 200 to 230°C (5.0°C/min, hold 10 min), from 230 to 250°C (5.0°C/min, hold 5 min), from 250 to 320°C (5.0°C/min, hold 20

min). The peaks were analyzed based on GC retention time and mass spectral identity was by comparison to the NIST17.LIB library (Palmieri, et al., 2021).

2.3 Pharmacokinetic prediction

The pharmacokinetic prediction was used Swiss ADME software to estimate the individual ADME behaviors of the chemical composition of the Kaedhatuphikar recipe (Kamble & Mitkar, 2023).

2.4 Target Prediction

The target prediction of the chemical composition of the Kaedhatuphikar recipe was used target prediction tools that are available as web server, namely Swiss target prediction software (Mayr et al, 2020).

3. Results and Discussion

3.1 GCMS analysis

The chemical composition from Kaedhatuphikar recipe was analyzed by GCMS technique. The GCMS chromatogram showed in Figure 1. The 34 compounds were identified in Table 1. The results showed the 11 compounds that high percentage of peak area than 1% which are piperine (20.49%), (2E,4E,14E)-N-isobutylicosa-2,4,14-trienamide (9.47%), (2E,4E,10E)-N-isobutylhexadeca-2,4,10-trienamide (7.75%), pipericine (6.95%), (2E,4E,14E)-1-(piperidin-1-yl)icosa-2,4,14-trien-1-one (3.75%), piperanine (3.69%), (2E,4E)-N-isobutylicosa-2,4-dienamide (3.37%), piperlonguminine (3.25%), (2E,4E,12E)-1-(piperidin-1-yl)octadeca-2,4,12-trien-1-one (1.97%), (2E,4E)-N-isobutylhexadeca-2,4-dienamide (1.48%) and tetrahydrocannabinol (1.46%), respectively.

Figure 1: GCMS chromatogram of Kaedhatuphikar recipe

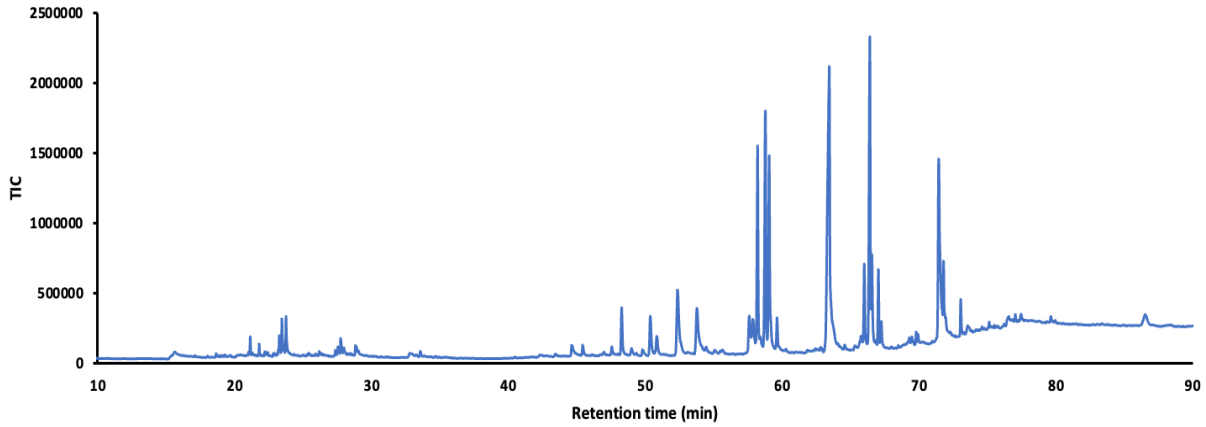

Table 1: Chemical composition of Kaedhatuphikar recipe by GCMS

No.	Retention time (min)	Formula	MW	KI	% Peak area	Compound name
1	21.15	$C_{15}H_{24}O$	220	1507	0.27	Caryophyllene oxide
2	21.80	$C_{15}H_{24}O$	220	1592	0.15	Humulene epoxide II
3	22.22	$C_{15}H_{24}O$	220	1569	0.07	Isospathulenol
4	23.20	$C_{15}H_{24}O$	220	1699	0.08	ent-Germacra-4(15),5,10(14)-trien-1β-ol
5	23.27	$C_{16}H_{34}O$	242	1854	0.42	1-Hexadecanol
6	23.46	$C_{21}H_{42}$	294	2099	0.82	Henicos-1-ene
7	23.76	$C_{21}H_{44}$	296	2109	0.85	Heneicosane
8	27.37	$C_{15}H_{26}O_2$	238	1813	0.09	Platambin
9	28.84	$C_{14}H_{25}NO$	223	1765	0.40	Pellitorin
10	44.65	$C_{16}H_{21}NO_3$	275	2277	0.36	Dihydropiperlonguminine
11	45.44	$C_{21}H_{30}O_2$	314	2486	0.28	Cannabichromene
12	48.29	$C_{21}H_{30}O_2$	314	2475	1.46	Tetrahydrocannabinol
13	50.37	$C_{20}H_{37}NO$	307	2361	1.48	(2E,4E)-N-Isobutylhexadeca-2,4-dienamide
14	50.86	$C_{21}H_{26}O_2$	310	2582	0.66	Cannabinol
15	52.36	$C_{17}H_{21}NO_3$	287	2391	3.69	Piperanine
16	53.78	$C_{16}H_{19}NO_3$	273	2285	3.25	Piperlonguminine
17	58.43	$C_{21}H_{35}NO$	317	2484	0.73	(2E,4E,10E)-1-(Piperidin-1-yl)hexadeca-2,4,10-trien-1-one
18	58.78	$C_{20}H_{35}NO$	305	2369	7.75	(2E,4E,10E)-N-Isobutylhexadeca-2,4,10-trienamide
19	59.07	$C_{22}H_{41}NO$	335	2560	6.95	Pipericine
20	63.46	$C_{17}H_{19}NO_3$	285	2399	20.49	Piperine
21	66.42	$C_{24}H_{43}NO$	361	2767	9.47	(2E,4E,14E)-N-Isobutylicosa-2,4,14-trienamide
22	66.57	$C_{24}H_{45}NO$	363	2759	3.37	(2E,4E)-N-isobutylicosa-2,4-dienamide
23	67.05	$C_{23}H_{39}NO$	345	2682	1.97	(2E,4E,12E)-1-(Piperidin-1-yl)octadeca-2,4,12-trien-1-one
24	67.26	$C_{23}H_{41}NO$	347	2674	0.88	(2E,4E)-1-(Piperidin-1-yl)octadeca-2,4-dien-1-one

No.	Retention time (min)	Formula	MW	KI	% Peak area	Compound name
25	69.31	$C_{17}H_{32}O$	252	1907	0.37	14-Methyl-8-hexadecen-1-ol
26	69.95	$C_{21}H_{29}NO_3$	343	2789	0.50	(E)-9-(Benzo[d][1,3]dioxol-5-yl)-1-(piperidin-1-yl)non-8-en-1-one
27	71.81	$C_{25}H_{43}NO$	373	2881	3.75	(2E,4E,14E)-1-(Piperidin-1-yl)icosa-2,4,14-trien-1-one
28	73.07	$C_{29}H_{50}O$	414	2731	0.88	γ-Sitosterol
29	73.59	$C_{21}H_{25}NO_3$	339	2805	0.73	(2E,4E,8E)-9-(Benzo[d][1,3]dioxol-5-yl)-1-(piperidin-1-yl)nona-2,4,8-trien-1-one
30	76.58	$C_{24}H_{33}NO_3$	383	3088	0.70	(2E,4E,12E)-13-(Benzo[d][1,3]dioxol-5-yl)-N-isobutyltrideca-2,4,12-trienamide
31	76.85	$C_{38}H_{74}O_2$	562	3759	0.21	Phytyl stearate
32	77.07	$C_{36}H_{72}O_2$	536	3767	0.28	Hexadecanoicacid,eicosylester
33	77.48	$C_{29}H_{48}O_2$	428	2875	0.40	Stigmastane-3,6-dione, (5α)-
34	79.65	$C_{19}H_{34}O_2$	294	2241	0.20	E,E,Z-1,3,12-Nonadecatriene-5,14-diol

Note: MW as molecular weight and KI as Kovats index.

3.2 Pharmacokinetic prediction

The pharmacokinetic prediction of 11 compounds with a peak area greater than 1% was analyzed. The results showed the physicochemical properties in Table 2. The 11 compounds predicted the 4 parameters: absorption, distribution, metabolism, and excretion (ADME). The physicochemical properties showed a molecular weight of 273.33-373.62 g/mol which passes the criteria (<500 g/mol). The criteria were described by Sungthong et al., 2022. TPSA, HBA and HBD of 11 compounds showed lower than the criteria. While, tetrahydrocannabinol, piperanine, piperlonguminine and piperine showed NORTB value less than 10. The piperanine, piperlonguminine and piperine showed Lipinski violations value less than 0. Lipinski's rule is a rule to evaluate whether a compound has physicochemical properties that would make it likely to be an orally active drug in humans (Sungthong et al., 2022).

The 11 compounds predicted the 4 parameters: Absorption, Distribution, Metabolism, and Excretion (ADME) and a result of pharmacokinetic properties shown in Table 3. The percentage oral absorption (%ABS) showed a value of 92.59-101.99% which is a good absorption and oral bioavailability. The blood-brain barrier membrane permeability (BBB) was used to characterize the distribution of compounds which showed 6 compounds (such as tetrahydrocannabinol, (2E,4E)-N-isobutylhexadeca-2,4-dienamide, piperine, piperanine, piperlonguminine and (2E,4E,10E)-N-Isobutylhexadeca-2,4,10-trienamide) passed the BBB permeant criteria. Cytochrome P450s was an important enzyme system for drug metabolism in the liver. The 11 compounds were predicted to be different Cytochrome P450s inhibitors. This suggested that 11 compounds may be metabolized in the liver by different Cytochrome P450s. Moreover, only (2E,4E,14E)-1-(piperidin-1-yl)icosa-2,4,14-trien-1-one are substrates of P-glycoprotein that may be actively exuded from cells by P-glycoprotein. Therefore, 11 compounds showed a better pharmacokinetic than Trolox, a positive control.

3.3 Target Prediction

The target prediction of 11 compounds were predicted by Swiss target prediction software showed in Table 4. The result showed that the cannabinoid receptor 16 targets as a major target followed by Mu opioid receptor 7 targets, Delta opioid receptor 7 targets, Peroxisome proliferator-activated receptor gamma 3 targets, Monoamine oxidase B 3 targets, Peroxisome proliferator-activated receptor delta 2 targets, Sigma opioid receptor 2 targets and Acetyl-CoA carboxylase two 2 targets.

The major target as cannabinoid receptor is indicated in many disorders that impact the CNS including several neurodegenerative disorders such as Huntington's disease, multiple sclerosis and Alzheimer's disease (Kendall & Yudowski, 2017). The mu opioid (mu) receptor is a G protein-coupled receptor (GPCR) that neuromodulates several physiological functions, in particular, nociception (Ugur et al., 2018) and Delta opioid receptor as a target for the treatment of pain disease (Quirion et al., 2020). Moreover, the other target demonstrated for the treatment of several diseases in Table 4.

Table 2: Physicochemical properties of 11 compounds from Kaedhatuphikar recipe by GCMS

Compounds	Parameters							
	MW[a]	cLogP[b]	cLogS[c]	TPSA[d]	NORTB[e]	HBA[f]	HBD[g]	Lipinski violations[h]
Criteria	<500	-	-	≤140	≤10	≤5	≤10	≤0
Tetrahydrocannabinol	314.46	5.33	-7.40	29.46	4	2	1	1
(2E,4E)-N-Isobutylhexadeca-2,4-dienamide	307.51	5.83	-8.09	29.10	15	1	1	1
Piperanine	287.35	3.10	-3.90	38.77	5	3	0	0
Piperlonguminine	273.33	3.17	-5.03	47.56	6	3	1	0
(2E,4E,10E)-N-Isobutylhexadeca-2,4,10-trienamide	305.50	5.56	-7.13	29.10	14	1	1	1
Pipericine	335.57	6.56	-9.22	29.10	17	1	1	1
Piperine	285.34	3.03	-3.96	38.77	4	3	0	0
(2E,4E,14E)-N-Isobutylicosa-2,4,14-trienamide	361.60	7.00	-9.38	29.10	18	1	1	1
(2E,4E)-N-isobutylicosa-2,4-dienamide	363.62	7.27	-10.34	29.10	19	1	1	1
(2E,4E,12E)-1-(Piperidin-1-yl)octadeca-2,4,12-trien-1-one	345.56	6.15	-7.75	20.31	14	1	0	1
(2E,4E,14E)-1-(Piperidin-1-yl)icosa-2,4,14-trien-1-one	373.62	6.87	-8.88	20.31	16	1	0	1
Trolox (positive control)	250.29	2.47	-3.9	66.76	1	4	2	0

Note: [a]MW as molecular weight, [b]cLogP as calculated octanol/water partition coefficient, [c]cLogS as solubility parameter, [d]TPSA as topological polar surface area, [e]NORTB as Number of freely rotatable bonds, [f]HBA as Number of hydrogen bond acceptors, [g]HBD as Number of hydrogen bond donors and [h]Lipinski's violation: 0 violation is good.

Table 3: Pharmacokinetics properties of 11 compounds from Kaedhatuphikar recipe by GCMS

Compounds	Absorption	Distribution	Metabolism					Excretion
	%ABS	BBB permeant	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Pgp substrate
Tetrahydrocannabinol	98.84	Yes	No	Yes	Yes	Yes	No	No
(2E,4E)-N-Isobutylhexadeca-2,4-dienamide	98.96	Yes	Yes	No	Yes	No	No	No
Piperanine	95.62	Yes	Yes	Yes	No	Yes	No	No
Piperlonguminine	92.59	Yes	Yes	Yes	Yes	No	No	No
(2E,4E,10E)-N-Isobutylhexadeca-2,4,10-trienamide	98.96	Yes	Yes	No	Yes	No	Yes	No
Pipericine	98.96	No	Yes	No	No	No	No	No
Piperine	95.62	Yes	Yes	Yes	Yes	No	No	No
(2E,4E,14E)-N-Isobutylicosa-2,4,14-trienamide	98.96	No	Yes	No	No	No	No	No
(2E,4E)-N-isobutylicosa-2,4-dienamide	98.96	No	Yes	No	No	No	No	No
(2E,4E,12E)-1-(Piperidin-1-yl)octadeca-2,4,12-trien-1-one	101.99	No	Yes	No	No	No	No	No

Compounds	Absorption	Distribution	Metabolism					Excretion
	%ABS	BBB permeant	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Pgp substrate
(2E,4E,14E)-1-(Piperidin-1-yl)icosa-2,4,14-trien-1-one	101.99	No	Yes	Yes	No	No	No	No
Trolox (positive control)	85.97	Yes	No	No	No	No	No	No

Table 4: Top 4 ranking targets identified based on degree of interactions

Ranking	Name of target	Degree of interaction	Target class	Target of disease	References
1	Cannabinoid receptor 1	8	Family A G protein-coupled receptor	- Huntington's disease - Alzheimer's disease	Kendall & Yudowski, 2017
	Cannabinoid receptor 2	8	Family A G protein-coupled receptor	- Neuropathic pain - Neurodegenerative conditions - Alzheimer's disease	Bie et al., 2018
2	Mu opioid receptor	7	Family A G protein-coupled receptor	- Nociception	Ugur et al., 2018
	Delta opioid receptor	7	Family A G protein-coupled receptor	- Pain disease	Quirion et al., 2020
3	Peroxisome proliferator-activated receptor gamma	3	Nuclear receptor	- Metabolic disease - kidney diseases	Willson et al., 2001; Sharma & Patial, 2022
	Monoamine oxidase B	3	Oxidoreductase	- Parkinson's disease	Tan et al., 2022
4	Peroxisome proliferator-activated receptor delta	2	Nuclear receptor	- Cardiovascular disease	Ehrenborg & Skogsberg, 2013
	Sigma opioid receptor	2	Membrane receptor	- Neuropathic pain	Pergolizzi & Varrassi, 2023
	Acetyl-CoA carboxylase 2	2	Ligase	- Cancer disease - Diabetes disease - Obesity disease - Liver disease	Wang et al., 2022; Mateo-Marín & Alves-Bezerra, 2024
Total		42			

4. Conclusion

The chemical composition of Kaedhatuphikar recipe showed 34 identified compounds which is piperine (20.49%) as a major compound. There are 11 compounds that have a higher peak area than 1%. The 11 compounds demonstrated good pharmacokinetic properties which is better than Trolox, as a positive control. Moreover, the target prediction of 11 compounds predicted the cannabinoid receptor as a major target. Therefore, the Kaedhatuphikar recipe has the potential to develop medicine for treating several diseases.

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