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Nain-e Havandi *Andrographis paniculata* present yesterday, absent today: a plenary review on underutilized herb of Iran's pharmaceutical plants

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Abstract Nain-e Havandi (*Andrographis paniculata* Nees.) (AP) is an annual herbaceous plant belonging to the family Acanthacea. Only a few species of *Andrographis* genus out of 28 are medicinally concerned of which AP is the most important. Knowledge about the arrival of AP to Iran is extremely lacking but most probably it has been imported from India. However, evidence implies the familiarity of Iran's folkloric medicine with this plant, but it has been disappeared from contemporary medicine for unknown reasons. Presence of active ingredients from diterpenoids group such as andrographolide, neoandrographolide and 14-deoxy-11,12-didehydroandrographolide has given incredible unique medicinal properties to the plant. Traditionally, Nain-e Havandi has been used in the role of a non-farm plant as a remedy for skin problems, flu, respiratory disease, and snakebite in East and Southeast Asia for centuries. Recently, it has been utilized as a treatment for HIV, hepatitis, diabetes, cancer and kidney disorders. Intensive cultivation of the herb started only in the past decade in countries such as China, India, Thailand, Indonesia, West Indies, Mauritius and to some extent, in Malaysia. Availability of different ecological zones in Iran complies with reestablishment of AP in tropical and temperate regions of the country. This is killing two birds with one stone, supporting the conservational and economic aspects.

Keywords Nain-e Havandi · *Andrographis paniculata* (AP) · Medicinal plants · Income creation · Iran · India

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Introduction

Medicinal herbs are moving from margin to mainstream use with a greater number of people seeking remedies and health approaches free from side effects caused by synthetic chemicals [211]. Recently, considerable attention has been paid to utilize eco-friendly and bio-friendly plant-based products for the prevention and cure of different human diseases. It has been recorded that 80% of the world's population has fidelity in traditional medicine, particularly plant based drugs for their primary healthcare [1]. Medicinal plants have been applied to treat diseases for thousands of years. An estimate suggests that around 25% of the commonly used medicines contain compounds obtained from plants, and a few plants are proposed as rich reservoirs for drug discoveries to treat infectious diseases [2, 3]. The rising market demand for its products led the plant AP to become an alternative crop. Good-quality dried leaves of AP could be sold for US$5 per kg while the purified active ingredients, such as andrographolide and its derivatives, cost as much as US$100,000/kg from specialist chemical suppliers [4]. As a highlighted point the United States and China as two main super powers put their efforts to develop commercial products from the herb for different usages.

Historical background

According to references, Indians have used the leaves of AP as anti-venom against snakebite since ancient times [5]. Nain-e Havandi has been employed historically in epidemics, including the global flu epidemic of 1919 [6]. This pandemic is recognized as the most fatal infectious disease outbreak in human history and even more virulent than the Black Death of the fourteenth century, and AP was credited during that period as a wonder drug for arresting the spread of the contagious illness [7] as no country escaped its attack unless India. Evidence about the circumstances of this plant's arrival into Iran is exceedingly lacking but the most logical way to achieve the issue is looking at the history of the relationship between Iran and India. The existence of several empires spanning both Persia (preferably Iran) and northern India territories ensured the constant migration of people between the two regions [8]. However, relations between India and Iran date back to the Neolithic era, but the answer will specifically cover a period of time that officially commenced from 2,600 years ago during the Achaemenian dynasty [9], at the time that Indian emissaries were present at the courts of Cyrus (Kurush) the Great (590 BCE–529 BCE). Afterwards, within the Afsharid dynasty when Nader Shah or King Nader (1,688–1,747) campaigned in India during the eighteenth century [10] and until recent. Records showed that this medicinal herb has been extensively used in traditional herbal medicine in China, Southeast Asia and the Persian Gulf area for the treatment of several diseases, including inflammatory diseases [11].

Botany

Andrographis paniculata (Burm. f.) Wallich ex Nees. also known as the King of Bitters in English is a medicinal herb from the family Acanthaceae. Perhaps different ecological and climatic conditions caused the plant to be introduced as a perennial plant [12], while most of the references present another botanical definition of the herb as an annual plant [7, 13]. A brittle-branched stem, herbaceous plant erecting to a height of 30–110 cm with glabrous, simple, opposite styled leaves [7, 13] and white flowers with rose–purple spots on the petals [14]. Even though AP is known as a hermaphroditic, self-compatible and a habitual inbreeding plant [15], there is an assumed rate of 28% cross pollination for it [16]. Inflorescence pattern extends axillary with terminal panicle or raceme. AP has a fibrous or adventitious root system (Fig. 1).

Taxonomic position

Taxonomically *Andrographis paniculata* is classified as below:

Kingdom	Plantae, plants;
Subkingdom	Tracheobionta, vascular plants;
Superdivision	Spermatophyta, seed plants;
Division	Angiosperma
Class	Dicotyledonae
Sub-class	Gamopetalae
Series	Bicarpellatae
Order	Personales
Tribe	Justicieae
Family	Acanthaceae
Genus	*Andrographis*
Species	*Paniculata* (Burm. f) Nees [13]

Geographical distribution and preferred habitats

The genus *Andrographis* is composed of roughly 40 species several members of which enjoy a reputation in traditional medicine [17]. AP populations are distributed over a broad eco-geographical range in tropical Asian countries often in isolated patches. It grows abundantly in Southern and Southeastern Asia, including India, Sri Lanka, Pakistan and Indonesia [13]. So-called "native populations" occur only in the Indian subcontinent and especially South India and Sri Lanka, which perhaps represent the centre of origin and diversity of the species [18, 19]. Sabu [16], stated that the herb is an introduced species in the northern areas of India, Thailand, Brunei, Malaysia, Indonesia, the West Indies such as Jamaica, Barbados and Bahamas, Hong Kong and in the tropical areas of the Americas [18, 20–22]. This plant is also currently cultivated in southwestern Nigeria [23]. AP can be stemmed in a variety of habitats, for instance; plains, hill slopes, wastelands, farms, dry or wet lands, seashores, and even roadsides, but it has a preferred tendency to grow in moist shady places, forests, and wastelands [18, 20–22].

Terminology

We believe that the most probable reason for naming the plant as AP (Fig. 2a) is the presence of a diterpene lactone in the leaves namely andrographolide and also the existence of two flavones viz., andrographin and panicolin in the roots. Regardless of the above-mentioned case, the botanical name of the plant consisted of *Andrographis* and *paniculata* carrying other meanings as well. Andro is a place name in India. In fact, Andro is a town in Imphal East

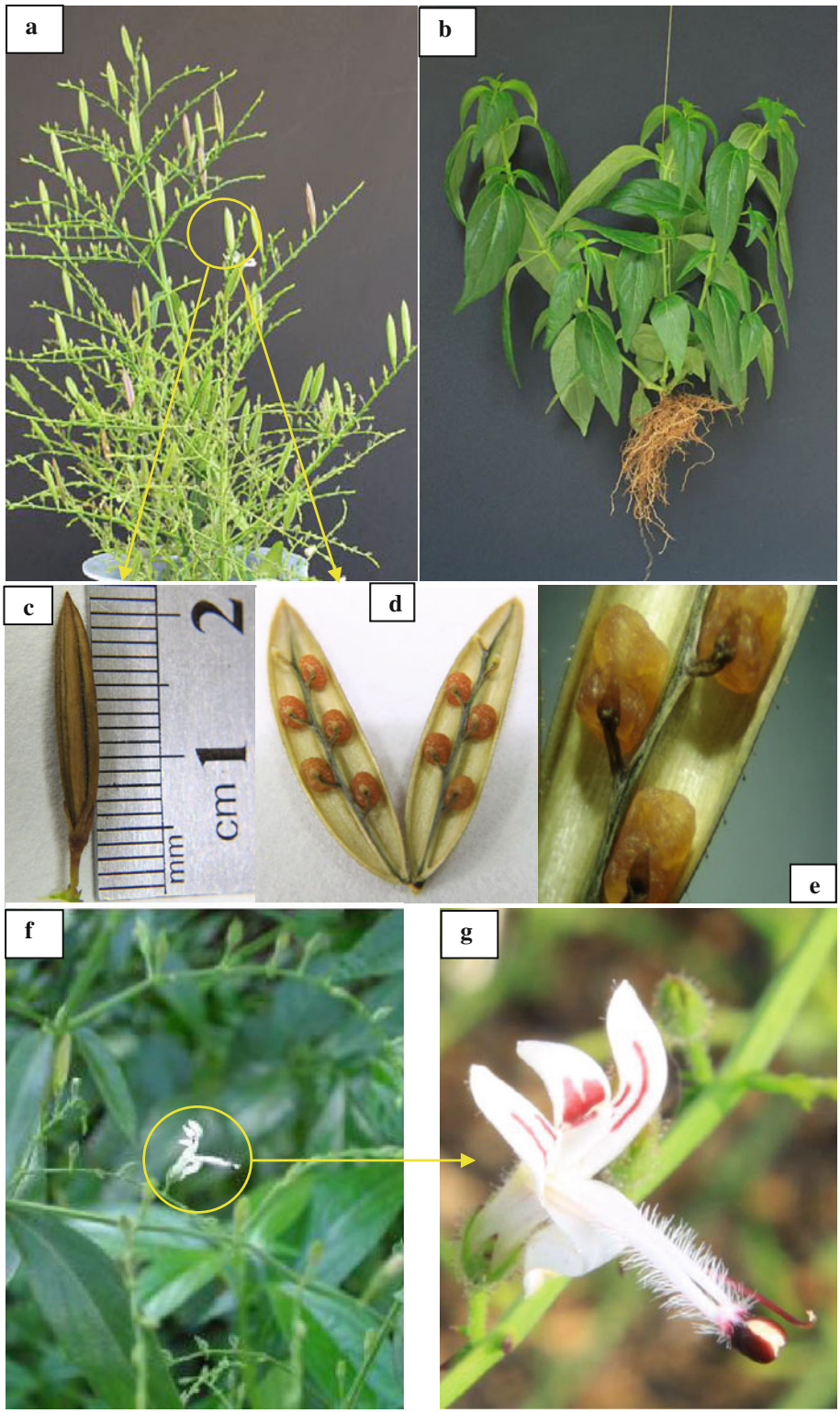

Fig. 1 **a** *Andrographis paniculata* herb in pod stage with terminal or axillary panicles. **b** Young plant: aerial and underground parts of AP. **c** Fruit of AP in capsule form. **d** Opened capsule. **e** Rugose seeds of AP inside the fruit. **f** flowering plant with a small flower. **g** A flower with opened anther and pollen grains

district, Manipur state, North East of India. Andro also is a prefix in the Greek language meaning "male" or "masculine" can refer to a number of things. *Graphis* (Fig. 2b) is a genus of lichens from the family Graphidaceae [24, 25] and in the Latin language means pencil, paintbrush or writing style, and *paniculata* performs a Latin pronunciation of paniculate or panicle, which refers to the inflorescence of the plant.

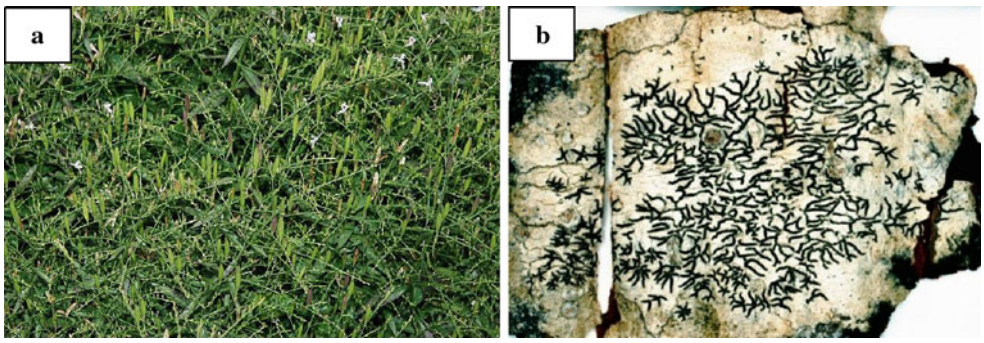

Fig. 2 **a** *Andrographis paniculata* plant in a spread-lying form (area ~900 cm^2). **b** A herbarium specimen of *Graphis scripta*, member of the Graphidaceae (area ~25 cm^2). *Source*: Flickr network and Wikipedia, respectively

Synonyms

Normally, most of the useful plants got a vernacular name in various languages. Hence, as a matter of fact, giving a specific Persian name to AP could be meaningful because it means that either the physicians of ancient Iran were quite knowledgeable about its curative effects in treating their patients or the ordinary people were familiar with the plant as a traditional folk remedy. Anyway, it is necessary to remind that Nain is a name of town in the central part of Iran. Possibly, herbalists and traditional apothecaries values AP due to its miraculous ability in treating ailments and this made it to possess different names from East to West. Azerbaijani and Turkish names of this plant have been given by the first author of the present article which has been inspired from the English name of AP (Table 1).

Cytology

To date, five conducted cytological studies on AP in the early 1980s, concur on 25 pairs of chromosomes ($2n = 50$) as the chromosome number for the species [26–30].

Genetic diversity

Initial steps to investigate the genetic diversity of AP using molecular approaches were taken only in the late 1990s. The first try was given by employing RAPD (randomly amplified polymorphic DNA) markers and resulted in a moderate level of variation engaged with intra-specific study of accessions collected from India and Southeast Asia. Additionally, the clustering analysis using unweighted pair group method with arithmetic mean (UPGMA) was limited to five major groups based on geographical distributions that generally reflected the expected trends among the genotypes [31]. Isozymes were the second molecular tool used to elucidate the genetic variations among AP genotypes while quantitative variations in content of the plant's major active component (andrographolide), were used to indicate phytochemical diversity [32]. AP has been exposed to ISSR (inter simple sequence repeat), SSCP (single strand conformation polymorphism) and PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) markers in different cases [7, 33, 36, 38, 40–43]. A summary of several conducted studies using various marker systems on AP to ascertain its genetic variation is presented in Table 2.

Table 1 Vernacular names of AP

Language	Name	Language	Name
Azerbaijani	Acılar Şahı, Acılar Xanı (khanı)	Turkish	Acılar Kralı, Acı Paşa, Acı Bey
Persian	Nain-e Havandi	Oriya	Bhuinimba
Chinese	Chuan Xin Lian	Kannada	Nelaberu
English	The Creat, King of Bitters	Sanskrit	Kalmegha, Bhunimba and Yavatikta
French	Chirette verte, Roi des amers	Tamil	Nilavembu
Burmese	Se-ga-gyi	Philippines	Aluy, Lekha and Sinta
Spanish	Andrografis	Telugu	Nilavembu
Hindi	Kirayat	Russian	Andrografis
Arabic	Quasabhuva	Bengali	Kalmegh
Indonesian	Sambiloto	Malayalam	Kiriyattu
Japanese	Senshinren	Scandinavian	Green Chiratta
Thai	Fa-Talai-Jorn, Fah-talai-jon (jone)	Gujarati	Kariyat
Malay	Hempedu Bumi	Marathi	Oli-kiryata

Refs. [13, 77]

Table 2 Genetic diversity in AP accessions using different marker systems

NSA[a]	Type of markers	Clustering method	Similarity indices	Ranges	Intensity of variation	References
38	RAPD	UPGMA	Nei and Li	0.23–0.89	Moderate	India [31]
15	Isozyme/Morphochemical	UPGMA	Nei and Li	0.48–1.00	Moderate	India [32]
26	ISSR/Phytochemical	UPGMA	Jaccard	0.72–1.00	Low/Moderate	Malaysia [33]
26	Morphological	UPGMA	EU[c]	0.02–0.24	Low/Moderate	Malaysia [34]
50	Morphological	UPGMA	EU	0.01–0.22	Moderate	Malaysia [35]
25	RAPD/SSCP/Morphochemical	UPGMA	SMC[e]	0.67–0.95	Low	Thailand [36]
76	Morphological	UPGMA	EU	–	Considerable	Malaysia [37]
44	RAPD	UPGMA	Jaccard	0.68–1.00	Moderate	Malaysia [38]
28	Morphochemical	ANOVA[d]	Tukey	–	Significant	Thailand [12]
53	RAPD/Morphochemical	UPGMA	Jaccard	0.33–0.81	High	India [40]
53	RAPD/Morphochemical	UPGMA	Shannon	3.08–8.70	High	India [40]
44	RAPD/ISSR	–	–	–	Very low	Thailand [41]
9	RAPD/PCR–RFLP	UPGMA	Nei and Li	0.03–0.35	Moderate	Australia[b] [42]
10	RAPD/Morphochemical	UPGMA	–	0.51–0.97	Moderate	India [7]
80	RAPD/Morphological	UPGMA	Jaccard	0.81–0.98	Low	Malaysia [43]
5	Morphochemical	–	–	–	Significant	India [44]

[a] Number of studied accessions

[b] This study has been done using AP population from Brunei Darussalam

[c] Matrix of Euclidean distances squared coefficient or EUCLIDSQ

[d] Analysis of variation

[e] Simple matching coefficient

Agrotechnology and tissue culture of AP

Despite numerous studies conducted on the pharmacology, phytochemical composition, and therapeutic features of AP, it has not been subjected to detailed agronomic studies worldwide except in a few Asian countries like India, China, Thailand and to a lesser extent in Malaysia.

Seed dormancy is a problem in AP propagation [39, 45]. Hormonal solutions and hot-water treatment are suggested to overcome the case [46, 47]. For herbs, where a leaf is the major plant part used for the medicinal purpose, promoting vegetative growth is the priority. Efforts to improve foliar production through proper management of fertilizer application should be of the main concern for commercial production [48]. Herbage yield of AP is influenced by date of planting and harvest [49, 50]. AP is mostly sown with spacing of 30 × 15 cm between May and July which result to a plant density of 222,222 plant/ha and average biomass of 3 t/ha [55, 56]. Conventional vegetative propagation of AP (through seed) is very difficult and too slow to meet the commercial quantities required. Hence, non-conventional biological strategies such as tissue culture are alternative methods for improving the propagation, yield and phytochemical content in AP [61]. Tissue culture has been successfully used as a technique for the formation of new flavones by differentiating callus cultures of the plant [62, 63]. Tissue culture is successfully used as a technique for formation of new flavones by differentiating callus cultures of the plant [64]. A list of agronomic field trials on AP is presented in Table 3.

Breeding and physiology of AP

Classical genetic scrutiny and breeding of AP using conventional schemes such as intra-specific hybridization have been neglected due to its troublesome procedure. On the other hand, the plant's weak response to manual crossing, acted as an obstacle to this approach.

Literatures about physiologic characreistics of the plant are extremely lacking. However, physiologic aspects of the plant, like relative growth rate (RGR) has been taken into consideration very recently [59]. However, initial researches suggests a critical model for leaf area index (LAI). This means that LAI increasing associated with increasing crop growth rate (CGR) during growth stage and CGR reaches the maximum at a specific level of LAI, beyond which it remains the same despite the increases in LAI. The LAI at which CGR reaches the utmost may be called the critical LAI [204]. Specific leaf area (SLA) increases up to 90 days after sowing (DAS) and there is gradual decreasing there after up to 120 DAS. This is the maturity sign of the herb [55].

Table 3 Agrotechnologic findings in yield improvement and agronomy of AP

Sowing date	Spacing (cm)	Fertilizer	Irrigation	Weeding	Pest/disease	Harvest	Total dry yield (t/ha)	Plant density Pl/ha	Country/source
May–June	20 × 20	–	2	2	–	September	1.25	250,000	India [51, 52]
–	75 × 75	–	–	–	–	–	1.23	17,778	India [53]
May–June	25 × 20	FYM 10 t/ha and NPK 75:75:0 kg/ha	–	–	Aphid, green leafhopper, semilooper & sclerotial rot	September	~1.6	200,000	India [54]
July	30 × 15	–	–	–	–	November	~3.1	222,222	India [55]
–	–	–	–	–	–	–	40.5 g/plant	–	India [7]
July	30 × 15	NPK 80:40:40 kg/ha	2	2	–	November	1.52–3.33	74,074	India [56]
	30 × 30	$FeSO_4$ 0.25% + citric acid 0.25%						111,111	
	45 × 30							222,222	
–	30 × 15	FYM, DCC, vermicompost 15:7:5 t/ha	–	–	–	–	0.72–2.79	222,222	India [57]
		NPK 75:75:50							
		panchagavya 3% as foliar spray							
1st July	–	–	–	–	–	16th Oct	0.57–1.65	–	India [58]
16th July						1st Nov			
1st Aug						16th Nov			
–	40 × 20	NPK 0.9 g/m^2	–	–	–	–	2.13–8.23 g/plant	125,000	Thailand [12]
–	30 × 15	NPK 205:24:232 kg/ha	Upon the requirement	1	–	–	1.4–2.7	222,222	India [60]
		FYM, poultry manure, AZO and VAM 15:2.7:RDF							
June	40 × 40	NPK 60:25:30 kg/ha and FYM 10 t/ha	–	–	–	25th Sep	0.32–5.37	62,500	India [50]
						25th Oct			
						25th Nov			

FYM Farm yard manure, *NPK* nitrogen, phosphorus and potassium, *DCC* digested coir compost isolate, *AZO Azospirillum brasilense*, *VAM* vesicular arbuscular mycorrhizal, *RDF* recommended dose of fertilizer, *t/ha* ton/hectare, *Pl/ha* plant/hectare

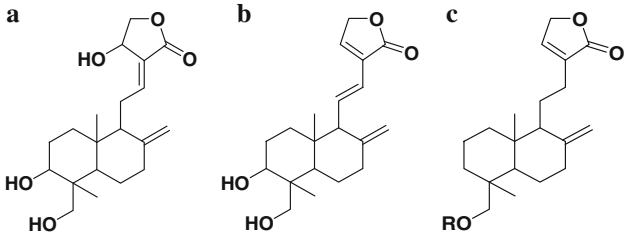

Fig. 3 **a** Andrographolide, **b** 14-Deoxy-11,12-didehydroandrographolide, **c** Neoandrographolide (R = Glucose)

Phytochemistry investigations and major constituents

Chemical explorations of AP began by the end of the nineteenth century when Boorsma [65] isolated an extremely bitter lactone diterpene in 1896 for the first time. Subsequently, Gorter [66], was the first scientist to name the above-mentioned constituent as andrographolide (ANDRO or AG or AP1). 41 years later, the second non-bitter component namely neoandrographolide (NAG or AP4) was discovered by Kleipool [67]. Isolation of the third relatively minor diterpene, 14-deoxy-11,12-didehydroandrographolide or 11,12-didehydro-14-deoxyandrographolide (DDAG or AP3) was reported by Balmain and Connolly [68], along with three other diterpenes, including andrographiside, 14-deoxyandrographolide and 14-deoxyandrographiside. Studies were also done in order to unravel the chemical structures of andrographolide [69], and neoandrographolide [70]. The important compounds isolated from different parts of the plant according to Rastogi and Mehrotra [71], were apigenin-7,4/-di-*O*-methyl ether, carvacrol, eugenol, myristic acid, hentriacontane, tritriacontane, oroxylon A, wogonin, and diterpenoids like andrograpanin, andropanoside, andrographolide and neoandrographolide. A few other active components, including 14-deoxy-11,12-dihydroandrographolide (andrographolide D), homoandrographolide, andrographosterin and stigasterol were subsequently reported [72]. Nevertheless, it is usually agreed that three diterpenic compounds namely andrographolide (AG), neoandrographolide (NAG), and 14-deoxy-11,12-didehydroandrographolide (DDAG) are the major constituents of the plant's extract (Fig. 3) responsible for its pharmacological activities [73–210].

In addition, leaves of AP contain andrographosterol and andrographone while flavones-apigenin-7,4-dio-*O*-methyl ether, 5-hydroxy-7,8,2′,3′-tetramethoxyflavone, andrographin, panicolin and a-sitosterol are accumulated in the roots [78, 79]. Series of newly reported semi-synthetic andrographolides are given below [80]. 14-Deoxy-11,14-didehydroandrographolide (AP10), 8,17-Epoxyandrographolide, 12,13-Dihydroandrographolide, 14-deoxy-12,13-dihydroandrographolide, 13,14-Didehydro-12-hydroxy-3,19-methene-*O*-andrographolide, 3,19-(*p*-methanoxylphenylmethene-*O*-)-andrographolide, 14-deoxy-11,12-didehydro-15-isopropylideneandrographolide, 14-Deoxy-11,12-didehydro-15-(2,8-dimethanyl-2,7-octanedieneylidene)-andrographolide, 15-Benzylidene-14-deoxy-11,12-didehydroandrographolide, 14-Deoxy-11,12-didehydro-15-*p*-fluorobenzylideneandrographolide, 14-Deoxy-11,12-didehydro-15-trimethoxylbenzylideneandrographolide, 14-Deoxy-11,12-didehydro-15-*p*-chlorobenzylideneandrographolide, 15-*m*-Bromoacylbenzylidene-14-deoxy-11,12-didehydroandrographolide, 14-Deoxy-15-(*p*-(dimethanylamino)-benzylidene)-11,12-didehydroandrographolide, 14-Deoxy-11,12-didehydro-15-*p*-methoxylbenzylidene andrographolide, 15-(Benzo[1, 3]dioxole-5-methanylidene)-14-deoxy-11,12-didehydroandrographolide, 14-Deoxy-11,12-didehydro-15-(-2-furanmethanylidene)-andrographolide, 14-Deoxy-11,12-didehydro-3,19-dinicotinateandrographolide, 14-Deoxy-11,12-didehydro-3,19-dinicotinate-15-(2,8-dimethanyl-2,7-octanedieneylidene)-andrographolide, 15-Benzylidene14-deoxy-11,12-didehydro-3,19-dinicotinateandrographolide, 15-(*p*-Chlorinebenzylidene)-14-deoxy-11,12-didehydro-3,19-dinicotinateandrographolide, 15-(*m*-Bromoacylbenzylidene)-14-deoxy-11,12-didehydro-3,19-dinicotinateandrographolide, 14-Deoxy-11,12-didehydro-3,19-dinicotinate-15-(*p*(-dimethylamino)benzylidene)-andrographolide, 14-Deoxy-11,12-didehydro-3,19-dinicotinate-15-(2-furanmethanylidene)-andrographolide, and 14-Deoxy-11,12-didehydro-3,19-dinicotinate-15-p-methoxylbenzylideneandrographolide.

Pharmacology and remedies

Conducted researches in the past three decades have confirmed that AP, properly administered, has a surprisingly broad range of pharmacological effects such as Inhibitory impact of its active diterpenoids on platelet aggregation [81] and lots of other extremely beneficial effects [82]. Almost all the review papers about AP have extensively focused on its medicinal properties [13, 83, 92, 120, 121] thus, we have prepared a comprehensive table concerning medicinal and curative effects of AP (Table 4).

Posology and dosage in clinical trials

Available instructions are varied due to the type of disorder, type of the formulation (crude extract, solid or liquid formulation or purified active ingredients), and nature of the study (clinical trials, in vitro or in vivo studies on animals or human). Nevertheless, most of the clinical tests used products standardized to 4–5 mg/kg of andrographolide with a typical dosage of a 400 mg tablet, 3 times a day for the first few days of flu [152]. Some of the clinical trials have chosen direct use of powdered crude material with 1,200 mg/day of AP extracts standardized to 5% andrographolide or a placebo for a period of 5 days [6, 153, 154]. A decoction of 3 g of crude drug twice daily is proposed for pyrexia treatment [123, 155, 156]. For the common cold

Table 4 List of some pharmaceutical and curative effects of AP

Application	Modern researches		Traditional claims[a]	References	Application	Modern researches		Traditional claims[a]	References
	In vitro	In vivo				In vitro	In vivo		
Abortifacient		A	H	[83]	Antiperiodic	–		H	[13]
Acrid	A		H	[82]	Antipregnancy		A	H	[13, 84]
Analgesic	Ex/A		H	[85]	Antipyretic		A	–	[86, 87]
Antiallergy	A	A	–	[11, 88]	Antithrombotic		A	H	[89, 90]
Antiangiogenic	A	A	–	[91]	Antityphoid			H	[92]
Antiarthritis	H/CT		H	[93, 94]	Antivenum	H	A	H	[5]
Antibacterial	A/H	A	–	[80, 95–98]	Cytotoxic		A	–	[99]
Anticancer	A/H	A	–	[100]	Cardioprotective	A	A	–	[101, 102]
Antidiabetic	A	A	–	[103–105]	Choleretic		A	–	[106, 107]
Anti-diarrheal		A	H	[108–110]	Depurative	–		H	[111]
Anti H1N1	H		–	[112]	Digestive	–		H	[113]
Anti-Hepatitis	A/H	A	H	[114–119]	Expectorant	–		H	[3, 12, 77, 120–122]
Antiherpes	H		–	[124]	Immunostimulant		A	–	[125, 126]
Anti HIV	A/H	H/Ex - CT	H	[76, 127–131]	Laxative	–		H	[13]
Anti-inflammatory	A/H	A	–	[132–134]	Neuroprotective		A	–	[135, 136]
Antimalarial	P/H	A	–	[137–139]	Parkinson	A/H	A	–	[85, 140, 141]
Antimicrobial	B/F	B/F	–	[142, 143]	Renoprotective		A		[144, 145]
Antiodema	Ex vivo/A	A	–	[146, 147]	Sedative	–		H	[148]
Antioxidant	A	A/H	–	[140, 149, 150, 202]	Vermicidal	–		H	[151]

A Animal, *H* Human, *B* Bacteria, *F* Fungi, *P* Parasite, *Ex* Ex vivo, *CT* Clinical test

[a] Traditional claims are from Ayurveda, traditional Chinese nedicine (*TCM*), folklore information and other ethno-medical systems

1.5–3.0 g of powdered crude drug 3 times daily after meals and at bedtime [155, 156]. For diarrhea a decoction from 3–9 g crude drug as a single dose is needed [123, 155], or two tablets of 500 mg 4 times daily, after meals and at bedtime [123, 156]. Recommended daily dose for AP powder ~850 mg or 1–2 capsules (500 mg/capsule) and intake 4 times/day [156]. Coon and Ernst [120], have reviewed that a daily dose of andrographolide up to 60–380 mg/day could be efficient in healing of upper respiratory tract infections. However, the treatment period can take a range from three to 8 days in different studies [153, 154, 157–161]. 200–300 mg of andrographolide daily in 2–3 times is recommended for relieving cold and fever symptoms. Doses in a range between 1,000 and 2,000 mg 3 times daily have been applied in some studies and a typical standardization for content of andrographolide in AP is 4–6% [153]. An advisory from the Langone Medical Center noted that virtually all the published studies of AP have involved a single proprietary product. It is not clear that the results of these studies apply to products using different AP sources, or different methods of extraction [162].

Adverse reactions and safety issues

Even though in general, AP has not been implicated with any serious side effects in the relevant experiments on humans, the main complain about this plant is that it may affect the fertility of the person receiving the drug. Nonetheless, several studies have proven its safety. No side effects were observed when participants were monitored for changes in liver and kidney functions, blood counts, and other laboratory measures when treated with 1,200 mg/day of AP for 5 days [6]. This regime has been mentioned as a short-term treatment with 15 times the clinical dosage of andrographolide [163]. Rare and minor side effects from AP in two cases of urticaria had been reported [157]. In another claim, large oral doses of AP may cause gastric discomfort, vomiting, and loss of appetite. These side effects emerged due to the bitter taste of andrographolide [164]. Intra-arterial or retrograde intravenous injections of AP's crude extract may cause anaphylactic reactions [83, 164, 165]. Limitations in direct testing of the drug on humans could be compensated by in vivo analysis on animals. There have been conflicting with results from such

animal studies. Studies on mice had raised concerns that AP may reduce fertility in male rats when fed with 20 mg/kg/day of AP powder daily [166]. In a toxicity survey on mice, the minimal lethal dose (MLD) of the main active components of AP, andrographolide (AG) and 14-deoxy-11,12-didehydroandrographolideos (DDAG) was 20 g/kg of body weight by mouth feeding, which was about more than 100 times higher than the recommended daily dosage [167]. No testicular toxicity was found in vivo with treatment of 20, 200 and 1,000 mg/kg during 60 days in rats [168]. However, degeneration of anatomical structures in testicles and testicular toxicity in male rats was reported when rats were treated with dried extracts of AP up to 1 g/1 kg of body weight daily for 2 months. One group of female mice also did not fare well on high dosages of AP when fed 2 g/kg of body weight daily for 6 weeks (1,000 times higher than the usual human dose). All female mice failed to get pregnant when mated with fertile males. Concurrently, 95.2% of the control females got pregnant when mated with a similar group of male mice [84]. Another study established a potential explanation that AP relaxes the uterus [169]. These results raised concerns regarding the use of AP by pregnant women, in case they take an overdose. Hence, the conclusion is that the anti-fertility effects of AP cannot occur in the normal situations. Related studies comply with no side effect as well as acceptable tolerance for Kan Jang treatment [170, 171]. One of the latest investigations in a human trial using the widely tested *Andrographis–Eleutherococcu's* combination discovered no negative effect on male semen quality and fertility. However, rather a positive trend with respect to the number of spermatozoids in the whole ejaculates, the percentage of active (normokinetic) forms of spermatozoids, and fertility indices, together with a decrease in the percentage of inactive (diskinetic) forms of spermatozoids were observed [172]. Gallbladder contraction could be stimulated by taking AP [173], so the drug must be avoided by persons with gallbladder disease, unless with physician's prescription.

Formulations and commercialization

Our review showed that AP as a medicine can be formulated solely or mixed with other species in different configurations such as a powder, pill, tablet, capsule, decoction and crude extract [174]. A crude mixture of AP along with five other species, including *Momardica charantia*, *Phyllanthus niruri*, *Terminallia chebula*, *Glycyrrhiza glabra* and *Punica granatum* in powder form was authenticated by Choudhari et al. [126] for treating HIV. Both fresh and dried AP leaves, as well as the fresh juice of the whole plant, have been widely used in traditional medicines and advanced biomedical studies. In research on diabetes, AP decoction was used in combination with *Momordica charantia* fruit juice [175]. Crude chloroformic, ethanolic and methanolic AP extracts have been administrated by numerous scientists as the most common form of application for different aims [102, 112, 137, 139, 146, 149, 176–178]. However, sometimes chloroform extracts in vitro appeared more competent than the methanol extract in controlling malaria [137]. Pharmaceutical products of AP are available in drop and syrup forms as well, while leaf juice of the plant is used as syrup for the treatment of liver diseases [179]. The syrup also is a healer of cold symptoms like coughs [153, 180]. The commercialization and branding of AP are proceeding swiftly in trade formulations for pharmaceutical products such as Liver tonics with hepatoprotective effects [181].

Wonderful application of AP in special fields

Although, an enormous proportion of AP's reputation is because of its medicinal properties but, in fact, this herb has been subjected to all sorts of studies in the twentieth century for possible applications in various fields such as agriculture, forestry, poultry and animal production, veterinary medicine and even for industrial applications.

Herbicidal capacity

Phytotoxic and allelopathic effects of AP are confirmed as its ground adversely affects the metabolism of the host plant (*Parthenium hysterophorus* L.) by allelochemical interference with photosynthesis and decreasing the total chlorophylls, polyphenols, amino acids, proteins, carbohydrates, starch and lipid contents. So, residues of *Pathenium hysterophorus* L. could be used as a potent bioherbicide [182].

Insecticidal function

Novel findings reveales that AP has the potential role in eco-friendly mosquito control programs. AP exerted a mosquitocide influence against the malaria vector, *Anopheles stephensi* Liston. The larvicidal, pupicidal, adulticidal and ovicidal properties of whole plant ethanolic extract were evaluated under laboratory conditions and the most effective results were obtained for larvicidal and pupicidal activities [183].

Alternative antibiotic in poultry

AP can be used as an alternative to antibiotics as a growth promoter of broiler chicken. Besides this, the FCR (total feed consumed by a bird/total weight gain) was significantly better in the group treated with a combination of

basal diet and AP's shredded dried leaves when compared to virginiamycin treated, and panchagavya treated groups [184, 185].

Animal production, aquaculture, and veterinarian utilization

AP has antimicrobial and growth promoting function and may be used as an alternative to antibiotics and tonic [186]. The nature of AP supports its capable role in acting as an antioxidant supplement along with vitamin E and *Curcuma longa* L. This can improve goat meat quality by preventing lipid oxidation, color stability, increasing drip loss of the *longissimus dorsi* (LD) muscle as well as the chevon tenderness particularly in post-mortem aging [187, 188]. A blend of AP extract and dry Indian almond leaf (*Terminalia catappa*) positively affected tail growth and hematocrit value in Fancy carp (*Cyprinus carpio Linn.*) [189]. Mix of AP and Noni (*Morinda citrifolia*) promotes pigmentation and phagocytosis in goldfish (*Carasius auratus*) [190].

AP leaves decoction in vitro appeared with promising impacts by killing the microfilaria of *Dipetalonema reconditum* in a short time in dog. Three subcutaneous injections of the extract into infected dogs and rabbits at 0.06 ml/kg body-weight decreased the number of microfilariae in blood by more than 85%. Although no toxic effect of the extract was observed in rabbits, but the treated dogs became lethargic initially for a week, probably due to the mass killing of microfilariae [191]. Microfilaricidal effect of AP is detected by controlling *Canine dirofilariasis* as a common tropical parasitic animal disease caused by *Dirofilaria immitis*. l, 10, 100 μg/ml and 1 mg/ml concentrations of dried aqueous extracts of each plant dissolved in dimethyl sulfoxide (DMSO), have been tested on infected samples of sheltered dogs [203].

Forestry (a protector element against fungal disease)

The upshot of a literature on subtropical jungles verified the ability of AP to control fungal diseases in plants together in line with its antifungal efficacy in humans. A protein extracted from AP leaves with molecular mass of 39.5 kDa can inhibit the spore germination and hyphal extension of *Trichosporium vesiculosum* fungus [192]. This fungus is the pathogenic agent that causes blister bark within a species of She-Oak tree (*Casuarina equisetifolia*).

Industrial application

Different techniques such as weight loss, electrochemical impedance spectroscopy, linear polarization, and potentiodynamic polarization assays revealed that the leaves extract of AP plant can serve as a powerful inhibitor of the corrosion of mild steel in hydrochloric acid media [193].

Conclusion

Despite AP's price decline in India's regional market [194] due to the global economic crisis demands for herbal medicinal products are boosted in general yet AP has been listed among prioritized plants for development and cultivation under the scheme of the National Medicinal Plants Board of India [195]. AP has been presented in the list of highly traded Indian medicinal plants [195]. In another survey, AP has been positioned as the 17th crop among the 32 prioritized medicinal plants of India with a demand of 2197.3 tons in year 2005–2006 and annual growth of 3.1% [7, 205, 206]. Priority of AP is regarded by herbal industries of developing countries such as Malaysia [207], Thailand [208] and Nigeria [23]. Furthermore, the profitable exploitation of biochemical compounds of AP is hampered due to their limited availability [196]. AP has taken the sixth place due to its role in attaining the United Nations millennium development goals (MDGs) target, which is fighting against HIV/AIDS, malaria and other diseases [197–199]. All these results imply that the absence of this plant in Iran's pharmaceutical market must be remedied by the implementation of precise programs to develop the cultivation of the herb as a new alternative crop in different agricultural ecosystems. Commencing such a plan in Iran will support the conservation and biodiversity of AP in this country since many experts have warned that the Indian AP's population is decreasing considerably [200, 209]. Besides, the government of Sri Lanka has prohibited the export of certain protected medicinal plant products such as *Coscinium fenestratum*, *Salacia reticulata* and even declared AP as an endangered species [201]. These circumstances provide an excellent opportunity for Iran to take its share in producing the plant and its commercial derivatives. Conducive natural conditions, availability of educated and skillful human resources and technicalities are supportive factors which can realize the dream of Nain-e Havandi's return into the plateau of Iran. Adding AP to the treasury of available medicinal plants will play a major role in Iran's herbal pharmaceutical industry.

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