



KEMENTERIAN KESIHATAN MALAYSIA

Application of margin of exposure approach to assess the cancer risk of aristolochic acids from herbal supplement consumption



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Introduction

- The assessment of traditional food-borne contaminants' risk in predicting and preventing human cancer is complex.
- Currently, margin of exposure (MOE) approach is preferred for low exposure of genotoxic and carcinogenic compounds in food such as aristolochic acids (AAs), the Group 1 carcinogen.
- In protecting public health, the contemporary practices must be adequate and strengthened to evaluate the exposure of AAs.

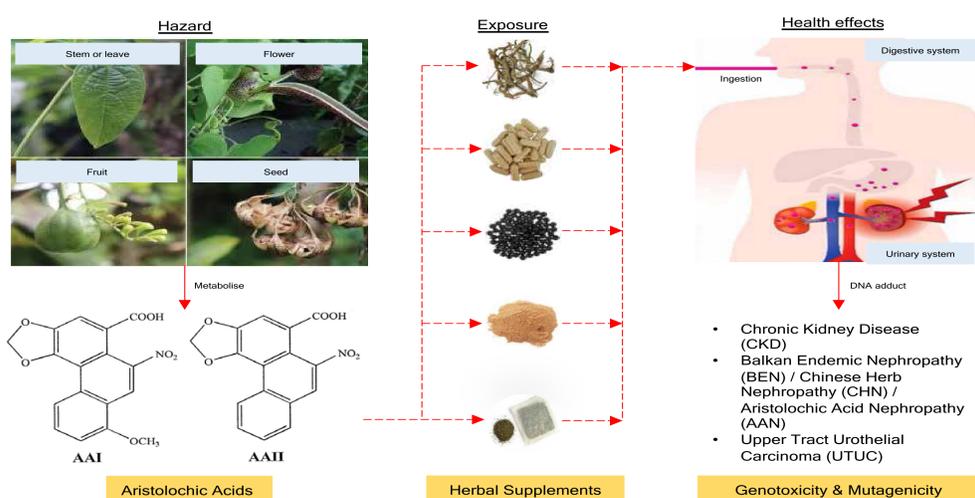


Figure 1. AAs exposure pathway

Objective

- This study aims to apply the MOE approach in the assessment of AAs cancer risk of herbal supplements from Malaysia.

Materials

Table 1. List of 30 targeted samples of herbal supplements were purchased from the Malaysian online market.

Sample number	Products	Products presentation	Suspected botanical ingredients
S1	Uniflex Cheng Hee Wan	Pill	<i>Herba asari</i>
S2	Ban Kah Chai Pil Sakit Perut	Pill	<i>Asarum heterotropoides herba</i>
S3	Ban Kah Chai Brand Jun Ging Pills	Pill	<i>Radix asarum heterotropoides</i>
S4	Dong Hua Zhui Feng Su Hup Wan	Pill	<i>Herba asarum sieboldii miq.</i>
S5	Pil 'Hong Sah' Cap Labu	Pill	<i>Herba asari</i>
S6	Chuan Mu Tong	Plant stem (dried)	<i>Aristolochia manshuriensis</i>
S7	Burung Merak Emas Serbuk Fong Sa Chan Tong San	Powder	<i>Saussurea lappa clarke</i>
S8	Ho Yan Hor Gold Herbal Tea	Tea	<i>Herba asarum canadense</i>
S9	Ho Yan Hor Original Herbal Tea	Tea	<i>Asarum canadense</i>
S10	Ubat Serbuk Batuk Cap Tangan	Tea	<i>Herba asari</i>
S11	Aristolochia	Fruit (dried)	<i>Aristolochia contorta Bunge</i>
S12	Akebia Stem Huai Mu Tong	Plant stem (dried)	<i>Akebia sp.</i>
S13	Asarum Powder	Powder	<i>Asarum heterotropoides</i>
S14	Min Shan Chuan Xiong Cha Tiao San	Globules (small pills)	<i>Aristolochia sp.</i>
S15	Ta Huo Lo Tan	Tablets (pills)	<i>Aristolochia sp.</i>
S16	Kenrix's Ren Shen Feng Shi Wan	Capsules	<i>Asarum sp.</i>
S17	Asarum	Plant stem (dried)	<i>Asarum canadense Linn</i>
S18	Bei Xi Xin	Plant stem (dried)	<i>Asarum canadense Linn</i>
S19	Coltsfoot Flower Jing fang ji	Flower (dried)	<i>Syn. Asarum canadense var. reflexum</i>
S20	Fruit of Fiveleaf Akebia	Fruit (dried)	<i>Akebia quinata (Houtt.) Decne</i>
S21	Wild Asarum	Plant root (dried)	<i>Asarum heterotropoides</i>
S22	Asarum	Whole plant (dried)	<i>Asarum heterotropoides</i>
S23	Xi Xin	Plant root (dried)	<i>Asarum heterotropoides</i>
S24	Zhu Po Chuanbei Hou Zao San	Powder	<i>Asarum heterotropoides</i>
S25	Chuan Qiong Cha Tiao San	Globules	<i>Asarum heterotropoides</i>
S26	Yin Onn Soo Hup Yuen	Globules (small pills)	<i>Asarum heterotropoides</i>
S27	Wei Ling Xian Mulberry Tea	Root (dried)	<i>Clematis chinensis</i>
S28	Wei Ling Xian	Powder	<i>Clematis chinensis</i>
S29	Stephania Tetranda Han Fang Ji	Plant stem (dried)	<i>Clematis sp.</i>
S30	Fangji Teabag	Plant stem (dried)	<i>Clematis sp.</i>

Methods

- This quantitative risk assessment involved analytical study of 30 herbal supplements, purchased from the Malaysia online market and analysed using ultra-performance liquid chromatography technique.
- The estimated daily intakes (EDIs) were calculated based on recommended daily consumptions determined by herbal supplement's product descriptions.
- The benchmark dose lower-bound confidence limit 10% (BMDL₁₀) for interest responses were derived based on selected animal studies.
- The MOE values were calculated and risk assessment was conducted based on the MOE values of 10,000 that represent 10 times cancer risk.

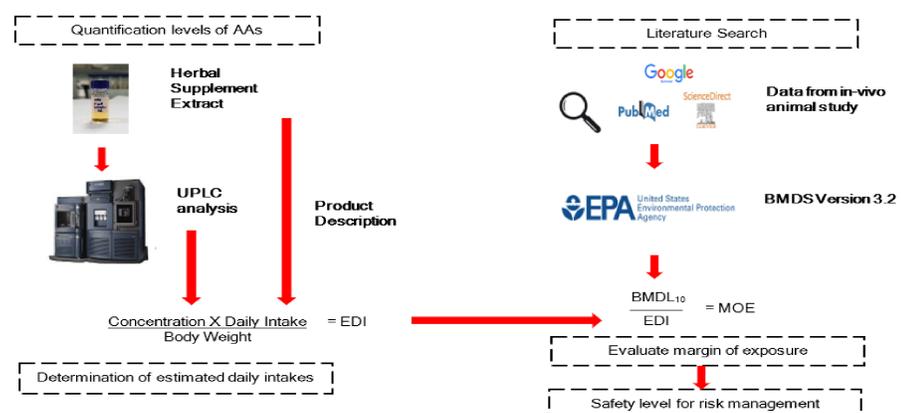


Figure 2. General workflow

Results & Discussions

- 5 out of 30 (16.7%) herbal supplements samples were positive with AAs ranged from 8.7 ± 0.2 to $4259.1 \pm 1231.3 \mu\text{g g}^{-1}$.

Table 2. Levels of AAI and AAII in positive samples of herbal supplements with three independent experiments

Sample number	Methanol extraction		Aqueous extraction	
	AAI ($\mu\text{g g}^{-1}$)	AAII ($\mu\text{g g}^{-1}$)	AAI ($\mu\text{g g}^{-1}$)	AAII ($\mu\text{g g}^{-1}$)
S3	8.7 ± 0.2	nd ^a	nd	nd
S9	nd	18.5 ± 1.6	nd	nd
S10	40.4	52.9	nd	nd
S11	339.3 ± 9.0	nd	4259.1 ± 1231.3	563.4 ± 141.4
S12	1644.8 ± 165.4	611.5 ± 133.0	nd	681.3 ± 43.5

- The EDI values were much higher than the BMDL₁₀.

Table 3. EDIs of AAs

Sample number	Daily consumption of the herbal supplement (g)	EDI ($\mu\text{g kg}^{-1} \text{ bw day}^{-1}$) ^a	
		Methanol	Aqueous
S3	4	0.6	nd ^b
S9	6	1.9	nd
S10	1	1.6	nd
S11	2	11.3	160.8
S12	2	75.2	22.7

^aaddition of AAI and AAII
^bnot detected

- The MOE values of all AAs-containing samples were much lower than 10,000 indicated the high cancer risk among the AAs-containing herbal supplement consumer.

Table 4. MOE values of AAs from herbal supplements

Sample number	MOE	
	Methanol	Aqueous
S3	17.3	nd ^a
S9	5.4	nd
S10	6.4	nd
S11	0.9	0.1
S12	0.1	0.4

^anot detected

Conclusion

- The MOE approach can be used to assess the cancer risk of AAs through the consumption of herbal supplements, revealing a significant cancer risk and highlighting the need for risk management.

Acknowledgement

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References

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