Indian Journal of Natural Products and Resources
Vol. 17(1), March 2026, pp. 65-79
DOI: 10.56042/ijnpr.v17i1.16930

A comprehensive review of the therapeutic potential of the ingredients of *Aya Bringaraja Panitham,* a Siddha medicine for iron deficiency anaemia

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Received 05 February 2025; revised received 25 February 2026; accepted 26 February 2026

Anaemia due to iron deficiency is a serious medical condition, especially in children, adolescent girls, and women of reproductive age. *Aya Bringaraja Panitham* (ABP) is a classical Siddha medicine used to treatiron-deficiency anaemia (IDA). The goal of this study is to compile results from relevant publications, with emphasis on the toxicity, safety, preclinical, and clinical studies of the ingredients in ABP for the treatment of IDA. Data from electronic databases like PubMed, Cochrane, ScienceDirect, Scopus, Google Scholar, and Web of Science, published in English, were collected. The outcome of this article demonstrates the effectiveness of the materials in the ABP formulation and provides evidence of ABP's efficacy & safety in treating IDA. Among 111 articles listed from said databases, 93 were included, and the remaining articles were excluded because they were not related to anaemia, did not discuss the ingredients of ABP, or the haematinic action of ABP ingredients. The included articles comprised 28 literature reviews, 17 studies focused on clinical trials, 23 examined the efficacy, safety, and toxicity of the ingredients, and 25 articles related to IDA.

Keywords: Anaemia, *Aya bringaraja panitham*, *Paandu*, Siddha medicine

IPC code; Int. cl. (2021.01)– A61K 36/00, A61P, A61P 7/06

Introduction

Anaemia is characterised by haemoglobin concentration and red blood cell counts below the normal range for a particular age and sex[1]. It is the most common deficiency disease globally, affecting 1.8 billion[2]. Anaemia leads to higher rates of illness and death in women and children. It also affects cognitive and behavioural development in children and women, particularly in reproductive age[3]. The progress of anaemia in reproductive age women (15-49) and children below 5 years is not up to the WHO target of 50% reduction[4,5]. However, the prevalence of anaemia among Indian women has increased since 2016, rising from 52.6% in 2016 to 53% in 2020[6]. The National Family Health Survey-5 (NFHS-5) fact sheets indicate that anaemia prevalence among women aged 15 to 49 years rose from 53% in NFHS-4 to 57% in NFHS-5[7].

The Anaemia Mukth Bharat campaign aimed to address iron-deficiency anaemia (IDA) on a broad scale through iron (ferrous sulphate) and folic acid supplements. However, despite these endeavours, success has remained elusive. One contributing factor to this challenge is the ineffective assimilation of iron by the body[8].

According to NFHS-5 data, there has been a notable increase in the prevalence of anaemia among women of all age groups over the past five years. Hence, there is a need for restructuring and enhancing the implementation of the program[9]. Integrating modern and traditional medical systems can improve public health due to synergistic interactions. However, significant gaps in evidence-based traditional medicine require further research to prove their efficacy scientifically[10].

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Siddha is an ancient traditional system of medicine that originated in South India. In Siddha, anaemia is called *paandu* or *vellupunoi*. The symptoms of *vellupunoi* include discolouration of the skin, conjunctiva, nailbeds, weight loss, tiredness, dyspnoea, nausea, giddiness, fatigue, palpitation, and anorexia[11]. The above symptoms are correlated with anaemia. In Siddha, diseases are classified into three groups based on the imbalance of the three humours, predominant symptoms, and treatment approaches. Among the three humours, *Azhal (pitham) kutram* is essential for nourishing body tissues (thathukal) by optimising metabolism and eliminating waste products, thus maintaining good health. *Anal pitham* and *Ranjaga pitham* help to increase the blood and give a red colour to the essence derived from the digested food in the *Iraikudal* (stomach). Vitiation of the *Azhal kutram* (humour) may be caused by changes in the other *Vali* and *Iya kutram*, resulting in *paandu*[12].

Anaemia is treated with iron-based formulations such as *Aya parpam*, *Aya chenduram*, *Aya veera chenduram, Aya kantha chenduram, Aya mezhugu, Aya bringa raja karpam, Aya Bringaraja Panitham,* etc. In the classical text, *Gunapadam thathu jeeva vaguppu*, *Aya Bringaraja Panitham* (ABP) is outlined as a remedy for correcting anaemia (*Paandu*). Its application extends to treating conditions like *kamalai* (jaundice), *peruvayiru* (ascites), and *sobai* (anasarca). ABP is an iron-based herbo-mineral formulation mentioned in the text that belongs to the *Manapaggu* (syrup) form of the 32 types of internal medicines[13]. The ingredients in this formulation are known for their hematinic activity and also have laxative, carminative, digestive, and anthelmintic activities. In a clinical study, it has been shown that ABP increases haemoglobin levels and other parameters related to RBC and iron metabolism in patients with iron deficiency anaemia[14].

ABP is a classical Siddha formulation comprising ingredients such as *Bavanai Ayam* (Ferrum-Iron), *Chukku-Zingiber officinale Roscoe*. (driedrhizome), *Kadukkai-Terminalia chebula* Retz. (pericarp of mature fruit), *Nellikai-Emblica officinalis Gaertn*. (pulp of fresh fruit), *Thandrikai-Terminalia bellerica* (*Gaertn*.) Roxb. (pericarp of dried ripe fruit), *Milagu-Piper nigrum* L. (mature dried fruit), *Tipilli-Piper longum* Blume. (dried fruit), *Tipilli moolam - Piper longum* Blume. (stem), *Thaen*-honey, *Panaivellam*-palm jaggery, and *Karisalai Charu -Eclipta prostrata*(L.) L. (juice)[13].

The objective of this literature review is to document the role of ABP ingredients in treating iron deficiency anaemia and to document the safety and efficacy of these ingredients in the treatment of anaemia.

Methodology

A manual search was employed to locate research articles published on the actions of ingredients of ABP. The primary search engines utilised for this review included PubMed, Cochrane, ScienceDirect, Scopus, Google Scholar, and Web of Science. The searches were performed in December 2023 to identify papers that might meet the inclusion criteria and have been published since 2006. The searches identified studies using terms such as “anaemia”, “haemoglobin”, “anaemia-related medicines in Siddha”, and components of ABP such as “*Eclipta prostrate* (L.)L.”, “*Emblica officinalis Gaertn*.”, “honey”, “palm jaggery”, “*Piper nigrum* L.”, “*Piper longum* Blume.”, “*Terminalia chebula* Retz.”, “*Terminalia bellerica* (*Gaertn.*) Roxb.”, and “*Zingiber officinale* Roscoe.”

Inclusion and exclusion criteria

Articles, theses, literature, research articles, and dissertations published in English were considered for the review. Furthermore, original research was also considered. Articles unrelated to the ingredients of ABP, which are not categorised under anaemia, and did not mention the hematinic action of ABP ingredients in clinical or preclinical studies, were excluded from the review. The selected articles were assessed based on their relevance and evidence from *in vivo*, *in vitro*, and clinical studies to elucidate the potential benefits of ABP components and their associated clinical manifestation of altered iron metabolism (Fig. 1).

Emblica officinalis Gaertn.

Emblica officinalis Gaertn. is a small tree, reaching a height of 8 to 18 m with irregularly extending branches. Leaves are small and elliptical, and the flower appears yellowish-green; the fruit is round with six vertical bands. The major chemical constituents of *E. offcinalis* include ascorbic acid, gallic acid, chebulinic acid, chebulagic acid, ellagic acid, 3-ethylgallic acid, corilagin, and other constituents such as isocitric acid, terchebincorilagin, emblicanin A and B, punigluconin, pedunculagin, 1-O-galloyl-beta-D-glucose, 3,6-di-O-galloyl-D-

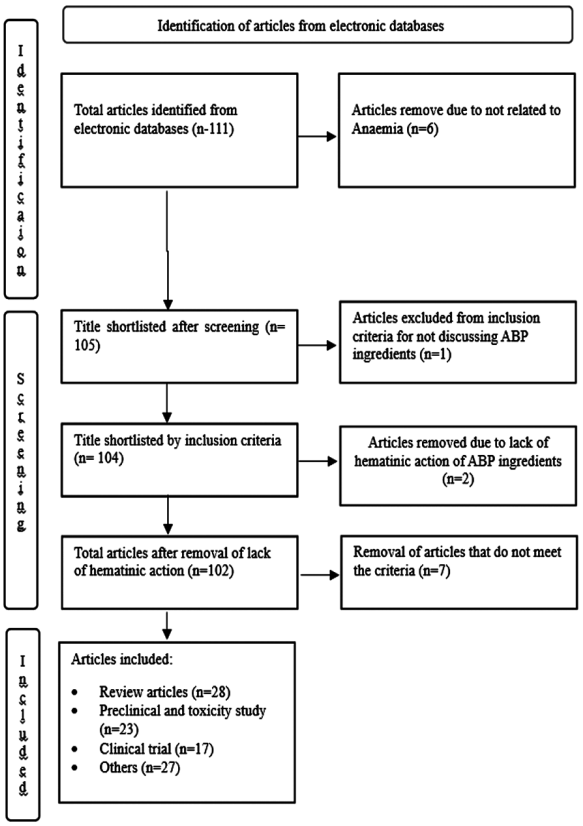

Fig. 1 — Flow chart showing the selection of articles for review.

glucose, 1,6-di-O-galloyl-beta-D-glucose, trigalloyl glucose, and quercetin[15].

E. officinalis is utilised in a Siddha traditional herbal formulation called *Triphala*, which includes *E. officinalis*, *Terminalia bellerica* (*Gaertn.*) Roxb. and *Terminalia chebula* Retz.[16]. *E. officinalis*, known as *Amla*, treats diseases such as anaemia, jaundice, fever, chronic ulcers, and constipation. The high amount of ascorbic acid (Vitamin C) in fruits is an essential nutrient, contributing to its efficacy as a natural cure for anaemia by facilitating better iron absorption[17].

Indumathy *et al.* demonstrated the anti-anemic potential of aqueous extract of *E. officinalis* using Wistar rats. The treated group received vitamin C and aqueous extract of *E. officinalis.*, when compared with the untreated animals in the negative control group, significant improvement in Hb levels was observed[18].

Akter *et al.* conducted an interventional study involving pregnant women to evaluate the efficacy of *E. officinalis*; 24 participants in the study group were supplemented with oral amolki (*E. officinalis*) capsules, iron tablets, and folic acid, whereas 19 participants in the control group received only iron tablets. The results revealed that the study group experienced a significant increase in serum iron levels and a significant decrease in serum TIBC levels compared with the control group[19]. Another study by the same author reported that *E. officinalis* could be the remedy for the side effects of iron supplementation in pregnancy. The pregnant women participants were divided into two groups: group A received both amla and iron supplements, and group B received only iron supplements; group B had higher rates of nausea, constipation, and hyperacidity compared to group A, which had no diarrhoea or constipation. Loss of appetite was prevalent in both groups[20].

Pandey *et al.* conducted an acute and chronic toxicity study in rats. The hydroalcoholic extract of *E. officinalis* was administered orally to different groups of rats at doses of 250, 500, and 1000 mg/kg. No mortality was observed for up to 48 h, indicating that the LD_{50} of *E. officinalis* extract exceeds 1000 mg/kg. Chronic toxicity was also assessed, and no significant observational effects were noted at any dose. The study concluded that *E. officiinalis* extract is a safe drug, which was evidenced by both acute & chronic toxicities[21].

Kapoor *et al.* highlighted amla's acceptable sensory and safety profiles, emphasising its substantial potential to promote a healthy lifestyle. Chronic toxicity studies involving oral doses of *E. officiinalis* 300,600, and 1200 mg/kg for 270 days showed no pathological changes in treated animals. Previous studies also reported no toxicity with fruit extract doses of 200, 400, 300, and 500 mg/kg[22].

Furthermore, Uddin *et al.* found that the ethanolic extract of *E. officinalis* is safe up to a dose of 2000 mg/kg body weight in rats, with no toxic effects observed in haematological, behavioural, motor, and neuronal functions[23]. Thiennimitr *et al.* reported that consuming *Lactobacillus* sp. mediated fermented *E. officinalis* fruit juice at doses up to 9 mL/kg per day for 60 days was safe in both male and female rats, with no adverse effects on body weight, internal organs, haematology, or biochemical parameters[24]. Table 1 shows the bioactivity of the phytoconstituents in *E. officinalis.*

***Eclipta prostrata*(L.)L.**

E. prostrata (L.) L., a member of the Asteraceae family, is a multi-branched plant that can grow up to 60 cm tall. The phytochemicals present in this plant

are wedelolactones[31-33], demethyl wedelolactone[31-33], eclalbatin, ursolic acid, olealonic acid, stigamasterol, and beta stigamasterol. It is recognised for its medicinal properties, particularly in the form of a plant powder, which is used to treat conditions such as anaemia, jaundice, and dropsy[34-36]. Additionally, *E. prostrata* is also beneficial in the treatment of numerous ailments and diseases, including hepatitis, snake venom poisoning, and antihaemorrhagic activity[37,38].

Mishra *et al.* performed a study to gauge the impact of aqueous or ethanolic extracts of the root of *Eclipta alba*(L.) on haematological variables in Asian catfish. Red blood cells, Haemoglobin, Packed cell volume (RBC, Hb, PCV), and corpuscle counts were increased significantly[39]. In a preclinical study, Rama *et al.* reported the potential of the extract of *E. alba* on phenylhydrazine-induced hemolytic anaemia in rats. Twenty animals were initially treated with phenylhydrazine at a dose of 10 mg/kg body weight for one week to induce hemolytic anaemia. Group I received distilled water and 1% gum acacia, while the other groups were treated with phenylhydrazine and then administered *E. alba* extract at doses of 125,250, and 500 mg/kg. The results indicated that *E. alba* significantly improved anaemia-related parameters, demonstrating the potential for anaemia recovery[40].

A clinical study further explored the efficacy of *karisalakanni chooranam,* which contains *E. prostrata* as its main ingredient. A total of 40 patients, both sexes, aged between 3 and 12 years, were treated with the compound formulation. The clinical symptoms of anaemia observed 50% good improvement, 32.5% moderate improvement, and 17.5% mild improvement, highlighting the potential therapeutic benefits of *E. prostrata* in this age group[41]. In a toxicity study, the safety of a compound formulation of *E. prostrata*, known as *karisalai chooranam*, was evaluated. A study, which included both acute and 90-day long-term toxicity trials, found that *karisalakanni chooranam* did not produce any harmful effects in animal experiments, indicating its safety for traditional medicinal use[42]. Table 2 shows the bioactivity of the phytoconstituents in *E. prostrata*.

Table 1 — Bioactivity of phytoconstituents of *Emblica officinalis Gaertn.*

Phytoconstituents	Class	Bioactivity
Gallic acid	Phenolic acids	Anti-inflammatory[25]
Phyllantidine	Alkaloids	Antioxidant[26]
Phyllantine		
Chebulic acid	Phenolic compound	Antiatherogenic[27]
Ellagic acid		Antimutagenic, antimicrobial, antioxidant[28]
Corialgin	Hydrolysable tannin	Anticancer[29]
Geraniin		Antioxidant[30]

***Zingiber officinale* Roscoe**

Ginger, a member of the *Zingiberaceae* family, has been utilised as a spice for over 2000 years[52]. In traditional practices, ginger is utilised in postpartum dietary routines[53]. The functional components of ginger enhance iron bioavailability and promote erythropoiesis[54], making it an effective addition to oral iron therapy for IDA supplements[55].

The major phytochemicals reported from *Zingiber offiicnale* Roscoe are 6-shogoal[56], 6-gingerol, zingiberol[57], *β*-phellandrene, *α*-Zingiberne, *β*-bisabolene[58], and other minor constituents like gingerenones A, B & C,isogingerenone B, gingerdiols, gingerenones, *α* and *β*-pinene, camphene,

Table 2 — Bioactivity of phytoconstituents of *Eclipta prostrate* (L.)L.

Phytoconstituents	Class	Bioactivity
Luteolin	Flavanoids	Antitumour[43]
Tricetin		Anticancer [44]
Diosmetin		Anti-inflammatory[45]
Eriodictyol		Neuroprotective[46]
Quercetin		Antimicrobial[47]
Kaempferol	Flavnol	Antibacterial[48]
Cholorogenic acid	Polyphenol compound	Mitigating the effects of cardiovascular disorders, diabetes mellitus, liver and kidney injuries[49]
Eclalbasaponins	Saponin	Anthelmintic[50]
Crinumaquine	Alkaloid	Inhibit the proliferation of epithelial cells[51]

sabinene, myrcene, limonene, 1-8-cineole, aliphatic alkanes, alcohols aldehydes, ketones and sulphides[59,60].

Subodh Kumar *et al.* reviewed inflammation as one of the main culprits of anaemia and its associated disorders. In this study, inflammation and the acute phase response interact with iron metabolism, leading to its dysregulation, resulting in anaemia. NF-κB activation is widely recognised as a primary mediator of inflammation in most diseases. *Z. officinale* is known for its potent NF-κB inhibitory action and suppression of COX2, 5-LOX expression, most likely through downregulation of NF-κB activation. Therefore, *Z. officinale* may serve as an anti-inflammatory agent by inhibiting the activation of NF-κB by suppressing pro-inflammatory cytokines[61].

In an *ex vivo* study, *Z. officinale* was identified as the most important spice to increase the absorption of iron; it increased iron uptake by 28.5±2.09% in the jejunum of rats compared to the control group, and an *in vivo* investigation was done for the effects of ginger on erythropoiesis in Zebrafish embryos. Ginger, with its bioactive components,8-gingerol, and 8-shogaol, promotes the expression of Gata 1(GATA-binding factor 1, a zinc finger transcription factor and key regulator of erythropoiesis) in erythroid cells through the bone morphogenetic protein (BMP) signalling pathway[62]. Kulkarani *et al*. conducted a clinical study involving two groups and demonstrated that ginger and iron supplementation were more effective in correcting anaemia than the control group, which received only iron tablets[63]. In a clinical study, aqueous ginger extract was administered to 68 male Saudi health workers, comprising 33 smokers and 35 non-smokers, daily for 21 days. Before consuming the extract, smokers had significantly lower mean neutrophil counts and higher mean RBC counts than non-smokers. During the study period, smokers experienced increases in the mean lymphocyte, RBC, and Hb levels, suggesting that ginger may be beneficial for smokers with anaemia. Additionally, non-smokers showed increased mean IgM levels, which could enhance humoral immunity against infections. Therefore, aqueous ginger extract had different effects on cells and antibodies of the immune system for both smokers and non-smokers[64]. In an acute toxicity study, no toxic signs and symptoms or mortality were observed in animals fed ginger extract (containing 8% total gingerols) at the maximum recommended dose of 2000 mg/kg body weight (LD50 >2000 mg/kg). In the subacute study, the repeated oral administration of ginger extract for 28 days at a maximum dosage of 1000 mg/kg did not induce any observable toxic effects compared with the control group[65]. Table 3 shows the bioactivity of the phytoconstituents in *Z. officinale*.

***Piper nigrum* L.**

P. nigrum L. is a perennial vine belonging to Piperaceae that may reach to a height of 4 meters, which contains the bioactive compound piperine, piperonal, piperoleine B, pipercide[71-73], N -*trans* feruloyltyramine, gunineensine, feruperine, dihydroferuperine, trachyone, pergumidiene, isopiperolein B, pellitorine, pipyahyine, (E)-beta-ocimene, delta-guaiene,(Z), (E)-farnesol, delta-cadinol, guaiol, alpha pinene, sabinenne, d-limonene, beta caryophyllene[74-77], dehydro retro fractamide C, retro fractamide A 1-piperylpyrrolidine 8 has been shown to enhance the effects of iron supplementation[78]. Combining iron and piperine significantly improves several parameters related to iron metabolism. Notably, *P. nigrum* contains approximately 8.5 mg of iron per unit, further supporting its role in hematinic formulations[79].

In a preclinical study, group I, which received a combination of bio iron and bio piperine as a single oral dose via a feeding tube, showed greater bioavailability than group II, which received only bio iron administered in the same manner[80]. Additionally, both *in vitro* and *vivo* studies have studied the potential of *P. nigrum* (piperine) to attenuate the over-expression of hepcidin, thus preventing the diseased condition of anaemia caused by inflammation[81]. In a clinical study on iron deficiency anaemia with bio iron demonstrates the hematinic potential of bio iron (900 mg of bio iron containing 8.5 mg of elemental

Table 3 — Bioactivity of phytoconstituents of *Zingiber officinal*e Roscoe

Phytoconstituents	Class	Bioactivity
Zingiberol	Sesquiterpene alcohol	Anti-cancerous[66]
Beta bisabolene	Sesquiterpene	Cytotoxicity against cancer cells[66]
Gingerdiols	Phenols	Antimicrobial, anti inflammatory[67]
Shogaol	Phenol	Antioxidant[68]
α-Pinene	Monoterpene	Anti-inflammatory, antimicrobial[69]
Farnesol	Alcohol	Apoptotic[70]

iron and 2.5 mg of bio piperine) taken twice a day before meals as a dietary supplement for 56 days. Treatment of IDA with bio iron resulted in a significant increase in hematologic values[82]. Acute and subchronic toxicity were evaluated, and the acute toxicity study in rats was divided into two groups: the treated group received a single oral dose of 5000 mg/kg body weight of the aqueous extract, while the control group received only water. In sub-chronic toxicity, treated groups of each sex were orally given the extract of 300, 600, and 1200 mg/kg body weight daily for 90 days. The observations revealed that the water extract of *P. nigrum*, did not produce significant damage in the internal organs, however, it was concluded that it does not produce any acute or subacute toxicities in male and female rats[83]. Table 4 shows the bioactivity of the phytoconstituents in *P. nigrum*.

***Piper longum* L.**

Piper longum L. is a small, perennial, aromatic shrub and climber belonging to the Piperaceae family. It contains several bioactive constituents such as piperine, piperlongumine (piplartine[90]), piperlonguminine, and also methyl 3-4-5-trimethoxycinnamate[91], sesamin, lignin, *α*-thujene, terpinolene, zingiberine, *p*-cymene, L-tyrosine, L-cysteine hydrochloride[92], sylvatine, and dieudesmin, palmitic, stearic, arachidic and behenic acids[93].

Piperine has been shown to improve the therapeutic efficacy of numerous drugs, vaccines, and nutrients by enhancing their oral bioavailability through the inhibition of various metabolising enzymes. Piperine stimulates pancreatic and intestinal enzymes, which aid in digestion[94].

Table 4 — Bioactivity of phytoconstituents of *Piper nigrum* L.

Phytoconstituents	Class	Bioactivity
Limonene	Monoterpenes	Anticancer[84]
α-phellandrene		Antimicrobial[85]
β-Myrcene		Anticancer[86]
α-cadinol	Terpenoids	Antioxidant[87]
Nerolidol	Sesquiterpenes	Antibacteria[88,89]

A clinical study was conducted over 45 days with three groups: group A received two 500 mg capsules of *P. longum*, group B received 125 mg capsules of Lauha bhasma(LB), and group C received both *P. longum* and LB. The results showed that group C had significantly better outcomes compared to groups A and B. *P. longum* enhances the efficacy of LB in Hb deficiency[95].

In a clinical study involving 39 patients, with group A administered *Thippili chooranam* and group B *Vasa churna*; 90.48% group A patients did not develop any adverse events or reactions during therapy[96].

An acute toxicity study on albino rats administered the test drug at a maximum dose of 5 times higher (3750 mg/kg) than the therapeutic equivalent dose (750 mg/kg); no mortality was observed in any of the groups. In a sub-chronic toxicity study conducted over 45 days in two groups receiving therapeutic-equivalent doses (750 mg/kg) and three times the therapeutic dose (2250 mg/kg), no significant changes were observed in important biochemical parameters. Based on the findings, it was suggested that *P. longum* has no serious toxicity potential at the dose level studied for an extended period[97]. Table 5 shows the bioactivity of the phytoconstituents in *P. longum*.

***Terminalia bellerica* (*Gaertn.*) Roxb.**

Terminalia bellerica (*Gaertn.*) Roxb. is a tree belonging to Combretaceae, commonly found throughout the Indian subcontinent, characterised by its large deciduous species, recognised by its buttressed trunk and thick, brownish-grey bark with shallow longitudinal fissures, and upon reaching maturity, it typically grows to a height of 20 to 30 m tall[102]. The major constituents of the fruits are 20 to 30 per cent tannins like gallic acid, ellagic acid, ethyl gallate, chebulagic acid[103], bellericannin, phyllemblin[104], termilignan, thaninilignan,7-hydroxy-3',4'–(methylenedioxy) flavan, and anolignan B[105].

Jegadeesan presented a straight forward approach for the biogenic synthesis of iron (Fe) nanoparticles using aqueous extracts derived from various plant sources, notably *T. bellerica* fruits, *Moringa oleifera*

Table 5 — Bioactivity of phytoconstituents of *Piper longum* L.

Phytoconstituents	Class	Bioactivity
Pipercide	Unsaturated amides	Antiviral[98]
Pellitorine	Alkaloid	Anticancer[98]
Piper longum Blume.ine		Anti-inflammatory[99]
Piperidine		Inhibition of choline esterase receptors[100]
Brachystamide A	Alkamide	Dendrite elongation inhibition[101]

Lam. fruit, and *M. oleifera* leaves. Examination of Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) images unveiled distinct characteristics of the synthesised iron nanoparticles. Particles synthesised from *T. bellerica* exhibited a uniform spherical morphology, with an average size of 21.32 nm. XRD analysis further confirmed the presence of hematite and ferric oxyhydroxide phases within the synthesised Fe nanoparticles. Significantly, *T. bellerica* extract demonstrated the highest antioxidant activity among the extracts tested[106].

In a preclinical study, *T. bellerica methanol exract* (TBME) exhibited the capability of reducing iron chelation. This extract effectively reduced toxic iron levels in mice with iron overload, thereby protecting against oxidative stress and liver fibrosis. Additionally, the administration of TBME resulted in notable reductions in serum ferritin and serum enzymes, which serve as key indicators of serum iron overload. These findings highlight the potential of TB extract as a therapeutic agent for managing iron-related disorders and mitigating associated liver complications[107].

In a toxicity profile study with female Wistar albino rats, a single acute dose of the aqueous extract of *T. bellerica* was given at levels up to 2000 mg/kg body weight. Throughout the study, no significant alterations were observed in the food and water intake or behaviour patterns of the treated animals. No abnormalities were found on relative organ weight, biochemical parameters, haematological parameters, and histopathological analysis. The gathered data suggest that the aqueous extract of *T. bellerica* fruit is safe for use. It's effectively used in traditional polyherbal formulations due to its antioxidant properties and other health benefits. This study confirms that *T. bellerica* is safe for use in herbal remedies[108]. Table 6 shows the bioactivity of the phytoconstituents in *T. bellerica*.

Table 6 — Bioactivity of phytoconstituents of *Terminalia bellerica* (*Gaertn.*) Roxb.

Phytoconstituents	Class	Bioactivity
Belleric acid	Terpenoid	Antispasmodic and broncho dilatory[109]
Rhamnose	Glycosides	Anti-inflammatory[110]
Termilignan	Lignans	Anti-malarial[111]
Bellericoside	Saponin	Wound healing[112]
Quercetin and Kaempeferol	Flavanoids	Antithrombotic[113]

***Terminalia chebula* Retz.**

Terminalia chebula Retz., a medium-sized tree used in traditional medicines, belongs to the family Combretaceae. The major phytochemicals reported from *T. chebula* are tannins (20 to 40 per cent), which on hydrolysis give chebulic acid and a D-galloyl glucose, chebulagic acid, ellagic acid, gallic acid, a tannin terchebin[114], an ellagitannin terchebulin, syringic and gallic acids. The protective effects of the 5% ethanolic extract of *T. chebula* against liver damage caused by anti-tuberculosis drugs were linked to its strong antioxidant and membrane-stabilizing properties[115].

In *kadukkai mathirai, kadukkai*, as the main ingredient, combined with various herbs to improve oral bioavailability, reduced the adverse effects of iron and was regarded as a safe drug due to heavy metal levels within acceptable limits[116].

In the preclinical trial focusing on *T. chebula*, the study investigates the protective effects of *T. chebula* methanol extract (TCME) against iron accumulation and oxidative damage in the liver of mice with iron overload in the *in vitro* iron chelation. It is evidenced by its ability to bind iron ions effectively. *In vivo*, findings indicate that administering TCME to iron-overloaded mice significantly restores antioxidant enzyme levels. These findings highlight the potential therapeutic benefits of TCME in mitigating iron-related oxidative stress and its associated complications[117].

In a clinical study on *T. chebula*, three groups were examined: the first group received 3 g of *T. chebula*, the second group received the same dosage of *T. chebula* and an equal quantity of jaggery, a traditional sweetener, for the same duration, and the control group received a placebo, administered as one capsule daily for 30 days. Haemoglobin values were measured before and after treatment for each group. The results were highly significant in groups A (76.08%) and B (68.01%) and insignificant in group C (7.70%). The clinical investigations shed light on the potential benefits of *T. chebula* supplementation, particularly, it enhanced Hb levels and signs[118]. Table 7 shows the bioactivity of the phytoconstituents in *T. chebula*.

Table 7 — Bioactivity of phytoconstituents of *Terminalia chebula* Retz.

Phytoconstituents	Class	Bioactivity
Tannins	Polyphenol	Antioxidant[119]
Chebualagic acid	Benzopyran tannnin	Immunomodulator[119]
Ellagic acid	PPhenol	Anti-inflammatory[120]
Gallic acid	Polyphenol	Antioxidant[121]
Syringic acid		Antimicrobial[122]

***Ayam* (Iron)**

In iron deficiency anaemia, the primary indication is to supply the necessary material for hemoglobin synthesis[123]. Iron, commonly referred to as Ayam in Siddha literature, can serve as a primary ingredient in various anaemia-related medicines. It is considered one of the *panchalogam* (group of five basic metals). The therapeutic use of iron in the Siddha system of medicine has been documented for many centuries in classical Siddha texts. Iron-based formulations are commonly used to treat conditions like anaemia, jaundice, ascites, etc. Some of the Siddha formulations made from iron include *Aya parpam, Aya chenduram, Aya veera chenduram, Aya kantha chenduram, Aya mezhugu, Aya bringha raja panitham, Aya jambira karpam, and Aya bringha raja karpam*. *Ayam* refers to iron, which is astringent, mildly sour, and bitter, with a hot potency and pungent biotransformation. *Bavanai ayam* (purified iron powder was soaked in herbal juice over an extended period) is used for ABP preparation[18].

Kanmani evaluated the hematinic activity of *Aya chenduram*. The study included two groups of five subjects each. Group I, which received the trial drug, showed an increase in haemoglobin levels compared to the control group[124]. The clinical trial involved 50 anaemic antenatal mothers at the MCH centre in Poonamallee. Participants were tested for their haemoglobin levels before and after one month of daily treatment with 200 mg of *Aya chenduram* with honey. The pre-test haemoglobin level was 63.5%, which increased to 82.5% post-treatment, showing a 19% enhancement. The paired t-test confirmed a significant improvement in haemoglobin levels, indicating the effectiveness of Siddha treatment for anaemia in antenatal mothers[125].

Selva Deepa described the efficacy of *Aya bringaraja karpam.* The result showed that the group treated with the trial drug at a dose of 100 mg/kg body weight had a significantly higher mean outcome (11.2±0.2) than the control group (6.24±0.3). This indicates that the trial drug was more effective than the control treatment over the five-week treatment[126].

The toxicity study was carried out to evaluate the immediate and long-term toxic effects on *Ayapodi ilagam*and to determine the LD_{50}. In the acute toxicity study, no significant toxicity was observed in albino rats at a dosage of 5000 mg/kg body weight. Throughout the study period, no pathological changes were observed in the internal organs, ensuring the safety of the *Ayapodi ilagam*[127].

Discussion

ABP is an effective herbomineral formulation for managing iron-deficiency anaemia across all age groups, including paediatrics, geriatrics, and adults. ABP does not require any adjuvant for enhanced absorption in the body. Additionally, honey and palm jiggery make it palatable and suitable for all age groups[18]. Table 8 briefly summarises the synergistic actions of each ingredient in ABP, which contribute to its therapeutic potential for treating IDA. These ingredients boost the efficacy of ABP in reducing the burden of IDA in different dimensions, highlighting this as a unique formulation.

Siddha perspectives

Siddha has a different view on the role of ABP in reducing anaemia, which is primarily directed towards *Azhal kutram*. This concept is related to the mechanism and absorption of iron in the gastrointestinal tract through the processes of *Anal pitham* and *Ranjaga pitham*[18].

Of the seven herbal ingredients, kadukkai, chukku, karisali, nelli, and milagu are kaya karpa medicines known for their rejuvenating effects. Drugs such as *P. longum Blume.*, *P. nigrum*, and *Z. officinale* Roscoe. have appetiser, carminative, and digestive properties, improving digestive power and ultimately absorption of the drug. Components like *kadukkai* act as laxatives that help in relieving habitual constipation, mainly found in children. *Kadukkai, nellikai,* and *karisalai* were mentioned as *kuruthiperuki mooligai* (haematinic property drugs) in various Siddha literature. ABP drugs are immunomodulators with antioxidant properties, and have the potential to provide beneficial health benefits[18].

The Siddha system of medicine is unique due to its use of metals and minerals in its formulations. The ingredients of ABP are very effective for treating anaemia, especially Ayam, which is considered safe for long-term use. The ferric and ferrous fractions of *Ayam* provide sufficient iron needed for normal erythropoiesis[18]. Studies have shown that *Ayam* contains various forms of iron, including magnetite (Fe_3O_4). Raw iron and processed (*Bavanai*) iron were compared, and it was found that processed iron samples contained carbon, oxygen, and iron

Table 8 — Traditional uses and actions of the ingredients of ABP in IDA

S. No.	Name of the ingredient	Siddha classical uses	Siddha medicines	Actions of the ingredients in this formulation
1	*Emblica officinalis Gaertn.*	Laxative, diuretic. It is indicated for sinusitis, vomiting.	Nellikai legium, thiripala.	Contains vitamin C and enhances the iron absorption[17].
2	*Eclipta prostrata* (L.)L.	It is indicated for anaemia, Hair growth, eye diseases.	Karisalai legium, kaiyan thylam.	Haematinic, improved anaemia-related parameters, demonstrating the potential for anaemia recovery[40].
3	*Z. officinale* Roscoe.	Carminative, good appetizer. It is indicated for anaemia, dysentery, indigestion.	Soubagya suundi.	It helps in absorption of iron, reduces inflammation, supports erythropoiesis[61,64].
4	*Piper nigrum* L.	Antidote, carminative, antiperiodic. It is indicated for gastritis, anaemia, jaundice, common cold.	Thirikatuku.	It helps in absorption of iron, metabolism of iron, supports haematinic action[79].
5	*Piper longum* L.	Carminative. It is indicated for cough, cold, bronchial asthma, anaemia.	Thipili rasayanam.	It helps in digestion. Improves blood health, enhances the production and quality of blood cells[95].
6	*Terminalia bellerica* (*Gaertn.*) Roxb.	Astringent, tonic, expectorant It is indicated for cough, cold.	Thiripala.	Reduces iron chelation, iron overload, increases Hb[107].
7	*Terminalia chebula* Retz.	Laxative, anti obesity drug. It is indicated for anaemia, anasarca, eye diseases, hypertension, indigestion.	Thiripala, kadukai mathirai, kadukai legiyum.	A laxative, it activates the bowel and reduces constipation. It has protective effects against iron accumulation and oxidative damage in the liver with iron overload[117].
8	Ayam (Iron)	Astringent It is indicated for anaemia, anasarca, jaundice.	Aya parpam, Aya chenduram, Aya sambira karpam.	Haematinic[124].
9	Pam jagggery	Enhances strength. It is indicated for anaemia.		Improves Hb levels in individuals with IDA. This supplementation offers a tasty and cost-effective alternative that lacks the significant adverse effects seen with oral and parenteral iron preparations, potentially improving compliance, particularly among children[128].
10	Honey	Improves general health, good for digestion.		Increases haemoglobin levels in mothers post-Caesarean section. Honey contains iron (Fe), an essential micromineral, supports red blood cell function and heme synthesis, and helps in increasing haemoglobin levels[129].

pentacarbonyl [$Fe(CO)_5$], and in the raw iron sample, $Fe(CO)_5$ was absent[18].

Pharmacological action of ABP

In a scientific view, natural polyphenols are abundant in *Z. officinale*, these bioactive polyphenols are prebiotics that support gut microbiota. These compounds promote gut health and reduce the unwanted side effects of iron tablets. The effectiveness of erythropoiesis can be enhanced by ginger polyphenols. The phytoconstituents of ABP are known for their biological activities that target various mechanisms related to anaemia and its associated complications. For instance, gallic acid and chebulic acid are antioxidants with anti-inflammatory properties that help reduce oxidative stress, a common factor associated with anaemia. Phyllantidine and luteolin aid in nutrient supply and enhance the absorption of red blood cells, while belleric acid and rhamnose play an essential role in promoting cardiovascular health and enhancing blood circulation. The tannins present in ABP are potent antioxidants and exhibit antimutagenic properties, helping protect cells from damage and supporting the body's hematopoietic processes. Zingiberol, tricetin, and diosmetin exhibit anti-thrombotic and wound-healing properties that are beneficial in managing complications related to blood health. It is highly effective not only in treating anaemia but also in preventing and managing aggravating conditions of anaemia[68-70].

Ferri-Lagneau *et al.* reported that ginger may contain constituents that activate the erythropoietic system to produce red cells. Iron supplements have various side effects like heartburn, nausea, upper gastric discomfort, constipation, and diarrhoea. Dry ginger has emerged as an alternative therapy and digestive aid, so it may overcome the problems related to the side effects. Also, as an antioxidant agent, it helps to reduce oxidative stress caused by allopathic iron supplements. It was concluded that dry ginger aids in iron absorption and proves beneficial as a supplement in the treatment of anaemia[130].

Role of individual compounds of ingredients

Majeed Vaidyanthan *et al.* described that BioIron (elemental iron with piperine) improved serum iron, total Iron Binding Capacity and serum ferritin levels significantly[131]. Diego Fernandez *et al.* explored the impact of combining iron with *P. nigrum* in physically healthy individuals. Athletes have a high risk of iron deficiency and often require iron supplements to maintain adequate iron levels. However, oral iron tablets can cause Gastro Intestinal Tract side effects, reducing tolerance and adherence to treatment. Piperine, a compound found in pepper, may enhance iron absorption by increasing its bioavailability, potentially alleviating these side effects and improving the effectiveness of iron supplementation[132]. Iron chelation and hepatoprotective nature of *T. bellerica* and *T. chebula* contribute to its effect in IDA. The presence of vitamin C in *amalaki*, facilitates the conversion of ferric to ferrous form, thus maintaining ferrous salts in a soluble state for better absorption. Phytochemicals present in *E. officinalis* might help reduce gastrointestinal side effects caused by iron supplements. In a preclinical study, *P. nigrum* extract enhanced the absorption and bioavailability of the nutrients. Potential ligands from *T. chebula* were screened and docked against the inflammatory molecules, which are responsible for stress-induced anaemia[132].

Research gap and recommendations

Adverse effects are common with iron preparations used in modern medicine, particularly epigastric pain, nausea, vomiting, staining of teeth, metallic taste, blotting, and constipation. These adverse effects often restrict the usage of iron tablets. Although the therapeutic iron dose is lighter, the daily requirement is 1 to 2 mg orally. Herbo-mineral drugs like ABP provide an effective therapeutic option[133].

T. chebula, *P. nigrum*, and *E. prostrate* are the ingredients of ABP that have been shown to significantly increase gastric emptying and act as an apokinetic agent. *P. longum*, *E. alba*, and *E. officinalis* acts as liver tonics. *E. officinalis*, which contains ascorbic acid, doubles the oral iron absorption in the intestinal tract. This supports ABP to treat iron deficiency anaemia.

Iron absorption is significantly influenced by its physical state, particularly whether it is in the ferrous (Fe^{2+}) or ferric (Fe^{3+}) form. Ferric ion tends to precipitate in solutions with a pH above 3, while ferrous iron remains soluble even at neutral pH levels. Therefore, ferric iron must first be solubilised and chelated in the stomach[133]. To be absorbed in the less acidic proximal small intestine, this chelation process occurs quickly with the help of other components in ABP, which is prepared by using *Aya chenduram*, and facilitates the release of iron in the intestinal lumen. These chelators may act as enhancers or inhibitors, influencing the absorption of nonheme iron. Therefore, it appears more beneficial to use *Aya chenduram* for preparation instead of regular iron. Alpha iron oxide also known as hematite, is easily absorbed and has more potential than regular iron forms. Generally, Fe^{2+} is better absorbed than Fe^{3+} as Fe^{2+} is more soluble in the duodenum, where most iron absorption occurs. Additionally, the herbal constituents enhance the absorption of iron[134].

The presence of ascorbic acid in the *nellikai, kadukkai*, and *thippili* enhances the absorption of non-heme iron. Ascorbic acid facilitates iron absorption by forming a chelate with Fe^{3+} in the stomach's acidic environment, which remains soluble in the alkaline pH of the duodenum, the first part of the small intestine. In addition, ascorbate (ascorbic acid salt) donates an electron, acting as a free radical scavenger and reducing iron from its Fe^{3+} to Fe^{2+}state. Fe^{2+} is the only form of iron that iron transporters of intestinal enterocyte cells can absorb[135].

A previous study was conducted on a public health initiative to address anaemia among adolescent girls in Virudhunagar district, Tamil Nadu, India. As part of this program, 14,179 adolescent girls were screened, and 3,783 were found to be anaemic. Among these 2,648 girls agreed to undergo Siddha medicine. They were administered a 45-day supplementation consisting of *Annapethi centuram*, *Bavanai katukkay*, *Matulai Manapaku*, and *Nellikay lekiyam* (ABMN). A total of 2300 girls from rural, low-income, and poor sanitation backgrounds

completed the treatment. The ABMN treatment reduced the clinical features of anaemia, such as fatigue, hair loss, headache, loss of interest, etc. Additionally, it improved menstrual irregularities and increased haemoglobin levels as well as PCV, MCV, and MCH levels in all categories of anaemic girls[136].

Based upon these findings, it is essential to conduct similar research for the ABP treatment. Randomised controlled trials comparing ABP with modern iron tablets are required to understand the rationale of using ABP in iron deficiency anaemia. Additionally, RCTs may provide evidence to prove that ABP is patient-friendly and also serve to validate traditional Siddha medicine claims about its efficacy. This literature review revealed a lack of existing research on ABP, therefore, an attempt was made through this research to collect and analyse the clinical, preclinical, and toxicity profiles of each component of ABP, which can shed light on the pharmacological action of the medicine as such. In contrast, the phytochemicals in each ingredient might transform into chemically different artefacts when preparing the formulation by mixing and following different processes like powdering, boiling, concentrating, etc. Owing to the synergistic action of the master mix of all the phytochemicals, the pharmacological action cannot be simply predicted with the established action of phytochemicals of each ingredient of the formulation.

Conclusion

The ingredients of *Aya bringaraja panitham* have been proven to enhance the absorption of iron and ensure its delivery to the necessary sites, and it is easily palatable. In ABP, *ayam* is the main ingredient; in modern medicine, iron deficiency anaemia can be treated with elemental iron supplementation; however, improvement in Hb levels is often limited due to intolerance, non-compliance with iron tablets, and poor absorption. Consequently, ABP can be effectively used to manage anaemia and related conditions. Additionally, all the formulation's ingredients possess anti-inflammatory, hepatoprotective, and antioxidant properties, significantly improving health and quality of life.

Acknowledgement

The Authors are thankful to the Central Council for Research in Siddha, Chennai, for funding the project (F.No.1-117/2022-23/CCRS/Tech./IMR dtd 22.12.2023).

Conflict of interest

The authors declare that there is no conflict of interest.

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