ADMET predictions of pharmacokinetics properties from chemical composition in Plai (*Zingiber cassumunar Roxb*) oil

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Abstract

Zingiber cassumunar Roxb. (Plai) is a medicinal plant in Thailand, the traditionally used to treat inflammation, pain, and respiratory problems. The Plai oil is a Thai traditional medicine for muscle relaxation. In this study, Plai oil was analyzed the chemical composition by GCMS technique and pharmacokinetics were predicted. The result showed that the 6 identified compounds which are menthol 42.71% followed by (+)-2-bornanone21.44%, endo-borneol 17.9%, isoborneol 8.3%, caryophyllene 0.99% and grandlure IV 0.48%, respectively. The pharmacokinetics predictions demonstrated a good physicochemical and pharmacokinetics properties than diclofenac, as a positive control. From the result, it was concluded that Plai oil has the potential to treat inflammation, pain and muscle relaxation based on ADMET prediction data.

Keywords: Plai oil, ADMET, pharmacokinetics, GCMS

1. Introduction

Zingiber cassumunar Roxb. belongs to the family Zingiberaceae and is an herbaceous and perennial plant consisting of an underground part consisting of rhizomes. In Thailand, Indonesia, and other Asian countries, *Z. cassumunar* has traditionally been used as a medicinal plant in folk remedies for the treatment of various illness, such as inflammation, including arthritis, rheumatisms, sprains, respiratory problems such as asthma and cough, and pain caused by musculoskeletal, menstrual, or gastrointestinal disorders (Han, et al., 2021).

The formulation contains no less than 90% hot oil extract of Plai, which is suitable for alleviating swelling, bruising, and sprains in both forms. Nonetheless, the plain oil products from industrial firms are frequently derived as essential oils by distillation methods, resulting in elevated costs. Consequently, small hospitals and the general public encounter challenges in obtaining such products. The extraction of oil from fried fingerroot represents a viable, cost-effective solution that encourages the use of herbs in families and fosters self-sufficiency (Singsai et al., 2022).

The production of muscle relaxation herbal oil was developed by using the Plai oil in the muscle relaxation herbal oil product to develop an anti-inflammatory product in the form of Plai oil. It can penetrate the skin to the muscle layer, relieving pain and inflammation in the skin, muscles, ligaments, and joints well.

1.1 Research Objective

1.1.1 To study the chemical composition of Plai oil for muscle relaxing by GCMS technique

1.1.2 To study the pharmacokinetic prediction of chemical composition in Plai oil

2. Materials and Methods

2.1 Sample preparation

Briefly, the *Zingiber cassumunar* Roxb (Plai) was washed the fingerroot thoroughly and then sliced thinly. The *Z. cassumunar* 200 g and coconut oil 100 ml into a pan at 100°C for 1 h, stirring occasionally. The fingerroot fragments were removed, leaving only the yellow oil. Pour the oil into a bottle and preserve it at room temperature after straining it through a white cloth.

2.2 GCMS analysis

GCMS using by SHIMADZU QP-2010 with DB-5MS column 30 m x 0.25 mm ID x 0.25 mm 25 mm (non-polar fused silica capillary with a 5% phenylmethylpolysiloxane stationary phase) set the helium gas flow rate to 1 mL/min by injecting 1 μL of sample material, starting at 50°C for 2 minutes, then increasing the temperature by 5°C/min to 200°C for 10 minutes, and then increasing the temperature by 5°C/min to 230°C for 10 minutes. The temperature was increased by 5°C/min to 320°C for 20 minutes, and the ion source temperature was 250°C in the Electron Impact Ionization (EI) system, resulting in the separation of the extract components into a Total Ion Chromatogram (TIC) in the Scan Mode (Anorach et al., 2024).

2.3 Pharmacokinetic prediction

The ADME parameters were estimated with the online available SwissADME software and toxicity properties were obtained by resorting to pkCSM software (Flores-Holguín et al., 2021).

3. Results and Discussion

3.1 GCMS analysis

The GCMS analysis of Plai oil showed the 6 identified compounds (Figure 1.). The menthol was a major compound with a percentage of peak area of 42.71% followed by (+)-2-bornanone21.44%, endo-borneol 17.9%, isoborneol 8.3%, caryophyllene 0.99% and grandlure IV 0.48%, respectively (Table 1.). Moreover, the menthol has been used as a non-opioid pain reliever (Pergolizzi et al., 2018). Isoborneol have been reported to anticoagulant, neuroprotective, sedative and analgesic properties (Cheng et al., 2013). In addition, β-caryophyllene, an ancient remedy to treat pain (Ceccarelli et al., 2020).

Figure 1: GCMS chromatogram of Plai oil

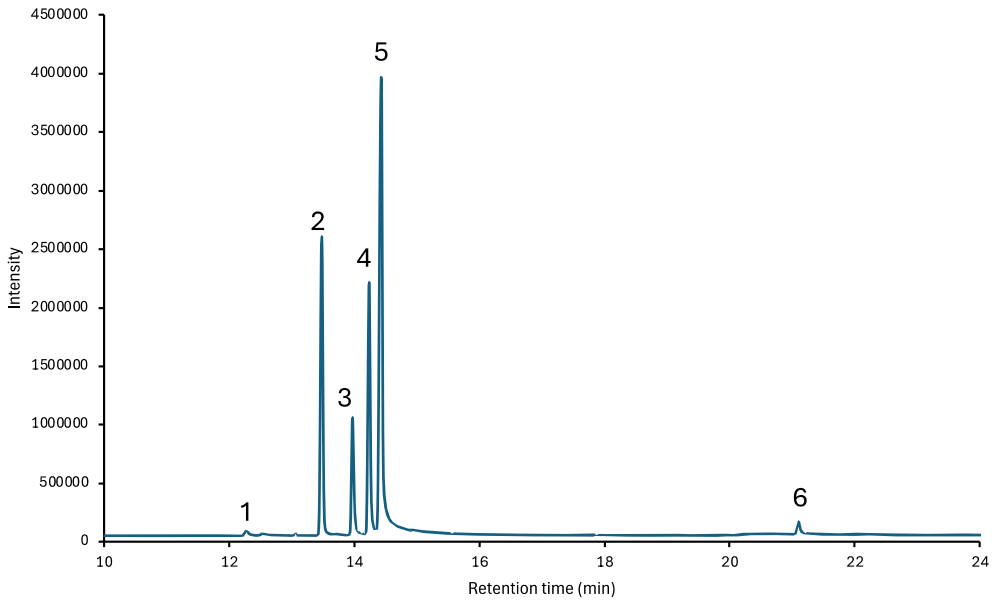


Table 1: GCMS analysis of Plai oil

Compound No.	Retention time (min)	Formula	MW	Peak area (%)	Compound name
1	12.27	$C_{10}H_{16}O$	152	0.48	Grandlure IV
2	13.48	$C_{10}H_{16}O$	152	21.44	(+)-2-Bornanone
3	13.19	$C_{10}H_{18}O$	154	8.30	Isoborneol
4	14.23	$C_{10}H_{18}O$	154	17.9	endo-Bornanone
5	14.43	$C_{10}H_{20}O$	156	42.71	Menthol
6	21.09	$C_{15}H_{24}$	204	0.99	Caryophyllene

3.2 Pharmacokinetic prediction

The 7 compounds were predicted the Physicochemical properties showed in Table 2. The molecular weight range 152.23-296.15 g/mol. The caryophyllene showed moderately water solubility, menthol as soluble water solubility. However, grandlure IV, (+)-2-bornanone, isoborneol and endo-bornanone were very water solubility. The 7 compounds passed the TPSA, NORTB, HBA and HBD criteria. There are only caryophyllene demonstrated not pass the Lipinski's violation properties. In addition, all compounds have a high physicochemical property more than diclofenac was used as the standard drug for anti-inflammation.

Table 2: Physicochemical properties of 7 compounds from Plai oil recipe by GCMS

Compounds	Physicochemical properties							
	MW[a]	cLogP[b]	cLogS[c]	TPSA[d]	NORTB[e]	HBA[f]	HBD[g]	Lipinski violations[h]
Criteria	<500	-	-	≤140	≤10	≤5	≤10	≤0
Grandlure IV	152.23	2.5	-2.37	17.07	1	1	0	0
(+)-2-Bornanone	152.23	2.37	-2.18	17.07	0	1	0	0
Isoborneol	154.25	2.38	-2.8	20.23	0	1	1	0
endo-Bornanone	154.25	2.39	-2.8	20.23	0	1	1	0
Menthol	156.27	2.58	-3.5	20.23	1	1	1	0
Caryophyllene	204.35	4.24	-4.1	0	0	0	0	1
Diclofenac (positive control)	296.15	3.66	-5.15	49.33	4	2	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.

All compounds were predicted the pharmacokinetic properties which are Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) parameters. The 7 compounds have %ABS range from 91.98-109.00% which is a good absorption and oral bioavailability. Skin permeability (log Kp) refers to the ability of substances to pass through the skin barrier via different pathways such as the stratum corneum, hair follicles, and sweat ducts. Skin permeability refers to the ability of substances to pass through the skin barrier via the stratum corneum and indicates the significance of skin absorption (Chen et al., 2018). Caryophyllene showed a high skin permeability with log Kp of -4.44 cm/s better than other compounds and diclofenac, as a positive control. For distribution, the 6 compounds passed a BBB permeant criteria without caryophyllene. For metabolism, CYP450s are involved in drug biotransformation, exogenous and endogenous substrate metabolism, and maintaining the normal physiological function of the skin, as well as facilitating homeostasis of the internal environment (Chen et al., 2024). Caryophyllene was metabolized by CYP2C19 and CYP2C9 inhibitors. In contrast, 6 compounds are not excreted by cells by P-glycoprotein. For toxicity, 6 compounds were predicted to be a skin sensitization. There are 6 compounds showed no genetic toxicology (AMES toxicity) and no hepatotoxicity which is associated with disrupted normal function of the liver (Flores-Holguín et al., 2021).

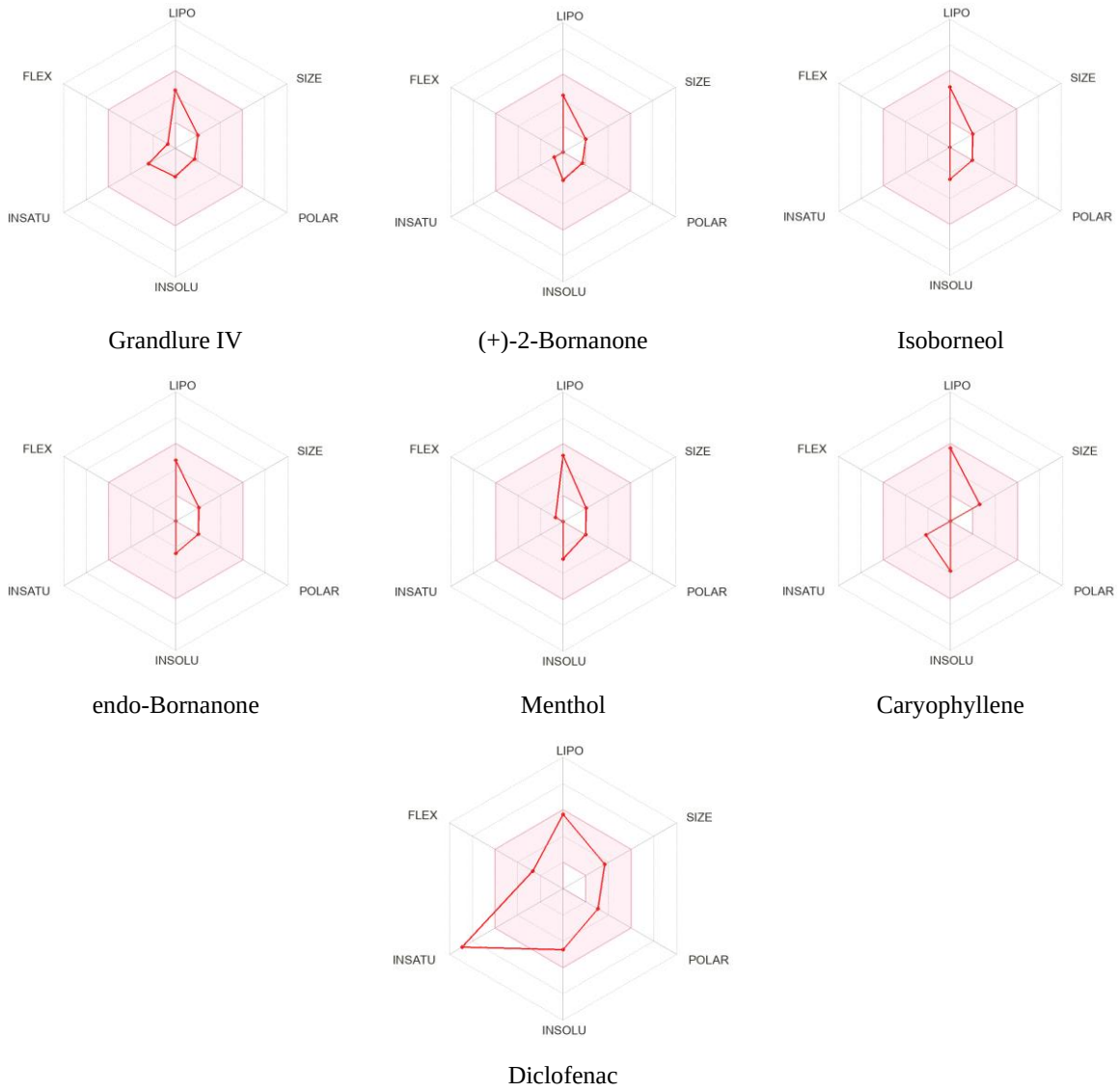
Table 3: Pharmacokinetics properties of 7 compounds from Plai oil recipe by GCMS

Properties	Parameter	Compounds						
		Grandlure IV	(+)-2-Bornanone	Isoborneol	endo-Bornanone	Menthol	Caryophyllene	Diclofenac
Absorption	%ABS	103.11	103.11	102.02	102.02	102.02	109.00	91.98
	Skin permeability (cm/s)	-5.55	-5.67	-5.31	-5.31	-4.84	-4.44	-4.98
Distribution	BBB permeant	Yes	Yes	Yes	Yes	Yes	No	Yes
Metabolism	CYP1A2 inhibitor	No	No	No	No	No	No	Yes
	CYP2C19 inhibitor	No	No	No	No	No	Yes	Yes
	CYP2C9 inhibitor	No	No	No	No	No	Yes	Yes
	CYP2D6 inhibitor	No	No	No	No	No	No	Yes
	CYP3A4 inhibitor	No	No	No	No	No	No	No
Excretion	Pgp substrate	No	No	No	No	No	No	No
Toxicity	Skin Sensitisation	Yes	Yes	Yes	Yes	Yes	Yes	No
	AMES toxicity	No	No	No	No	No	No	No
	Hepatotoxicity	No	No	No	No	No	No	No

The effect of the geometrical and structural properties on the bioavailability of the 6 compounds and diclofenac in Table 2 can be better visualized considering the bioavailability radars displayed in Figure 2. The 6 compounds showed that all analyzed parameters are in the

optimal range, which is greater than diclofenac. Its showed the exception of saturation (INSATU), which falls out of the set borders. The pink area represents the optimal range for each property: lipophilicity (LIPO) (XLOGP3 between −0.7 and +5.0), molecular mass (SIZE) (between 150 and 500 g/mol), polarity (POLAR) (TPSA between 20 and 130 $Å^2$), solubility (INSOLU) (log S not higher than 6), saturation (INSATU) (fraction of carbons in the sp^3 hybridization not less than 0.25), and flexibility (FLEX) (no more than nine rotatable bonds) (Beus et al., 2019).

Figure 2: SwissADME bioavailability radar reports of 7 componds



4. Conclusion

The Plai oil for muscle relaxing found the 6 identified compounds which is menthol was a major compound. These compounds have a good physicochemical and pharmacokinetics properties than diclofenac, as a positive control. Therefore, Plai oil can be used for muscle relaxation and confirms the knowledge of Thai traditional medicine to produce the pharmaceutical product.

5. Acknowledgment

The authors would like to express thanks to the College of Allied Health Sciences, Suan Sunandha Rajabhat University for their support.

References

Anorach, R., Panyatip, P., Datham, S., Siripru, P., Bangthong, B., Ratha, J., Puthongking, P., and Yongram, C. (2024). Phytochemical analysis and antioxidant activities from the methanolic leaves extract of *Clausena harmandiana* (Pierre) Guillaumin. *Journal of Allied Health Sciences Suan Sunandha Rajabhat University*, vol.9, pp. 49-46.

Beus, M., Fontinha, D., Held, J., Rajić, Z., Uzelac, L., Kralj, M., Prudêncio, M., and Zorc, B. (2019). Primaquine and chloroquine fumardiamides as promising antiplasmodial agents. *Molecules*, vol. 24, pp. 2812.

Ceccarelli, I., Fiorenzani, P., Pessina, F., Pinassi, J., Aglianò, M., Miragliotta, V., and Aloisi, A. M. (2020). The CB2 agonist β-caryophyllene in male and female rats exposed to a model of persistent inflammatory pain. *Frontiers in Neuroscience*, vol. 14, pp. 850.

Chen, C. P., Chen, C. C., Huang, C. W., and Chang, Y. C. (2018). Evaluating molecular properties involved in transport of small molecules in stratum corneum: a quantitative structure-activity relationship for skin permeability. *Molecules*, vol.23, pp. 911.

Chen, Q., Wang, T., Wu, X., Yuan, H., Wei, Y., and Xiao, Y. (2024). The role of the cytochrome P450 superfamily in the skin. *Expert Reviews in Molecular Medicine*, vol. 26, pp. e15.

Cheng, C., Liu, X. W., Du, F. F., Li, M. J., Xu, F., Wang, F. Q., Liu, Y., Li, C., and Sun Y. (2013). Sensitive assay for measurement of volatile borneol, isoborneol, and the metabolite camphor in rat pharmacokinetic study of *Borneolum* (Bingpian) and *Borneolum syntheticum* (synthetic Bingpian). *Acta Pharmacologica Sinica*, vol. 34, pp. 1337-1348.

Flores-Holguín, N., Frau, J., and Glossman-Mitnik, D. (2021). *In silico* pharmacokinetics, admet study and conceptual dft analysis of two plant cyclopeptides isolated from *Rosaceae* as a computational peptidology approach. *Frontiers in Chemistry*, vol. 9, pp. 708364.

Han, A. R., Kim, H., Piao, D., Jung, C. H., and Seo, E. K. (2021). Phytochemicals and bioactivities of *Zingiber cassumunar* Roxb. *Molecules*, vol. 26, pp. 1-16.

Pergolizzi J. V. Jr, Taylor, R. Jr, LeQuang, J. A., Raffa, R. B and NEMA Research Group. (2018). The role and mechanism of action of menthol in topical analgesic products. *Journal of Clinical Pharmacy and Therapeutics*, vol. 43, pp. 313-319.

Singsai, K., Charoongchit, P., and Utsintong, M. (2022). The comparison of the oil types in Plai (*Zingiber cassumunar*) oil extraction and analysis of the chemical constituents in Plai oil by gas chromatography-mass spectrometry technique. *Naresuan Phayao Journal*, vol.15, pp. 18-28.