

Physico-chemical evaluation of kadukkai maathirai and its tablet formulation, a Siddha iron preparation used in anemia

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ABSTRACT

Background: Siddha system of medicine is one among the great heritages of India. Iron deficiency anemia is described as “azhal paandu” in siddha system and more formulations are mentioned in literatures to treat anemia. Kadukkai maathirai (KM) is one of the widely used drugs for the treatment of iron deficiency anemia with good patient compliance. It was claimed that this drug is devoid of adverse effects which are seen with other oral iron preparations.

Objective: Present study was carried out to standardize kadukkai maathirai by evaluating its physical and chemical properties using modern scientific instruments.

Materials and methods: KM was prepared following standard procedures mentioned in the Siddha Hospital Pharmacopeia. Physical properties such foreign matter, loss on drying, total ash content, acid insoluble ash, alcohol soluble extract value and water soluble extract value were evaluated. Amount of iron and heavy metals such as cadmium, mercury, arsenic and lead were estimated. HPTLC chromatogram and photograph were also done. KM was again formulated into tablet form by standard procedures. Kadukkai maathirai tablet (KMT) was analysed for Angle of Repose, bulk density, tapped density, carr's index, Hausner's ratio, general appearance (shape, color, texture and odor), thickness, uniformity of weight, coating uniformity, coating process efficiency, hardness and friability.

Result: Amount of iron in KM was 18.03%. Whereas amount of heavy metals such as mercury (0.0578 ppm), cadmium (0.0064 ppm), arsenic (0.0405 ppm) and lead (0.2144 ppm) were within the permissible limit.

Conclusion: In KM, iron is combined with few herbals which is claimed to facilitate oral bioavailability of iron and nullify iron induced side effects. As heavy metals are within the permissible limit, KM could be considered as safe drug. HPTLC fingerprint could serve for future references.

KEY WORDS: Iron deficiency, anemia, Ayurveda, herbometallic, traditional medicine

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INTRODUCTION

Siddha system of medicine is one of the ancient medical systems in India which reflects the life style and culture of the people. Siddhars, the founders of Siddha medicine had designed the health practices including seasonal discipline and food regulation. Siddha system relay on the concept of “Food is Medicine”. Thus, siddha system prepares therapeutic drugs from green herbals. The herbal formulations serve as both therapeutic drug and nutrient supplements.^[1]

Siddha system describes anemia as paandu or veluppu noi, which means paleness. Anemia is further classified into six subtypes based on clinical signs and symptoms. They are; vali paandu, azhal paandu, iyya paandu, mukutra paandu, nanju paandu and mannun paandu. The symptoms of iron deficiency anemia are

described as azhal paandu.^[2] Siddha provides patient-friendly medication to overcome the anemic condition. As per the literature kadukkai maathirai (KM) plays a vital role in the treatment of anemia.^[3] Although KM has been playing a vital role in the management of anemia without any iron induced adverse effects for hundreds of years, no attempts were made to validate it scientifically. To enlighten the scientific basis for the use of KM in iron deficiency anemia, this study was done to characterize its physico-chemical properties.

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MATERIALS AND METHODS

Raw materials

Ingredients such as annabedhi (ferrous sulphate), kadukkai (*Terminalia chebula*), milagu (*Piper nigrum*) and fresh leaves of karisalai (*Eclipta alba*) were purchased from Ramasamy Chetty Country Drug Store, Chennai, India. All the ingredients were authenticated by Prof. Pandiperumal, Principal, Government Siddha Medical College, Chennai, India. Samples of all the ingredients were preserved for future reference.

Preparation of KM

KM was prepared with strict adherence to the traditional methods mentioned in the Siddha Hospital Pharmacopeia - Government of Tamilnadu, India. Ferrous sulphate was soaked in lemon juice for twenty four hours. After drying, the same was ground with *Eclipta alba* herb juice for a period of three hours and allowed for drying. Next day, these were placed in a mud vessel, which was closed with other mud vessel and sealed air tightly with the help of clay and cloth. Then, it was subjected to heat by firing cow dung cakes of thirty in numbers. Next day, the mud vessel was opened; red colored coins were collected carefully and finely powdered. This powder was named as powder A. Epicarp of *Terminalia chebula* dry fruit was collected and the inner nuts were removed. Then the epicarp of dry fruits was made into fine powder B. Pepper, after a shallow fry, was also finely powdered as powder C. When prepared, each 100mg of KM had 60mg of powder A, 20mg of powder B and 20mg of powder C. The above prepared powders, A, B and C in the above mentioned proportions were ground for three hours in a stone mortar. The resultant red color fine powder was made as pills called KM using traditional method.^[4]

Evaluation of physical properties of KM

KM was evaluated for foreign matter, loss on drying, total ash content, acid insoluble ash, alcohol soluble extract value and water soluble extract value.^[5]

Estimation of the elements in KM

Amount of iron was quantified by titration method.^[6] Presence of heavy metals such as cadmium, mercury, arsenic and lead were estimated by using Thermo Fisher M Series, 650902 V1.27 model atomic absorption spectrometer (AAS).^[7]

HPTLC fingerprint of KM

The fingerprinting of KM was done using certain chromatographic conditions.^[8] Chromatography was performed on a 10x10 cm pre activated HPTLC silica gel 60 F 254 plate. Samples were applied to the plate as 6 mm wide band with an automatic TLC applicator Linomat 5 with N₂ flow (CAMAG, Switzerland), 8 mm from the bottom. Densitometric scanning was performed on CAMAG scanner III. The plates were pre-washed by methanol and activated at 60^o C for 5 minutes prior to chromatography. The slit dimension was kept at 5 mm x 0.45 mm and 20 minutes scanning speed was employed. A 10 ml of mobile phase was used per chromatography. Linear ascending development was carried out in 20 cm x 10 cm twin glass chamber saturated with the mobile phase.

The extracts of the trial drug and standard of required concentration was prepared and were spotted using CAMAG Linomat 5 applicator. The method was optimized by selecting appropriate mobile phase for test drug and developed in a twin trough chamber, 20 x 10 cm at 25^o C. The plates were dried by hair dryer. The developed plates were scanned at appropriate wavelength using Camag TLC scanner 3 and photo-documented using Camag reprostar 3. Sample (KM) was prepared in methanol. Silica gel GF₂₅₄ plate served as stationary phase and Toluene: Ethyl acetate: Formic acid: Methanol (3:3:0.75:0.25) served as mobile phase. Sample concentration was kept constant as 50 mg/ml. Two tracks were run, in which, first track received 5 μ l and second track received 10 μ l of sample. Sample was scanned in the wavelength of 366 nm and 254 nm.

Preparation of kadukkai maathirai tablet (KMT)

For this study, KMT was prepared by wet granulation technique. All three powders and excipients (talc, magnesium stearate and colloidal silicon dioxide) were passed through sieve no.60 before granulation and lubrication. The powders were weighed and mixed uniformly. Then the mixture was made to a damp mass using starch paste. Prepared mass was passed through sieve no. 16. The prepared granules were dried in an oven at a temperature of 50^oC for one hour. Talc and magnesium stearate were added and mixed with above granules and lubricated with colloidal silicon dioxide. The lubricated granules were punched using Cadmach eight station tableting machine. The hardness of the tablet was adjusted with the required amount of compressional force.^[8]

Evaluation of physical properties of KMT

Formulated granules were assessed for Angle of Repose, bulk density, tapped density, carr's index and Hausner's ratio by standard procedures.^[9] Formulated tablet was analyzed for its general appearance (shape, color, texture and odor), thickness, uniformity of weight, coating uniformity, coating process efficiency, hardness and friability.^[9]

RESULTS

Physical properties of KM

Table 1 shows the physical properties of KM.

Estimation of the elements in KM

The active ingredient of KM is iron. In our study we found that the iron content of KM was 18.03%. Heavy metals such as cadmium, mercury, arsenic and lead were also present, but within the permissible limits (Table 2).^[10]

HPTLC finger Print of KM

HPTLC chromatogram of KM showed 10 peaks, on which 9th peak (area% is 74.3%) could serve as a marker (Figure 1, 2 and table 3).

Physical properties of KMT

The obtained data are summarized in table 4 and figure 3.

Figure 1: HPTLC chromatogram of kadukkai maathirai

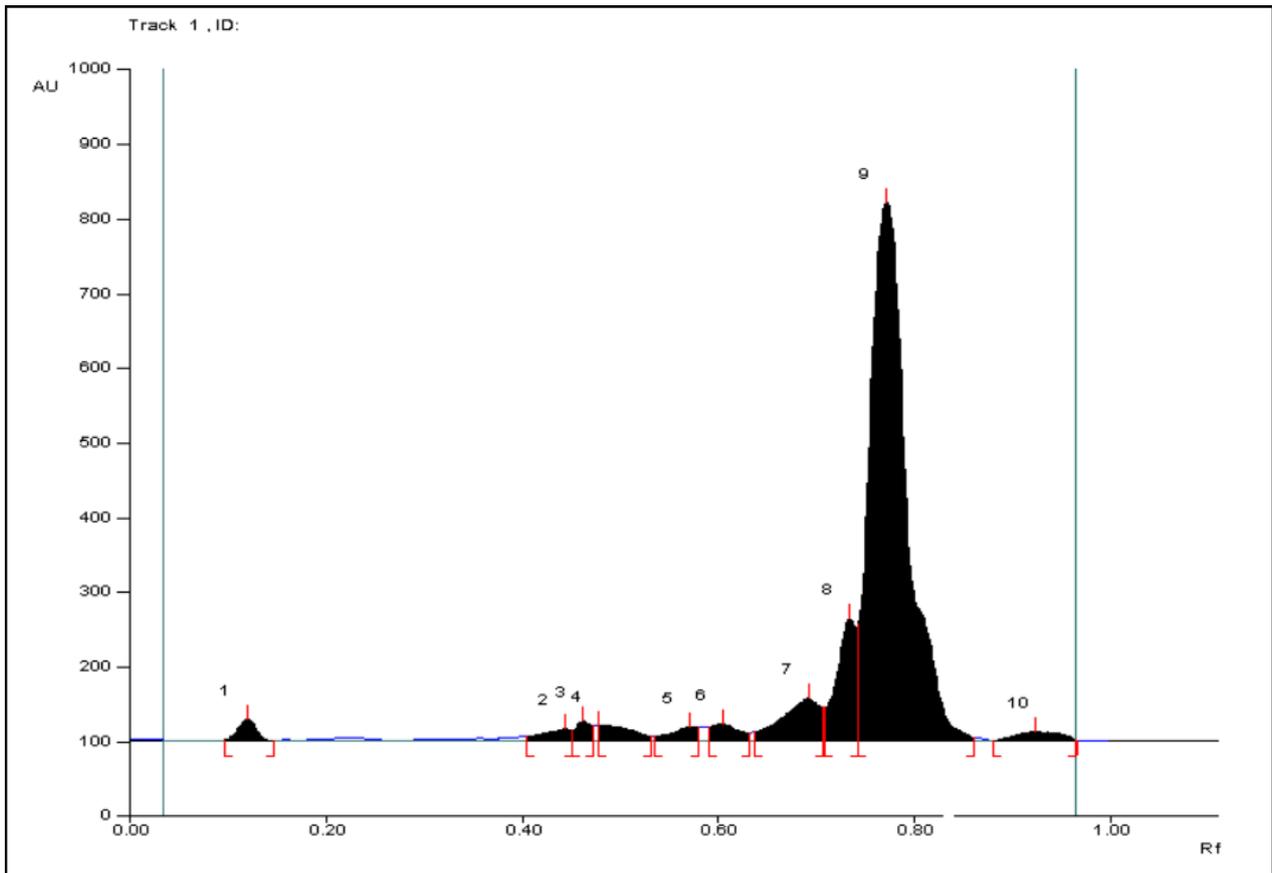


Figure 2: HPTLC photographs of kadukkai maathirai

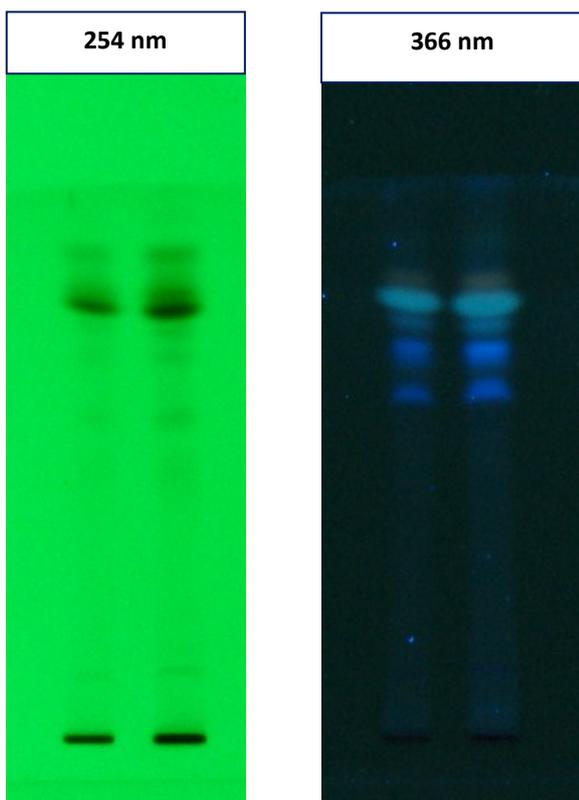


Figure 3: Formulated kadukkai maathirai



Table 1: Physical properties of kadukkai maathirai

Property	Result
Loss on dry at 105°C	7.95%
Total ash	37.85%
Acid insoluble ash	31.55%
Alcohol extract value	3.58%
Water extract value	17.72%

Table 2: Chemical analysis of kadukkai maathirai

Element	Result	Permissible limits
Iron #	18.03%	-
Cadmium	0.0064 ppm	0.3 ppm
Mercury	0.0578 ppm	1 ppm
Arsenic	0.0405 ppm	3 ppm
Lead	0.2144 ppm	10 ppm

Elemental quantification was done by Atomic Absorption spectroscopy

Analysis done by titration method

DISCUSSION

Maximum daily requirement of iron for an adult male, adult female and pregnancy are 1 mg, 2 mg and 5 mg respectively.^[11] During pregnancy, KM is usually given to patients at the dose of 400 mg per day in two divided doses, which contains 72.12 mg iron. Though the amount of iron is high, it is claimed by Siddha physicians that, this drug is devoid of anticipated adverse effects which are seen with iron preparations used in modern medicine. Epigastric pain, heartburn, nausea, vomiting, staining of teeth, metallic taste, blotting and constipation are the expected and inevitable adverse effects seen with other oral preparations. These adverse effects often restrict the usage of iron tablets in most of the cases.^[11]

Table 3: HPTLC fingerprint of kadukkai maathirai

Track	Peak	Start Rf	Start Height	Max Rf	Max Height	Height %	End Rf	End Height	Area	Area %
1	1	0.1	0.9	0.12	28.5	2.62	0.15	0.1	453.6	1.49
1	2	0.4	5.2	0.44	15.8	1.45	0.45	14.5	374	1.23
1	3	0.45	14.6	0.46	26.1	2.41	0.47	20.7	347.6	1.14
1	4	0.48	21.4	0.48	21.4	1.97	0.53	6.8	604.1	1.98
1	5	0.53	6.4	0.57	18.7	1.72	0.58	18.5	422.5	1.39
1	6	0.59	18.4	0.6	22.3	2.06	0.63	10.6	524.3	1.72
1	7	0.64	11.7	0.69	56.6	5.21	0.71	44.5	1856.7	6.1
1	8	0.71	45	0.73	163.3	15.05	0.74	151.1	2764.6	9.08
1	9	0.74	155.4	0.77	720.3	66.38	0.86	4.3	22624.1	74.3
1	10	0.88	0.4	0.92	12.3	1.13	0.96	0.8	477.9	1.57
2	1	0.1	1.6	0.13	54.6	3.86	0.15	0.2	750	1.67
2	2	0.19	3.5	0.23	11.9	0.84	0.26	1.3	387.5	0.86
2	3	0.39	7.7	0.49	41.9	2.97	0.53	15	2695.3	6
2	4	0.54	15.2	0.58	40.5	2.86	0.59	39.4	1241.2	2.76
2	5	0.59	39.3	0.61	47.7	3.37	0.64	31.6	1383	3.08
2	6	0.64	32	0.69	123.6	8.74	0.71	95.6	3945.7	8.79
2	7	0.71	97	0.73	289.1	20.45	0.74	262.3	4640.9	10.34
2	8	0.74	264.4	0.77	792.2	56.04	0.88	0.1	29537	65.8
2	9	0.89	0.1	0.93	12.2	0.86	0.94	9.9	310.2	0.69

Table 4: Physical properties of kadukkai maathirai granules and formulated kadukkai maathirai tablet

Property	Result
Formulated kadukkai maathirai granules	
Angle of Repose	34 degree
Bulk density	0.352 g/ml
Tapped density	0.512 g/ml
Carr's index	31.25%
Hausner's ratio	1.45
Formulated kadukkai maathirai tablet	
Thickness	3.4mm
Uniformity of weight	200 mg
Hardness	4.5 kg/cm ²
Friability	0.42 % w/w

Terminalia chebula, *Piper nigrum*, *Eclipta alba* and lemon juice are the other ingredients in KM. Studies on *Terminalia chebula* had shown that it significantly increased the gastric emptying and acted as a prokinetic agent.^[12] Siddha medicine considers *Piper nigrum* and *Eclipta alba* as liver tonics. Animal study has proved the hepatoprotective activity of *Eclipta alba* against ethanol induced liver damage.^[13] Lemon juice contains ascorbic acid. By adding lemon juice obtained from 100 gm lemon fruit, doubles the oral iron absorption intestinal tract.^[14] Thus, this supports the claim that KM is useful in iron deficiency anemia and anemia due to liver diseases.

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Not reported.

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KM had trace amount of elements. It is possible that these elements were from herbals used for the preparation of KM. Plants have the property to store heavy metal elements if it is available in the earth where it actually grows. Since the amount is within permissible limits, the KM could be considered as safe drug and is acceptable for human therapeutic use.

There were ten peaks observed in HPTLC analysis. Each peak denoted the presence of different organic compounds in this formulation. These organic compounds might have derived from the four herbals (*Terminalia chebula*, *Piper nigrum*, *Eclipta alba* and lemon juice) which were the ingredients of KM. Hence attempts have to be made to characterize individual ingredients along with evaluation of its therapeutic role. However, HPTLC results obtained in this study could serve as fingerprint for future comparison of KM.

Further scientific studies such as randomized control trail (RCT) comparing KM with modern iron formulations are required to understand the rationale of using KM in iron deficiency anemia. Furthermore, RCT may generate evidences to prove that KM is patient friendly and also serve to validate the traditional Siddha Medicine claim regarding KM.

CONCLUSION

Kadukkai maathirai, a combination of herbals, with iron as active ingredient is known for its hepatoprotective, prokinetic and iron absorption enhancing property. KM is used in the treatment of anemia. This study revealed the physical property and chemical composition of KM. HPTLC results obtained in this study could serve as fingerprint for future comparison of KM. In addition, individual compounds found in KM have to be characterized. However, future studies are required for the optimization of formulation of KM.

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