

# Threatened Ayurvedic Herb (Seeta Ashoka) Substitution Options for Menorrhagia-based on Bioactive Principle's Molecular Docking Study

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## ABSTRACT

Molecular docking studies are used to identify cultivated/ abundant herbs such as Coriander, Burmuda grass or Asparagus as potential replacement for Seeta Ashoka- *Saraca asoca* (Roxb.) De Wilde, syn. *S. indica* Linn. a rare Indian medicinal forest plant, threatened with extinction due to over harvest. Its bark is used to make the famous Ayurvedic medicine "Ashokarishta" to treat menorrhagia and as a uterine tonic like ergot but is mostly adulterated. We tested using molecular docking studies Quercetin and other polyphenols from Coriander as potent anti-inflammatory ingredients, similar to NSAID (Non-steroidal anti-inflammatory drugs)., *Polyalthia longifolia*, the common adulterant is also be noted to be effective

as its bark contains 30-50% of tannin than *Saraca asoca*, so may help in thrombosis.

**Keywords:** Herb, Ayurveda, Menorrhagia, Polyphenol, *In silico*.

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## INTRODUCTION

Menorrhagia i.e. heavy menstrual bleeding (HMB) and related endometriosis including Pelvic inflammatory disease (PID) is a common ailment that haunt among 20-30% middle age women- aged 30 to 50 in USA<sup>1</sup> and similar levels in Europe,<sup>2</sup> China<sup>3</sup> and India.<sup>4</sup> Modern medicine has limited or costly and complex treatments and with adverse drug reactions (ADR) so herbal or traditional medicines continue.<sup>1</sup> These consist of daily oral dose of 2-3 teaspoon of decoction/ syrup as an easy remedy and prevail world-wise with different herbs. The tree Seeta Ashoka {*Saraca asoca* (Roxb.) De Wilde}, occurs streamside in wet forests in south Asia and its bark is a very effective traditional medicine across south Asia<sup>4,5</sup> which is used to prepare the famous Ayurvedic product "Ashokarishta". It is also an ingredient in many other Ayurvedic medicines for many diseases and is among the top 30 raw drugs though is very rare and is threatened with extinction vide IUCN criteria.<sup>6</sup> We examine here the active ingredients of its main substitutes based on literature to identify the most suitable candidate for further clinical studies. We also conducted molecular docking study of potent phytochemicals in it and its likely substitutes.

Growing herbal trade has threatened species and led to their substitution (legitimate options) or adulteration. It is a common and major problem in the Ayurvedic industry, with over 100 important traded medicinal plants in India at risk.<sup>6-7</sup> Ayurvedic pharmacopeia consists of about 2,000 species while folk medicinal traditions records consists of 7,500 species of flowering Plants used medicinally. Hence we aim to find out substitute plants having similar properties and effects and propose a methodology for other threatened species.

The main constraint in including new species to Ayurvedic pharmacopeia is the difficulty to identify *Tridosha* (i.e. peculiar person and disease

specific combination of 3 humors- Kapha, Pitta and Vata akin to solid, liquid and gaseous resp.) profile due to absence of an established, clear methodology. There is an unworked USA patent<sup>8</sup> on - Tridosha profiling of new herbs using chromatography. There is also DNA based method invented by Gujarat Ayurveda University<sup>9</sup> but its costly. Human experiment are also attempted and found useful<sup>10</sup> but are time taking and complex. Hence simulation based on phytochemical profiling may offer a reasonable, affordable and initial step for further research as exemplified here with Seeta Ashoka.

Seeta Ashoka is a threatened tree in the wet evergreen forests of the Western Ghats and also sparsely found in Eastern Ghats. Its found even in Sri Lanka or South East Asia, through some consider the later as distinct species and is amongst the top anti-oxidant activity and phenol content herbs in south east Asia.<sup>11</sup> It is used mainly for treating menorrhagia and as uterine tonic for smooth birth process. It is used as spasmogenic, oxytocic, uterotonic, anti-bacterial, anti-implantation, anti-tumour, anti-progestational, anti-estrogenic. Its main active ingredients are epicatechin, gallic acid, pro-anthocyanidin, besides epigallocatechin-3-gallate (EGCG) and these regulate progesterone.<sup>12</sup> It also contains Beta-sitosterol, which is used as aphrodisiac, tonic, anti-inflammatory, analgesic, menopause, wounds and burns (all related to gynaecological health) besides enlarged prostate, immunity booster, cancer relief, psoriasis, reduce cholesterol, gallstone.<sup>13</sup>

Seeta Ashoka leaf also contains similar chemicals and properties so can substitute its bark.<sup>14</sup> However, Ashoka is a slow growing tree and even leaves cannot suffice the large and ever-growing demand. Hence, finding other abundantly available tree species and their bark is necessary. False Ashoka i.e. Mast tree (*Polyalthia longifolia* L.), Sal (*Shorea robusta*

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Gaertn.) are its commonly used adulterants comprising perhaps most of the raw drug.<sup>15</sup> They have also been shown to possess comparable chemical profile viz. polyphenols and B-Sitosterol.<sup>16-17</sup> National Botanical Research Institute in India mentions False Ashoka to contain tannins to the extent of 30% of Sita Ashok and responsible for its medicinal effects.<sup>18</sup> Kerala Agriculture University study claims that the former contains 50% of the tannin of the later<sup>19</sup> and hence may be effective partly or in large dosage/ longer term. Tannin is known to be a hemostatic agent.<sup>20</sup> Hence, the Ashokarishta may be effective and popular despite adulteration and Mast tree may be effective unlike presumed.

Among the potential substitutes to Ashoka bark in Ayurveda, coriander is a promising remedy mentioned in Ayurveda texts<sup>21</sup> and industry portals.<sup>22-23</sup> So its active ingredients were assessed for potential medicinal effects with respect to menorrhagia.

## MATERIALS AND METHODS

We adopted a 2-step approach to test common/ cultivated plants having similar (bio-) active ingredient with the Seeta Ashoka,

- Find the main active ingredient in the rare herb and other commons/ cultivated with similar compound based on literature search, mainly those already listed in Ayurvedic pharmacopeia, and not endangered and conduct *in vitro* and *in vivo* tests, including molecular docking studies.
- Compare Dravya-guna profile of such substitute candidates and if it matches with the threatened species, provide pharmacopeia references for assessment by the pharmacopeia committee/ clinical trials to validate it.

We studied important spice chemicals in terms of molecular docking (done at Rasa Life Science co., Pune city- www.rasalsi.com), to find most powerful anti-inflammatory agent to address cyclooxygenase (COX)-2 as it is considered desired target<sup>24</sup> and active site with PDB id 5IKR was studied. The ligands selected are well known active ingredients i.e. "bioactive molecules"- Black pepper (Piperine), Clove (Eugenol), Coriander (Apigenin, Quercetin), Fenugreek (Diosgenin), Ginger (Gingerol and Shagaol), Turmeric (Curcumin).<sup>25</sup>

## RESULTS

Piperine and quercetin are the best molecules with binding energy of -9.99 Kcal/mol and -9.94 resp. as anti-inflammatory agent as seen in Table 1, while Apigenin follows closely (-9.63). But pepper has hot properties while Coriander balances all Doshas and especially Pitta and Vata that are aggravated in menorrhagia (Table 1). Turmeric (Cucumin) is the next best option (-8.66 kcal/ mol) while Ginger, Fenugreek and Clove active ingredients reflected subcritical energy below the threshold of 8, though used traditionally for joint pain relief.

The Dravyaguna profile of Ashoka and its likely options is similar as seen in the Table 2.

## DISCUSSION

S. V. Lal opined in 1953 that both the plant *Saraca indica* and *Polyalthia longifolia* contain two pharmacologically active fractions with similar action on pain muscles like ergot, but the mode of action of the stimulant fractions is different.<sup>26</sup> He concluded that the stimulant fraction of the former acts by liberation of acetylcholine, while the latter acts directly on the muscle fiber. Others also described its pharmacological action.<sup>27-29</sup> We just focus here on menorrhagia, the commoner condition, not other related gynecological conditions.

Some other potential substitutes mentioned for Seeta Ashoka are too rare and hence, unviable for industry e.g. Nagkesar- *Mesua ferrea* L.<sup>29,6</sup> a large, rare tree in the Western Ghats forest. Similarly, another tree

**Table 1: Docking Study Results- (PDB id 5 IKR).**

Spice	Ingredient (no of conformations)	Site activity (interactions)	Binding energy (Kcal/ mol)	Remark
<b>A) High Scope</b>				
Pepper	Piperine (53)	SER530 and ARG 120 (2)	-9.99 (very low)	High probability, Stable
2. Coriander	Quercetin (34)		-9.94	
	Apigenin (20)	TRP 387 and ASN 382 (2)	-9.63 (very low)	
Turmeric	Curcumin (35)	TYR 385- good activity (1 interaction)	-8.66 (very low)	
<b>B) Low Scope</b>				
Ginger	8-shogaol (40)	Amino acid residues- SER530 and MET522 (2)	-7.51 (very low)	Stable, good activity, high prob.
	6. 10- Gingerol (40)	TYR385- Good activity (1 interaction)	-7.34 (very low)	
Fenugreek	Diosgenin (20)	HIS214 (outside site)	-6.80	outside, not feasible
Clove	Eugenol (13)	TRP 387 and TYR385.	-6.33	stable, high probability

found effective on mice trial is *Kingiodendron pinnatum*<sup>29</sup> is a rare tree, endemic to the Western Ghats,<sup>6</sup> and slow growing, so is commercially unviable. Also, tree or bark is harvest prohibited by southern Indian forest departments and can't be traded (openly). The article also lacks information on its active ingredient and mode of action. Other options of Ashoka tree used in the market are *Aphanmyxis polystachya* (Wall.) Parker and *Caesalpinia pulcherrima* ] but these are rare too.<sup>6,29</sup> Arya Vaidya Shala, Kotakkal found experimentally that Sal (*Shorea robusta* L.) is the best option for Seeta Ashoka pharmacologically.<sup>15</sup> It also belongs to the same "gana" of 10 herbs with similar properties and can be used interchangeably (named "Kashayaskanda, vedanastahpana" cf Charakasamhita) as per Ayurvedic pharmacopeia<sup>30</sup> with properties such as "Grahi- Styptic, Shoshahara- avoids wasting/ depletion of tissues, Shotajit- relieves inflammation, Asrajit- checks excessive menstrual bleeding". But as its a forest tree, so its bark harvest may face restrictions. Alternatively, it can be bought officially from the timber depots in northern Indian forest departments where it is common in the forests. This can comply with the Indian biodiversity law, 2000 that requires disclosure of legitimate source of the raw material (to ensure sustainability), an ignored provision of the law.<sup>31</sup> Kerala Forest Research Institute (KFRI), Peechi studied Ashoka options *in vitro* and *in vivo* and found *Polyalthia longifolia* to be also effective in mice model.<sup>32</sup> Other aforesaid species that they studied are all wild and rare/ endemic so their harvest is untenable. *Polyalthia longifolia* is also rich in flavanoids and Calcium and thus may be very effective against inflammation and is common roadside and garden tree so amply available.<sup>33</sup>

Coriander (*Coriandrum sativum* L.) has similar profile as Seeta Ashoka vide Table 2 and is used to treat inflammatory, pain hot skin conditions<sup>34,35</sup> and is commonly grown globally, It is a popular food, so it is safe, but its routine consumption may be sub-optimal for medical effect (1,200 mg/ day). Hence, its special decoction is advised by experts or herbal industry to

**Table 2: Ayurvedic profile of Ashoka and its Options.<sup>42</sup>**

Attributes	Seeta Ashoka	Mast tree AshoK	Sal	Dhanyaka	Dub	Satavar
Botanical name	<i>Saraca asoka</i>	<i>Polyalthia longifolia</i>	<i>Shorea robusta</i>	<i>Coriandrum sativum</i>	<i>Cynodon dactylon</i>	<i>Asparagus racemosus</i>
Rasa [Taste]	Kashya [Astringent], Tikta [Bitter]	Tikta [Bitter], Katu [Pungent]	Kashaya [Astringent]	Dry- tikta, Kashya, Fresh-Madhura	Madhura [sweet] Kashaya [Astringent]	Bitter, Sweet
Guna [Properties]	Laghu [Light], Ruksha [Dry]	Laghu [Light], Ruksha [Dry]	Ruksha [Dry]	Laghu [light], Snigdha [oily]	Laghu [light]	Unctuous (heavy)
Virya [Potency]	Shita [Cold]	Ushna [Hot]	Sheet [cold]	Dry- Ushna, Fresh- Shita	Sheet [cold]	Cooling
Vipaka [post digestive effects]	Katu [Pungent]	Katu [Pungent]	Katu [Pungent]	Madhura [sweet]	Madhura [sweet]	Sweet
Dhatu [tissues]	Muscle, fat, reproductive system	Plasma, Blood	Plasma, Blood, Muscle, Fat, reproductive system	Plasma, Blood, Muscle		All tissues
Karma [actions]	Shohta [Inflammation], Daha [burning], Apachi [tumours], Rakta Doshha [blood disorders], Stri-roga [Gynecological], Rakta- yoni/ pitta [Menorrhagia], Shveta pradara [leucorrhoea], Mutra- krichhra [urine retention]	disorders Kapha, Pitta, Kriminashak [anthelmintic], Appetizer, Diabetes, Fever, skin disorders	disorders Kapha, Reduce fat, Wound healing, Anti toxic, Analgesic, antipyretic, Astringent	Promotes digestive fire, pacifies 3 Doshas, especially pitta, controls burning sensation, all fevers, cough, respiratory ills	Kapha pitta shamaka [calms aggravated Kapha and Pitta doshas], used to stop bleeding, menorrhagia, uterine prolapse, in eye cure, piles, diarrhea, herpes, burning, epilepsy	Adaptogenic, tonic, lactative, anti-toxic, immunomodulatory, Aphrodisiac, de-stressing

treat inflammatory ailments such as nasal bleeding<sup>36</sup> or menorrhagia in India<sup>21</sup> and even abroad.<sup>22-23,37</sup>

Dub/ doorva (both vernacular names in northern India)/ Bermuda Grass (*Cynodon dactylon* L.)<sup>38,39</sup> and Satavar (*Asparagus racemosus* L.)<sup>40-41</sup> are other similar Ayurvedic herbs used as anti-hemorrhagic and are cultivated/ common in the wild so can be promoted. Dub is a common garden grass/ weed and offered in prayers to God Ganesha and can be an option to Seeta Ashoka. It is hemostatic,<sup>42</sup> besides helping in wound healing and as analgesic.<sup>43</sup>

Table 3 enlists the active ingredients in the Seeta Ashoka bark and its potential substitutes

Anti-inflammatory, analgesic and haemostatic properties of Ashoka (*Saraca asoka*) are tested and proven by many, including Central Drug research Institute and NBRI- National Botanical Research institute.<sup>48</sup>

Quercetin, a flavanoid, is found to be stronger molecule than even non-steroidal anti-inflammatory drugs (NSAID) aspirin, celecoxib or Methotrexate using markers such as cyclooxygenase (COX) even in studies in Russia<sup>49</sup> and Gulf.<sup>50</sup> It is found in Satavar also as well as Ashwagandha [*Withania somnifera* L. (Dunnal.)], a potent Indian herb to fight even Covid-19<sup>51</sup> so can be studied further. Its whole synergistic composition rich in flavonoids may be responsible for the pharmacological effect than any single factor.

Even Fig genus trees such as Vad (*Ficus benghalensis* L.) that are worshipped for fertility and contain glycosides<sup>52</sup> but their bark harvest is a taboo, being considered sacred. However, common Fig species viz. *Ficus carica* L. has many similar properties vide this research so may also be studied as an eco-friendly option. As Fig is a common food item, it may be safe to consume and easy to assess though safety study. Indeed, Central Council for Research in Ayurveda and Siddha (CCRS), Govt. of India has published successful clinical trial results of using Fig species

bark with that of the Shirish (*Albizia lebbek*), a tree in the same "gana" as Seeta Ashoka, is treating Leucorrhoea.<sup>53</sup> So its use in Menorrhagia can be similarly explored in future.

Patrangasava is another famous Ayurvedic remedy to treat excessive, painful menstrual bleeding.<sup>54-55</sup> Its main ingredient as the bark of *Caealpinia sappan* (Patrang- vernacular), a thorny, climbing shrub, rich in tannin and is Brazilin, a novel platelet aggregator i.e. aid in blood clotting.<sup>56</sup> Other options such as Chandraprabha vati are also popular and need to be promoted further.<sup>57</sup>

Further, Pycnogenol is a famous western herbal medicine using tannin for similar conditions and is traditionally derived from the bark of the French, maritime pine tree (*Pinus maritima*) a resinous tree like Sal in India with tannin rich bark.<sup>58</sup> It is useful in wound healing, reducing vascular inflammation and contains polyphenols, including catechin, taxifolin, procyanidins, phenolic acids and has endothelial and blood clotting function vide clinical trials in USA. So even other tree barks such as Neem can be useful in menorrhagia<sup>59</sup> and but it is abortive like aforesaid Shirish tree so its use needs great caution similar to *Mimosa pudica* being explored by industry (Kimothi G. P., pers comm.).

*Asparagus* the famous women tonic, heals wound, bleeding, pain<sup>40</sup> and is proven to be useful in treating menorrhagia in human trials.<sup>60</sup> It is cultivated considerably today and is profitable so may not face future resource scarcity. Aonla (*Phyllanthus emblica*) another the famous Ayurvedic tonic is also used similarly can be another option.<sup>54</sup> Coriander and *Asparagus* are rich in Vitamin K and help in blood clotting so not recommended for consumption along side blood thinners like Warfarin in heart disease patients.<sup>61</sup>

There is need to replace the rare, threatened wild medicinal plants with cultivated species for the AYUSH sectoral growth due to the ever-growing demand and species extinction,<sup>62</sup> and biochemistry studies can help here.

**Table 3: Phytochemicals in Seeta Ashok (part-wise) and its options.**

Chemical/ Species	Actions	Saraca asoca	Polyalthia longifolia	Shorea robusta	Coriandrum sativum	Cynodon dactylon	Asparagus racemosus
Epi/catechin <sup>44</sup>	Antioxidant, Anti-inflammatory, Chemo-protective	+++	+	+	+		
Gallic acid <sup>45</sup>	Anti-inflammatory, Wound Healing	+++	+	+	+++		
Proantho-cynidin <sup>44</sup>	Hemorrhage, analgesic, anti-inflammatory, immunity builder	+	+	+	+		
B- sitesterol <sup>13</sup>	Analgesic and anti-inflammatory activity	++	-		+	+	+
Saponin <sup>46</sup>	Anti-Inflammatory, Analgesic	+	++	+	+	++	+
EGCG <sup>47</sup>	Anti-inflammatory	+			+		
Quercetin/ Glycoside <sup>5</sup>	Uterine contraction	+	+	+	++	++	+
Tannin	Uterine contraction, stops bleedings	+	+	+	-	+	+

Note- no. of + signs indicates strength of occurrence- the more the better.

The impressive growth of herbal industry globally and Chinese medicine is because of using mostly (>70% volume) cultivated herbs such as Mint, Oregano, Lavender, Basil and even Gingko, Ginseng.<sup>63</sup> Transdisciplinary University, Bangalore has demonstrated similar substitution approach for the threatened, Himalayan herb Ativisha (*Artemisia*) with Musta (*Cyperus rotundus*) a common and now cultivated herb, following the “Abhav Pratinidhi Dravya” (Rare herb representative) concept in Ayurveda<sup>64</sup> and is a trigger for this study. Already local Satavari (*Asparagus racemosus*) is used in Ayurvedic factories in Kerala to substitute the threatened Ashtavarga (eight classes) drugs of Himalayan mountains origin.<sup>62</sup> Ashokarishta is among the top 10 selling Ayurvedic medicines and its quality is also found to be acceptable as per Ayurvedic pharmacopeia standards.<sup>65-67</sup> So condemning the so-called adulteration may not help but we need to examine its pharmacological action to standardize and brand it for even exports. Such green options can benefit the patients and enable economic growth, cultivation globally. The current practice of using undisclosed or improper substitutes or adulterants is illegal under the FDA regime and aforesaid biological diversity act, 2000. Nestle company suffered huge losses when its noodles branded ad “Maggi” were banned in India for months due to misleading labels and excess quantity of harmful chemicals viz. lead.<sup>68</sup>

## CONCLUSION

We show that the currently sold drug Ashokarishta may be effective in treating menorrhagia due to tannin content and hence popular though containing bark of Sal trees (*Shorea robusta*) or False ashoka (*Polyalthia longifolia*) instead of *Saraca asoca* the key ingredient. Possible cultivated options to avoid species rarity and resource constraints include substitution by Satavar (*Asparagus racemosus*), Coriander (*Coriandrum sativum*) or Bermuda grass (*Cynodon dactylon*) after proper clinical studies and pharmacopial approval.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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