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Journey of humic substances in healthcare: Regulatory and development perspective

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ABSTRACT: Humic substances are not new to mankind. These straw-colored organic acids, primarily derived from soil humus and plants, with hydrophobic core and hydrophilic exterior, are used as raw materials (such as shilajit, peat, etc.) for oral and topical applications since antiquity, as mentioned in the text of indigenous medicines. With the advancement of science, different components (humic acid and fulvic acid) are isolated, characterized, and evaluated for physicochemical and pharmacological properties. Despite possessing unique properties, their exploitation for healthcare purposes hasn't been competitive. They are primarily present in the dietary supplement category of products, despite having the potential to be explored in therapeutic categories. Major impediments to their growth and scientific or regulatory solutions are discussed in detail in this manuscript. A comprehensive survey of different products available in the texts of indigenous medicines and the marketed products are also included. The clinical trials and patents on the topic give an idea about the ongoing investigations. This review aims to explore the multifaceted roles of HS in promoting human health, particularly focusing on recent innovations in the fields of nutraceuticals, pharmaceuticals, and cosmetic products. Overall, it is concluded that HS has achieved great success in irrigation as fertilizer and for soil health, and it has different pharmacological or therapeutic potentials for human health.

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1. INTRODUCTION

Humic substances (HS) are straw-colored organic acids mainly derived from soil humus and plants. They have unique properties of exhibiting hydrophobic core and hydrophilic exterior. The major components are humic acid (HA) and fulvic acid (FA). FA is a category of HS with low molecular mass, constituting a short-chain compound that dissolves in acid or base solutions (Table 1). It comprises functional groups, such as carboxyl, phenol, hydroxyl, amine, and quinine groups, exhibiting a high complexation capacity with heavy metals (Zhong et al., 2023). HA, with a comparatively higher molecular mass, dissolves in alkaline pH and possesses several nutraceutical (NC) properties, including anti-inflammatory, antimicrobial, and immune regulation abilities.

Humic substances exhibit favorable impacts on plant physiology by enriching soil structure and fertility, impacting nutrient uptake and root architecture. HS are the massive constituents of soil organic matter (~60%) and are speculated to be a key ingredient of the terrestrial ecosystem. It is responsible for various complex chemical reactions that occur in the soil. One of the notable traits of HS is their capability to interact with metal ions, oxides, hydroxides, minerals, and organic compounds, comprising toxic contaminants. The sources of HS are peat, lignite, leonardite, coal, and natural water sources, such as rivers, lakes, and streams.

Unlike other natural ingredients, the journey of HS, for example, HA and FA, as human healthcare products has been remarkable. In ancient times, HS was used as a drug in different systems of medicines that still exist in indigenous medicine streams, such as Unani (Perso-Arabic Medicine) Ayurvedic (ancient/traditional Indian system), Chinese (Zhou et al., 2014), Russian (Schepetkin et al., 2003), and other countries of the Himalayan region. With the progression of time and scientific temperament, the evidence or science-based medicine (e.g., allopathic medicine) took over, as the natural ingredient-based medicines lacked sufficient scientific evidence. Other than uses in indigenous systems of medicine, it is also being explored in other facets of healthcare. In the given scenario, HS products have following four options

- To continue to be a part of traditional and alternative medicines as mentioned Tables 2, 7 and 8 (i.e., no need to generate safety and efficacy data).
- To position itself in the category of dietary supplements (DS) or NC (i.e., without any therapeutic label claim) as mentioned Tables 3 and 4.
- To attract the scientific community to generate scientific data and validate evidence of safety and efficacy and to be marketed as prescription products.
- To be explored for other categories of healthcare products, like excipient, cosmeceuticals (Table 5), and veterinary medicines.

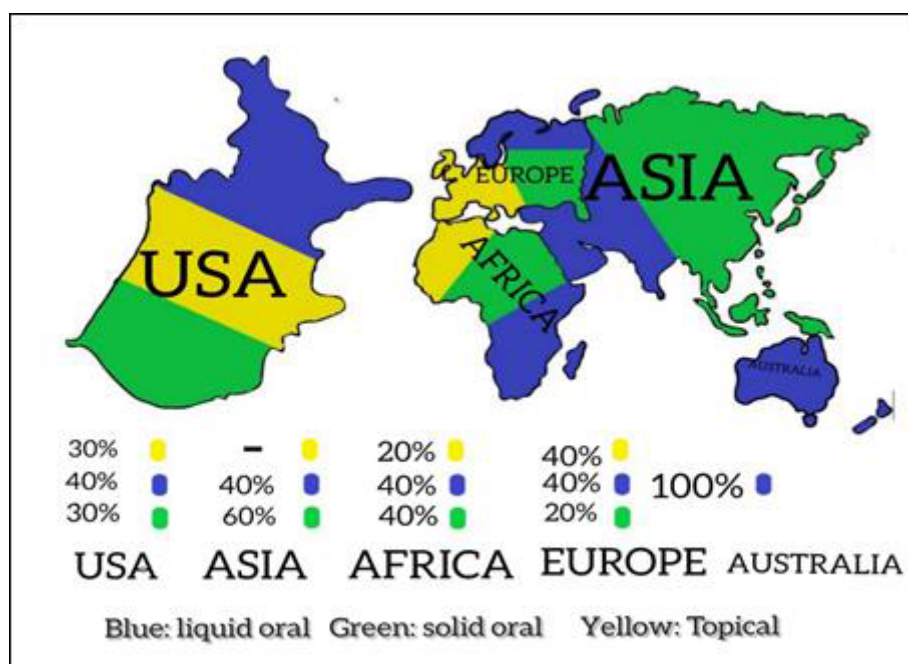


Figure 1. A pictorial presentation of all the available non-prescription HS-based products (dietary supplements and cosmetics/topicals). Each region is divided into three colors—blue (liquid oral HS products), green (solid oral HS products), and yellow (topical HS products). The area of any colored region is an approximate representation of percentage of that category of HS product in the particular region. For example, in Australia, almost all the HS products are of liquid oral category.

Table 1
Physicochemical properties of fulvic acid (FA) and humic acid (HA).

Humic substances	Color	Taste	Odor	Molecular weight (Daltons)	Total acidity	E4:E6 ratio	Solubility	Colloidal stability	Melting point	C:N ratio	Functional groups	Binding and complexation efficiency with metals and organic molecules
FA	Light yellow to yellowish brown powder	Bland	Odorless	200–3000	900–1400 mmol/100 g	High	Soluble in water at all pH values	Low	>300°C	High	Higher density of carboxyl and phenolic groups relative to its molecular size	High
HA	Dark brown to black amorphous powder	Bland	Odorless	3000–1,00,000	400–870 mmol/100 g	Low	Soluble in water above pH 3.0	High	>300°C	Low	Lower density of carboxyl and phenolic groups relative to its molecular size	Low

Note. Humic substances are complex organic macromolecules with a diverse range of properties and intricate structures; however, the physicochemical properties of humic substances are still not fully understood (Klučáková, 2016; Tarasevich et al., 2016).

Humic substances have the potential to be explored in all four categories, which is not a common phenomenon for all natural ingredients. Table 6 provides a list of some natural ingredients being explored in different categories. There are around 150 dietary DS-based products available globally, and research is being conducted to establish their safety profile and efficacy. Furthermore, it is also marketed as veterinary products, a unique aspect of HS, compared to other natural remedies. Its exploration as a pharmaceutical excipient is still under investigation. However, the journey so far and the way forward is not as simple as it appears. There are several reasons why HS are not explored extensively so far; this could be due to expensive raw materials (i.e., shilajit of Himalayan regions), structural complexity, and physicochemical properties (Gnananath et al., 2020). The manuscript discusses the challenges in acceptance of HS as healthcare products (prescription or dietary supplement category) generally asked by the stringent regulatory authorities worldwide. Despite successful sales as DS in the European Union (EU), United States, Commonwealth of Independent States (CIS) region, and Australia, the industry still faces tough questions during the approval (marketing authorization) process. The HS industry faces difficulties, unlike the pharmaceutical industry, because DS or NC marketing authorization in one country is difficult to be accepted as a reference for another region, although it supports the application.

2. MATERIALS AND METHODS

This study includes an extensive literature search (using different search engines, such as PubMed, Web of Science, Science Direct, Scopus, Embase, Google Scholar, and Ovid), company and regulatory agency's websites, and personal experiences in dealing with regulatory agencies during product approval.

3. HUMIC SUBSTANCES IN INDIGENOUS MEDICINE

Traditional or folk medicine is an indispensable facet of the global healthcare system. Its practices, passed down through generations, have proven to be effective in treating a myriad of ailments (Hill, 2009). From herbal remedies to acupuncture, traditional medicine offers an alternative to conventional treatments, and it has been an integral part of healthcare for centuries (Yuan et al., 2016). Therefore, it is important to embrace and respect the value of traditional medicine in order to provide holistic healthcare to all individuals. Indian traditional and folk systems, such as Ayurveda, Unani, Siddha, acupuncture, yoga, and indigenous therapies,

Table 2

Marketed herbal formulations containing shilajit.

S. No	Marketed herbal formulations	Ingredient(s)	Recommended dose (dosage form)	Proportion of shilajit used	Indication	Manufacturer
1.	Virya Shodhan vati	Calcined silver, Calcined tin, Coral calcium, shilajit , <i>Tinospora cordifolia</i> , <i>Cinnamomum camphora</i>	250-mg tablet	18%	Seminal disorders	Baidyanath
2.	Testoboost	Shilajit , <i>Withania somnifera</i> , <i>Chlorophytum arundinaceum</i>	250–500 mg (capsule)	40%	Low libido	Rasayanam
3.	Surge Max	<i>Withania somnifera</i> , shilajit , <i>Mucuna pruriens</i> , <i>Tribulus terrestris</i> , <i>Phyllanthus emblica</i> , and +5	250–500 mg (capsule)	15%	Low libido	Mars by GHC
4.	Shilapravang special	Shilajit , Coral calx, Calcined tin, Calcined chalcopyrites, and +16	250–500 mg (tablet)	15%	Adaptogen	Shree Dhootapapeshwar Ltd.
5.	Poweromin	Shilajit , <i>Withania somnifera</i> , <i>Ionidium suffruticosum</i> , <i>Mucuna pruriens</i> , <i>Asparagus racemosus</i> , and +4	As directed by physician (tablet)	25%	Adaptogen and immunomodulator	Apex Laboratories Private Ltd.
6.	Aswal Plus	<i>Withania somnifera</i> , <i>Asparagus racemosus</i> , <i>Pueraria tuberosa</i> , <i>Mucuna pruriens</i> , shilajit , and +7	250–500 mg (capsule)	8%	x	Gufic Biosciences Ltd.
7.	Goli Night Rider	Shilajit , <i>Withania somnifera</i> , <i>Asparagus racemosus</i> , silicate of magnesia, <i>Chlorophytum arundinaceum</i> , and +15	250–500 mg (pills)	5%	Aphrodisiac, erectile dysfunction, and premature ejaculation	Cure Herbal Remedies
8.	Mubhi Khas	<i>Bambusa arundinacea</i> , <i>Allium cepa</i> , <i>Orchis latifolia</i> , <i>Alpinia galangal</i> , shilajit , and +5	500 mg (capsule)	10%	General debility, and weakness of nerves	Hamdard Laboratories
9.	Hamdogen	<i>Allium cepa</i> , <i>Alpinia galangal</i> , <i>Zingiber officinale</i> , <i>Anacyclus pyrethrum</i> , shilajit , and +15	500 mg (capsule)	11%	Erectile dysfunction, and premature ejaculation	Hamdard Laboratories
10.	Active sperm	<i>Mucuna pruriens</i> , shilajit , <i>Pharis edulis</i> , <i>Glycyrrhiza glabra</i> , <i>Asparagus racemosus</i> , +6	5 g (semisolid)	8%	Low sperm count, premature ejaculation, and nocturnal emission	Cure Herbal Remedies
11.	VK4 Diacon	<i>Vasantakusumakara</i> , <i>Pachakarpur</i> , <i>Guduchisatva</i> , <i>Gomutra</i> shilajit , <i>Chandan</i> (Ht. wood), and <i>Abbraka bhasma</i>	250 mg (tablets)	27.4%	Diabetes and low libido	Venkateswara Ayurveda Nilayam Ltd.

Note. The table includes both prescription (Ayurvedic and Unani) and non-prescription products, such as dietary supplements or nutraceuticals.

are highly effective (Rizvi et al., 2022). According to the World Health Organization (WHO, 2023), an overwhelming number of countries, or 88% of the 170 member states, use traditional medicine.

Shilajit is used in the Indian subcontinent's traditional medicine as a rejuvenator and an adaptogen (Andrade et al., 2023). It is also known as *mumie*, *mumijo*, *asphaltum*, *punjabinum*, *arakul dshibal*, and *Hajar-ul-musa*. In traditional medicine of Tibet, it is called *zhaxun*, meaning the “Juice of rock” or “the essence of rock” (Frolova & Kiseleva, 1996). The word “*shilajit*” is derived from two Sanskrit words: *shila*, meaning rock, and *jeet*, meaning win, which collectively

means “conqueror of mountains” and “destroyer of weakness.” According to old traditional healers, there is hardly any curable disease that cannot be controlled or cured with shilajit (Agarwal et al., 2007). Shilajit is predominantly composed of paleohumus (80–85%), defined as “fully decomposed organic matter,” mainly derived from fossils that have been present inside the layers of rocks for many years, subjected to high temperature and pressure, ultimately metamorphosing into this material (Ghosal et al., 1997). It loses its viscosity in the summer season and oozes out from the rocks.

Chemically, shilajit contains gums, albuminoids, traces of resin and fatty acid, and a large quantity of benzoic and

Table 3

Solid oral dosage forms available in different countries.

S. No.	Products	Maximum daily dose with mentioned pack size/ recommended duration of use
1.	USA01	1/4 teaspoon per day (FA not quantified)
2.	USA02	2 capsules daily (250-mg shilajit–FA complex)
3.	USA03	4 capsules daily (200-mg shilajit–FA complex), 30 days pack size
4.	USA04	4 capsules daily (FA not quantified), 30 days pack size
5.	USA05	4 capsules daily (5% FA), 30 days pack size
6.	USA06	2 capsules daily (350-mg proprietary blend in each capsule)
7.	USA07	2 capsules daily (HA and FA not quantified), 45- and 30-day pack size
8.	USA08	10 g (HA+FA complex), dose not mentioned
9.	USA09	Adult: 2 capsules daily (FA not quantified), 90 capsules pack
10.	USA10	1 capsule daily (FA 10 mg), 60 capsules pack
11.	USA11	4 capsules daily (FA not quantified), 30 days' supply
12.	USA12	2 capsules daily (FA not quantified), 1-month supply
13.	USA13	2 capsules daily (FA not quantified), 1-month supply
14.	USA14	2 capsules daily (40 mg daily)
15.	USA15	1 soft gel daily (FA not quantified), 2 months' pack
16.	USA16	1 caplet daily (FA not quantified), 3 months' supply
17.	USA17	2 tablets daily (460-mg FA), 1 month's pack
18.	USA18	2 capsules daily (HA+FA not quantified), 2 months' supply
19.	USA19	2 capsules daily (70 mg daily), 2 months' supply
20.	USA20	4 capsules daily (HA+FA not quantified), 3 months pack size
21.	USA21	2 capsules daily for first 2–4 weeks, then 4 capsules per day
22.	USA22	48-g bar (HA+FA not quantified)
23.	USA23	2 capsules daily (FA: 600 mg (50% FA per capsule), 30-day supply
24.	USA24	4 capsules daily (400 mg per 4 capsules)
25.	USA25	Adult: 4 capsules daily, children: 2 capsules daily (FA not quantified)
26.	USA26	4 capsules daily (450 mg per 4 capsules)
27.	CA01	2 capsules daily (FA: 8.85 mg/capsule), 1 month's supply
28.	IND01	2 capsules daily (NLT 1% FA/cap)
29.	IND02	1–2 capsules daily (FA not quantified)
30.	IND03	40% FA per capsule
31.	IND04	2 capsules daily (FA 40%), 30-day supply
32.	SA01	Adult & children: 2 capsules daily (FA 150 mg)
33.	SA02	2 capsules daily (500-mg FA total)
34.	SA03	3 tablets daily (1000-mg FA/tablet)
35.	SA04	6 capsules daily (135-mg CHD-FA/capsule)
36.	SA05	CHD-FA 60%
37.	SA06	Adult: 4 capsules daily, children: 2 capsules daily (FA not quantified)

(continues)

Table 3

Continued.

S. No.	Products	Maximum daily dose with mentioned pack size/ recommended duration of use
38.	SA07	1/4 Teaspoon full daily, i.e., around 230-g product (FA not quantified)
39.	SA08	1 Capsule daily (FA not quantified), 90 days' supply
40.	SA09	3 Tablets daily (FA not quantified)
41.	SA10	3 Tablets daily (FA not quantified)
42.	NL01	Adult: 6 capsules daily, children: 3 capsules daily. (HA not quantified)
43.	NL02	HA+FA not quantified, 1 month's supply
44.	NL03	HA+FA not quantified, 1 month's supply
45.	HU01	1 bar contains FA (120 mg)+HA (50 mg), and other ingredients. Children: 1 bar, Adult: 2–4 bars
46.	HU02	Adult: 4 capsules daily (1200-mg FA/capsule), children: 1 capsule daily
47.	AU01	HA+FA (dose not clear)
48.	AU02	3 capsules daily (HA+FA proprietary blend), 60 capsules pack size
49.	AU03	4 capsules daily (FA not quantified)
50.	AU04	1 capsule daily (350 mg of HA+FA blend)

Notes. The names of the products have been given in alphanumeric form, prefixed with abbreviated country name. The data were collected from the products' labels, websites, emails, and chatbots of various company websites. The table includes information from companies, such as HealthForce SuperFoods™, Jarrow Formulas, Physique Enhancing Science, XYMOGEN, AI Sports Nutrition, Joy to Live, Prescript Assist, Huminal, Supreme Fulvic, Biotivia, Global Healing Center, Irwin Naturals, Life Extension, MuscleTech™, Natural Dynamix, Omica Health, Patient One MediNutritionals™, Systemic Formulas Inc., Morningstar Minerals, HUmineral, Roar to Life, Natural-ly, BlackMP – Foods for Athletes, Nutricology, Mineralife, Vital humic, Isha Agro Developers Pvt. Ltd., Dabur, Health Genuine India Pvt. Ltd, Bixa Botanical, CHD-Fulvic Acid, BioBalance, Fulvic Health, Biosil, Oshun Health, Health Solution, Hymato, Life Springs, Sisel International, Zeo Natural, and Healthy 100'. Abbreviations: USA: United States of America; IND: India; SA: South Africa; NL: the Netherlands; HU: Hungary; CA: Canada; and AUS: Australia. NLT: not less than.

Various humic substances were found in the products, and their names, as per label claims, have been provided.

hippuric acids and their salts. The main active substances among all the medicinal compounds present in it are benzoic acid and benzoates (Kamgar et al., 2023), including bioactive oxygenated dibenzo- α -pyrones, tirucallane triterpenes, phenolic lipids, and small amount of tannoids. Shilajit, obtained from different sources, is a complex heterogeneous mixture, rather than a well-defined natural product and has varying amounts of both FA and HA as well as other compounds; although the overall structures of these compounds are poorly defined. However, now it has been standardized on the basis of its major organic constituents that shilajit mainly includes organic matter, HA, FA, and volatile and fat soluble components (Ghosal et al., 1995).

Table 4

Liquid oral products available in the global market.

S. No.	Product	Maximum dose (per day) with mentioned pack size/ recommended duration of use
1.	USA01	30 mL
2.	USA01	5 mL (HA+FA not quantified)
3.	USA02	HA not quantified
4.	USA03	5 mL daily (HA+FA not quantified), 47 days' pack size
5.	USA04	15 mL (each 15 mL contains 5 g of CHD-FA)
6.	USA05	HA+FA not quantified
7.	USA06	Up to 4 tablespoons, child-graded into several ages, up to 1 year. 60 days' pack size
8.	USA07	Not quantified (FA)
9.	USA08	FA+HA not quantified
10.	USA09	7 drops (FA not quantified)
11.	USA10	1 mL (250-mg FA), 60-mL pack size
12.	USA11	1 teaspoon (FA not quantified), 1-month pack size
13.	USA12	0.5–1 mL diluted with water (10–15% FA)
14.	USA13	Adult: 36 drops/day; children: 4 drops/day, 3.5-month supply (FA not quantified)
15.	USA14	Adult: 48 drops daily; children: 12 drops per day (FA not quantified), 1-month supply
16.	USA15	Adult: 21 drops/day; children: 2 drops/day (FA not quantified), 6-month supply
17.	USA16	32 drops daily (proprietary blend), 39 days' supply
18.	USA17	32 drops daily (proprietary blend), 49 days' supply
19.	USA18	30 drops daily (FA not quantified), 46 days' supply
20.	USA19	7 drops daily, 4 months' supply (FA not quantified)
21.	USA20	0.5–1.0 mL daily (1–5% FA)
22.	USA21	1 mL daily (FA not quantified)
23.	USA22	Adult: 7.5 mL daily; children (11+yr): 7.5 mL daily (FA not quantified), 1-month supply
24.	USA23	1 fluid ounce daily (FA not quantified), 30 day's supply
25.	USA24	1 fluid ounce daily (FA not quantified), 30 day's supply
26.	USA25	5–10 mL daily (FA not quantified)
27.	USA26	Dose not mentioned (FA not quantified)
28.	USA27	15 drops in a day (FA not quantified)
29.	USA28	3 teaspoons daily (27-g FA complex)
30.	USA29	1 fluid ounce daily (25-g FA complex)
31.	USA30	1 fluid ounce daily (25-g FA complex)
32.	USA31	0.5 ounce (0.663%), 3.785 L pack
33.	USA32	30 mL daily, 1-month supply (FA not quantified)
34.	USA33	1 teaspoon (FA not quantified), 50 days pack
35.	USA34	8 sprays under tongue; children: 6 sprays (proprietary blend), 30 mL
36.	USA35	8 sprays under tongue; children: 6 sprays (FA not quantified)
37.	USA36	6 capsules daily (FA not quantified), 15 days' supply
38.	USA37	360 drops daily (proprietary blend)
39.	USA38	2 mL daily (proprietary blend), 15 day's supply
40.	USA39	40 drops daily (proprietary blend)

(continues)

Table 4

Continued

S. No.	Product	Maximum dose (per day) with mentioned pack size/ recommended duration of use
41.	USA40	7 drops (FA not quantified), 30 mL
42.	USA41	1.23 mL daily (FA not quantified), 1-month supply
43.	USA42	0.5 teaspoon daily (proprietary blend), 59.2-mL pack size
44.	USA43	39 drops daily (proprietary blend), 30 mL
45.	USA44	Adult: 9 drops daily; children: 1 drop daily (FA not quantified), 30-mL pack size
46.	USA45	4.5 mL daily (proprietary blend), 120 mL
47.	USA46	30 mL (FA not quantified)
48.	USA47	30 mL (100-mg FA), 1-month pack size
49.	USA48	Adult: 15 mL; children: 5 mL (FA not quantified)
50.	USA49	4 drops (FA not quantified)
51.	USA50	Adult: 15 mL; children: 5 mL, 1-month pack (FA not quantified)
52.	USA51	2 tablespoons (FA not quantified), 1-month supply
53.	USA52	Adult: 1 oz daily; children: 1 oz (FA not quantified), 1-month supply
54.	USA54	6 mL (FA+HA not quantified)
55.	USA55	180 mL, FA not quantified
56.	USA56	FA+HA, dose not given
57.	USA57	1 mL daily (FA not quantified), 6 months' supply
58.	USA58	3 mL daily (FA not quantified), 30 days' supply
59.	USA59	3 teaspoons (HA not quantified)
60.	USA60	21 drops a day (3% FA)
61.	USA61	15 mL daily (FA+HA not quantified)
62.	USA62	1 fluid ounce daily (FA+HA not quantified)
63.	USA63	3 fluid ounces (1 Oz FA)
64.	USA64	1 ounce daily (FA+HA not quantified)
65.	USA65	20 drops daily (70-mg black FA)
66.	USA66	1 ounce daily (FA+HA not quantified)
67.	USA67	1 ounce daily (HA+FA 325 mg)
68.	USA68	4 mL (60 drops) daily (FA > 10%)
69.	USA69	Adult: 9 drops daily; children: 1 drop daily (FA not quantified), 30-mL pack size
70.	USA70	2 mL daily (FA 6–8%)
71.	USA71	Adults: 18 drops/day; kids: 5 drops/day (100% humic/fulvic minerals), 60 mL
72.	USA72	1 fluid ounce (proprietary blend), 30 days' supply
73.	USA73	2 fluid ounce (9-mg FA/1 fl. oz), 30 days' supply
74.	USA74	30 mL (FA+HA complex)
75.	USA75	2 tablespoons (FA not quantified)
76.	USA76	3 tablespoons daily (FA 14.04 mg/1 tsp), 24 doses per 4-oz bottle
77.	USA77	16 drops daily (proprietary blend)
78.	USA78	2 capsules per day (FA+HA complex), 30 days' supply
79.	USA79	10 drops daily (38-mg FA/mL)
80.	USA80	1 mL (100-g FA), 60-mL pack

(continues)

Table 4
Continued.

S. No.	Product	Maximum dose (per day) with mentioned pack size/ recommended duration of use
81.	USA81	1 oz per packet (FA not quantified)
82.	USA82	1 oz (FA not quantified), 1-month pack size
83.	USA83	15 mL (FA not quantified)
84.	USA84	5 mL (FA not quantified)
85.	CA01	5 mL (2.7–5.7% FA), 10–1000-L pack size
86.	CA02	30 drops daily (FA not quantified)
87.	CA03	Dose not mentioned (3% FA)
88.	CA04	9 mL daily (FA 100% in solution)
89.	CA05	1 tablespoon daily (HA–FA: 400 mg/15 mL)
90.	SA01	FA not quantified, 100-mL pack size
91.	SA02	Adult: 15 mL daily (FA not quantified), 1-month supply
92.	SA03	60 mL daily (each 225 mL contains 45-mg FA)
93.	SA04	Adult: 4 sprays; children: 2 sprays (each 1 mL contains 0.6-mL CHD-FA)
94.	SA05	16–32 mL for 1 month (up to 15% FA)
95.	SA06	100 mL (FA not quantified)
96.	SA07	Children: 40 mL (3-mL FA/5-mL dose), 100-mL pack size
97.	SA08	Use 60 mL daily (each 225 mL contains 45-mg FA), 225-mL pack size
98.	SA09	15 mL daily (each 15 mL contains 14.5-mL CHD-FA), 500-mL pack size
99.	SA10	50 mL daily (FA 8%)
100.	SA11	32 mL daily (15% FA)
101.	AUS01	Adults: 120 mL/day; children: 1 teaspoon/25 lbs body weight (FA not quantified)
102.	AUS02	Adult: 10 mL daily; children: 2 mL daily (FA not quantified)
103.	AUS03	HA+FA not quantified
104.	AUS04	250 mL daily (FA not quantified)
105.	AUS05	24 drops daily (FA not quantified), 50-mL pack size
106.	UK01	Mineral water, FA not quantified
107.	UK02	Per serving of concentrate (20 fluid oz) 400 mg HA+FA complex), 1 serving per container
108.	UK03	Per serving of concentrate: 0.75 fluid oz (22 mL) contains 1252-mg HA–FA complex), 1 serving/concentrate
109.	UK04	Per serving of concentrate: 8 fluid oz (1252-mg HA–FA complex), 2.5 serving in a pack
110.	UK05	Fulvic/humic liquid concentrate 1%
111.	UK06	As much as you can
112.	UK07	Adult: 28 drops daily; children: 14 drops, (FA not quantified)
113.	UK08	Adult: 28 drops; children: 14 drops (FA not quantified), 50-mL pack size
114.	HK01	15 drops, 4–5 times daily (60% FA)
115.	HK02	Apply for skin irritations, cuts, or wounds for inflammation and prevent infection
116.	HK03	2.5 mL, two times a day (60% FA). 5×10-mL pack size
117.	HK01	10 mL daily. (FA 480 mg) & HA (200 mg)

(continues)

Table 4
Continued.

S. No.	Product	Maximum dose (per day) with mentioned pack size/ recommended duration of use
118.	NL01	90 mL daily (FA not quantified)
119.	NZ01	20 mL daily (FA not quantified)

Notes. The names of the products are given in alphanumeric form, prefixed with abbreviated country name. The data were sourced from product labels, websites, emails, and chatbots of various company websites. The table includes information from a diverse range of companies, such as Mineralife, Supreme Fulvic, Zenful (a subsidiary of Earthwater UK), Foods for Athletes, Trace Minerals Research, Elixia, Optimally, Organic, Omica Organics™, Pure Fulvic Minerals, Mineral Logic, Alpha Health Support, Vital Earth Minerals, Phyllia [de M.], ARCADIA, Drucker Labs, Mana Life Laboratory (a division of BioAg Corp), Nature's Sunshine, Ayurvedic Rasayanas, BodyHealth, Designs for Health, Get Healthy Again, Global Healing Centre, Global Health Trax, InfoWars Life, InfoWars Life Super, Liquid Zeolite Co. Inc., Purium, Nature's Sunshine, New Sun*, NOW*, NutraMedix, Protocol for Life Balance, Vitabase, Protect Cells, Morningstar Minerals, Trace Minerals Research, Dirobi, Doc of Detox, Vital Earth Minerals, Motherearthlabs, Pure Planet, Creative Concept Labs, Cell Cynergy Nutrition, Vital Earth Minerals, Natural Health Orgnics, Herb Anomic, Mommys Miracles, SBR Nutrition, Leaf Source, Trace Minerals, Athletic Elite 10, Sunwarrior, FulvicXcell Products Ltd., Humalife, American Nutraceuticals, Innotech Nutrition, Fulhold Pharma Ltd., Fulvic Force, CHD-Fulvic Acid, Sfera Bio Nutrition, Oshun Health, Oshun Health, Reach for Life, Life Springs, GO2 Liquid Minerals, Alkaline, Athletes Advantage, Blk Beverages, Earth water, 77 Blackwater, Ancient Purity, I.S. Natura, Hymato, Health Solution, and NuCell+.

Abbreviations of the countries: USA: United States of America, IND: India, SA: South Africa, NL: the Netherlands, HU: Hungary, CA: Canada, AUS: Australia, UK: United Kingdom, and HK: Hongkong.

Various humic substances were found in the products, and their names, as per label claims, have been provided.

In the given manuscript, two major Indian systems of medicine (Ayurveda and Unani) are included. Shilajit, a major raw material of the Indian subcontinent, mainly contains HS. Globally, FA is often extracted from other deposits, such as peat lignite, leonardite, and coal. On the other hand, FA is also found in natural water sources, such as rivers, lakes, and streams.

As a prescription product, also known as a prescription medication or drug, shilajit is legally available only with a valid prescription from a licensed healthcare professional. Such medications are typically regulated by health authorities to ensure their safe and appropriate usage. Shilajit is the only humic substance used in different products of Indian system of medicine. The products are included in the formulary and pharmacopoeia of indigenous medicines (see [Tables 7 and 8](#)).

4. HUMIC SUBSTANCES AS DIETARY SUPPLEMENTS IN GLOBAL MARKET

DS or NC are included in the category of non-prescription products. They have no label claims for any therapeutic

Table 5

Topical or cosmetic products available in global market, encompassing spritz, sprays, creams, lotions, gels, body cleanser, shampoo, eye drops, eye creams, conditioners, nasal spray, throat spray, wound care spray, cleansing balm, bath powder, and face mask.

S. No	Product name	Company	Country	Dose with mentioned pack size/recommended duration of use
1.	Humic/pure fulvic skin spritz	Humineral	USA	(HA+FA not quantified) 8 oz for 2 months
2.	Fulom moisturizing cream	Fulom	USA	50-mL cream (FA not quantified)
3.	Fulom hydrating lotion			236 mL (FA not quantified)
4.	Fulom face and body cleanser			237 mL (FA not quantified)
5.	Reconnect rephyl	Phyllia [de M.]	USA	FA not quantified
6.	Connect rephyl			
7.	Condition rephyl			
8.	Clean rephyl			
9.	Reconnect			
10.	Connect			
11.	Condition			
12.	Clean shampoo			
13.	Derma boost skin rejuvenator	Morningstar Minerals	USA	FA not quantified, adult & children both
14.	Fulvic acid × 100	Optimally Organic	USA	Adult: 48 drops daily; children: 12 drops per day. FA not quantified, 1-month supply
15.	Fulvic acid × 200			Apply directly to the affected area; FA not quantified
16.	Fulvic acid × 350			Apply at full concentration directly, 60 mL, 6-month supply
17.	Fulom moisturizing cream	Fulom	USA	50 mL, FA not quantified
18.	Bright eyes	Doc of Detox	USA	Apply as much, FA not quantified
19.	Glow	ARCADIA	USA	Quantity not specified; FA not quantified
20.	OccuFUL® G topical gel	CHD-FA	SA	CHD-FA, 75 mL
21.	FulviBan gel	Fulvi Ban	SA	25 g, each 1 g contains 0.6-g CHD-FA
22.	Fulvi act antifungal cream	Fulvi Ban	SA	25 g, each 1 g contains 0.6-g CHD-FA
23.	Fulvi ban wound care spray	Fulvi Ban	SA	50 mL (25 mL FA)
24.	Skoon retinin cream	CHD-FA	SA	30 mL, FA not quantified
25.	Skoon whitewash	CHD-FA	SA	100 mL, FA not quantified
26.	FulviAct Nasal Clear Spray	CHD-FA	SA	30 mL, each 30 mL contain 7.5-mL CHD-FA
27.	OccuFUL® T throat spray	CHD-FA	SA	30 mL, each 1 mL contains 0.6-g/mL CHD-FA
28.	Fulvic face cream	Victoria Health	UK	60 mL, FA not quantified
29.	Fulvic Mineral Face & Body Spritz	Golden Apple Organics		8 fl oz, FA not quantified
30.	Thermal cleansing balm	OMOROVICZA	UK	100 mL, FA not quantified
31.	Pure & Fulvic gel	Health Solution	NL	8%
32.	Pure & fulvic skin spray			50 mL, FA not quantified
33.	HUMASOAK Bath Powder			100 g, HA+FA not quantified
34.	Pure & Fulvic Skin Spray			50 mL, FA not quantified
35.	Avantari regenerating shampoo	I.S. Natura	HK	250 mL (FA not quantified)
36.	Bioactive face mask	Turbliiss	Estonia	60 mL, use thrice per week (FA not quantified)

Note. The data were collected from product labels, websites, emails, and chatbots associated with various company websites.

activity and are sold without prescription (a type of over-the-counter [OTC] products). This is the most common category of HS-based products and are available globally and even in some of the most stringent regulatory framework countries. Companies in this category typically operate on a small scale. The products are available in the form of oral solids (tablets,

capsules, caplets, bars, and powder), oral liquids (solution and suspension), and topical products. Table 3 and Table 4 present some surprising facts about the available products, such as the following:

There is a significant variation in the dose of HS up to 4.8-g FA per day for adults to 300 mg for children.

Table 6

Examples of some natural ingredients used across different categories of products.

Ingredients	Mol. wt./Mol. structure	Pharmaceutical excipient status			Dietary supplement	Drug status (indigenous systems such as Ayurveda, Unani, etc.)	Food status
		US FDA_IIG ^s	Pharmacopoeia	Non-official compendia*			
Acacia (CAS No 9000-01-5)	Complex, loose aggregate of carbohydrate. Mol wt 2,40,000–5,80,000	✓ (oral/topical)	USP-NF, BP, PhEur, JP	✓	✓	✓	Food additive-EU, FSSAI
Almond oil (CAS No 8007-69-0)	Not defined, mixture of different compounds	✓ (topical)	USP-NF, BP, PhEur	✓	✓	✓ (also as emollient)	Food and Chemical Codex-US, FSSAI
Guar gum (CAS No 9000-30-0)	(C ₆ H ₁₂ O ₆) _n ≈ 2,20,000	✓ (oral/topical)	USP-NF, BP, PhEur	✓	✓	✓	Food additive-EU & FSSAI
Olive oil (CAS No 8001-25-00)	Not defined, mixture of acids	✓ (oral/topical)	USP-NF, BP, PhEur, JP	✓	✓	✓	Well accepted

Notes. ^sThe Inactive Ingredients Database of US FDA can be accessed at <https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download>. ^{*}The *Handbook of Pharmaceutical Excipients* is a nonofficial compendium and is widely referred for information on excipients.

USP-NF: United States Pharmacopoeia (USP) and National Formulary (NF); BP: British Pharmacopoeia; PhEur: European Pharmacopoeia; JP: Japanese Pharmacopoeia; FSSAI: Food Safety and Standards Authority of India.

There is a substantial variation in the regimen of consumption. The recommended regimen is up to 6 months in some orally consumed products, while in some labels, the recommended duration hasn't been mentioned, allowing usage for unlimited period.

There is no quantification of HS in some of the products, and the daily intake of HS is not quantified for both adult and children.

5. ROLE OF HUMIC SUBSTANCES AS COSMECEUTICALS

Cosmeceuticals are the cosmetics exhibiting medicinal properties because of the existence of bioactive components corresponding to medicinal benefits (Choi & Berson, 2006). The distinct comparison between an inert cosmetic and a cosmeceutical can be relatively befitting, as an inert cosmetic is meant for aesthetic augmentation and quality enhancement whereas cosmeceutical is perceived for pharmacological healing (Kligman, 2000).

Humic substances have immense therapeutic potential, and hence cosmetics that include HS fabricate a significant proportion of cosmeceuticals. Globally, products constituting a specified combination of salicylic acid and HA in face cleansing and peeling creams serve manifold purposes, with skin enhancement being main function. The role of HS as bio-fertilizers and shoot growth-promoting agents is also worth acknowledging. HS are also often combined with herbal phytoconstituents, such as aloe, apple cider, and

epigallocatechin-3-gallate (EGCG), to constitute veterinary and infant cosmeceuticals that have wide applications across the globe. Advantages of HS in skin care are as follows:

- Promoting cellular uptake of nutrients.
- Having established detoxification properties.
- Being of natural origin with minimum involvement of chemicals during extraction.
- Claiming properties, such as healing, antioxidant, anti-aging, and astringent.

Today, mud, mineral and peat baths, as well as various natural packs and face masks, are offered in spas and wellness centers worldwide. Balneotherapy (a traditional bathing therapy) involves immersing a subject in natural mineral water or mineral-laden mud. The active substances in these mud baths are HS. For this reason, interest has increased in the use of HA and FA in dermatology and cosmetics.

6. HUMIC SUBSTANCES IN MODERN MEDICINE

Carbohydrate-derived FA (CHD-FA) is one of the products of this category that has undergone clinical trials to establish safety and efficacy for the topical treatment of eczema/dermatitis. Preclinical safety and efficacy data are available for this product with different indications. Manufacturers claim it to be a better FA than the naturally obtained HS. However, researchers working on HS find it debatable to be called CHD-FA, as the process of obtaining it does not adhere to widely accepted definitions.

Table 7

Formulations from the Unani system of medicine.

S. No.	Name of product	Ingredient (s)	Recommended dose (dosage form)	Proportion of shilajit used	Indication(s)	References
1.	Sufoof-e-Suzak Qawi	<i>Zizyphus jujube</i> , <i>Butea monosperma</i> , <i>Tinospora cordifolia</i> , shilajit , <i>Rheum officianale</i> , and +6	5–10 g	5%	Gonorrhoea	Yusufuddin, 2006
2.	Habb-e-Suzak Muzmin	<i>Bergenia ligulata</i> , <i>Ipomoea alba</i> , <i>Elettaria cardamomum</i> , <i>Terminalia chebula</i> , shilajit , and +3	3 g (tablet)	8.5%	Gonorrhoea and burning micturition	Yusufuddin, 2006
3.	Sufoof-e-Ziabetus Qawi	<i>Cochlospermum religiosum</i> , <i>Bambusa bambos</i> , <i>Aluminium silicate</i> , <i>marl</i> , shilajit , and +17	3–5 g	4%	Polyurea, diabetes insipidus, and renal insufficiency	Yusufuddin, 2006
4.	Habb-e-Luknat	<i>Myrica esculenta</i> , <i>Rosa damascena</i> , <i>Cymbopogon citratus</i> , <i>Syzygium aromatic</i> , shilajit , and +3	550 mg–1g (tablet)	5.5%	Stammer	Yusufuddin, 2007
5.	Majoon-e-Regmahi	<i>Sphenomorphus indicus</i> , <i>Holarrhena antidysentrica</i> , <i>Papaver somniferum</i> , <i>Curcuma zedoaria</i> , shilajit , and +30	5–10 g (Oral/semi-solid)	1%	Sexual weakness and spermatorrhoea	Yusufuddin, 2008
6.	Habb-e-Mumsik Tilai	<i>Hyoscyamus niger</i> , <i>Centaurea behen</i> , <i>Papaver somniferum</i> , <i>Datura metel</i> , shilajit , and +10	600 mg daily (tablet)	4%	Sexual weakness and nerve weakness	Yusufuddin, 2008
7.	Qurs-e-Salajeet	<i>Centaurea behen</i> , shilajit , <i>Accacia arabica</i> , <i>Calcined egg</i> , <i>Calcined tin</i> , and +5	260 mg b.i.d. (tablet)	15%	General weakness, spermatorrhoea, and polyurea	Yusufuddin, 2001
8.	Sharbat-e-Salajeet	<i>Trachyspermum ammi</i> , <i>Amomum subulatum</i> , <i>Apium graveolens</i> , <i>Cinnamomum zeylanicum</i> , <i>Zingiber officianale</i> , <i>Cinnamomum tamala</i> , <i>Piper nigrum</i> , shilajit , <i>Sugar</i> , and <i>Citrus aurantifolia</i>	Syrup 6 mL twice a day.	4%	Spermatorrhoea	Yusufuddin, 2001
9.	Habb-e-Muqawwi Khas	Shilajit , <i>Pistacia lentisus</i> , <i>Bezoar stone</i> , <i>Pinctada imbricata radiata</i> , <i>Bambusa arundinacea</i> , and +10	5 g	6%	Nerve weakness and sexual debility	Yusufuddin, 2001
10.	Habb-e-mumsik jadeed	<i>Cannabis sativa</i> , <i>Hyoscyamus niger</i> , <i>Peganum harmala</i> , shilajit , <i>Myristica fragrans</i> , and +7	5 g	8%	Premature ejaculation	Yusufuddin, 2001
11.	Habb-e-Nishat jadeed	Shilajit , <i>Calcined dust of zinc</i> , <i>tin</i> , <i>led</i> , <i>silver</i> , and <i>ruby</i> , <i>Crocus sativus</i> , <i>Rosa damascena</i> , <i>Myristica fragrans</i> , and +19	5 g	5.5%	Sexual debility	Yusufuddin, 2001
12.	Zehbi	<i>Melissa parviflora</i> , <i>Centaurea behen</i> , <i>Chiranthus cheiri</i> , <i>Salvia haematodes</i> , shilajit , and +11	6 g	8.5%	Cerebral asthenia, weakness of heart, neurasthenia, and palpitation	Yusufuddin, 2001
13.	Imsakeen	<i>Acacia arabica</i> , <i>Cannabis sativa</i> , <i>Hyoscyamus niger</i> , <i>Musua ferrea</i> , shilajit , and +14	6 g	4%	Premature ejaculation	Yusufuddin, 2001
14.	Majoon Nishat Angaiz	<i>Alpinia galanga</i> , <i>Myristica fragrans</i> , <i>Tribulus terrestris</i> , <i>Cinnamomum cassia</i> , shilajit , and +15	6 g	1%	Sexual debility, impotency, and debility of vital organs	Yusufuddin, 2001
15.	Muqawwi mumsik	Shilajit , <i>Cinnamomum zeylanicum</i> , <i>Pistacia lentisus</i> , <i>Myristica fragrans</i> , <i>Nardostachys jatamansi</i> , and +15	1 g	0.04%	Premature ejaculation and sexual debility	Yusufuddin, 2001

Notes. NFUM- National Formulary of Unani Medicine.

Each product contains several ingredients, with only the initial four ingredients specified. The humic material is highlighted in bold, while the remaining ingredients are presented as a total number.

Several clinical trials have been conducted and are ongoing to prove the therapeutic efficacy and potential of HA and FA (Table 9). An investigational randomized, double-blind clinical trial, comprising 15 males, was conducted to evaluate comparable efficiency with a placebo as

a control measure for the treatment of erectile dysfunction and to enhance sexual libido. Results of the study showed an improvement in the sexual health scores as well as augmentation in sexual quality score (NCT02794454) (Sandip & Shirish, 2016).

Table 8

Formulations mentioned from the Ayurvedic system of medicine.

S. No.	Ayurvedic formulation	Ingredient(s)	Recommended dose	Proportion of shilajit used	Indication	References
1.	Arogyavardhini gutika	<i>Mercury, sulphur, Calcined iron, Calcined mica, shilajit, and +8</i>	250 mg–500 mg	7%	Chronic fever, disorder of adipose tissue, and liver disorders	Ayurvedic Pharmacopoeia Committee, Ministry of Health and Family Welfare, Department of AYUSH, Govt. of India, 2000
2.	Siva gutika (laghu)	<i>Holarrhena antidysenterica, Terminalia bellerica, Terminalia chebula, Emblica officinalis, shilajit, and +17</i>	6 g	6%	Anemia, skin diseases, fever, bronchial asthma, hemorrhoids, dysuria, and tuberculosis	Ayurvedic Pharmacopoeia Committee, Ministry of Health and Family Welfare, Department of AYUSH, Govt. of India, 2000
3.	Traikantaka Ghrita	<i>Tribulus terrestris, Elettaria cardamomum, shilajit, Bergenia ligulata, Glycyrrhiza glabra, and +12</i>	12 g	5%	Dysuria, urinary disorders, and calculus	Ayurvedic Pharmacopoeia Committee, Ministry of Health and Family Welfare, Department of AYUSH, Govt. of India, 2000
4.	Satavari guda	<i>Saccharum officinarum, Asparagus racemosus, ghee, Zingiber officinale, shilajit, and +13</i>	6 g	5%	Dysuria, urinary disorders, menstrual disorder, and jaundice	Ayurvedic Pharmacopoeia Committee, Ministry of Health and Family Welfare, Department of AYUSH, Govt. of India, 2000
5.	Prabhakara vati	<i>Copper pyrite, Calcined iron, Calcined mica, Bambusa bambos, shilajit, and Terminalia arjuna</i>	125–250 mg	20%	Heart disease	Ayurvedic Pharmacopoeia Committee, Ministry of Health and Family Welfare, Department of AYUSH, Govt. of India, 2000
6.	Silajitvadi Lauha	<i>Shilajit, honey, Zingiber officinale, Piper nigrum, Piper longum, and Calcined dust of gold and iron</i>	250 mg	8%	Blood loss	Ayurvedic Pharmacopoeia Committee, Ministry of Health and Family Welfare, Department of AYUSH, Govt. of India, 2000
7.	Kantavallabha rasa	<i>Calcined iron, Iron oxide (Fe₂O₃), Borax, Realgar, shilajit, mercury, and sulfur</i>	250–500 mg	4%	Anemia, pthisis, cough, dyspnoea, disorder of spleen	Ayurvedic Pharmacopoeia Committee, Ministry of Health and Family Welfare, Department of AYUSH, Govt. of India, 2003
8.	Sarvatobhadra vati	<i>Calcined gold, Calcined silver, Calcined mica, Calcined iron, shilajit, and +3</i>	125 mg	14%	Kidney disorders and Disorders of urinary system	Ayurvedic Pharmacopoeia Committee, Ministry of Health and Family Welfare, Department of AYUSH, Govt. of India, 2003
9.	Yogaraja	<i>Terminalia chebula, Terminalia bellerica, Phyllanthus emblica, Zingiber officinale, shilajit, and +6</i>	250–500 mg	15%	Anemia, tuberculosis, cough, fever, and excessive flow of urine	Ayurvedic Pharmacopoeia Committee, Ministry of Health and Family Welfare, Department of AYUSH, Govt. of India, 2003
10.	Purnacandra rasa	<i>HgS, mica, Calcined iron, shilajit, Calcined pyrites, and Embelia ribes</i>	250 mg	15%	Aphrodisiac	Ayurvedic Pharmacopoeia Committee, Ministry of Health and Family Welfare, Department of AYUSH, Govt. of India, 2003

Notes. AFI: Ayurvedic Formulary of India.

While numerous ingredients are included in each product, the first four ingredients are listed individually, and the humic material is highlighted in bold.

The remaining ingredients are presented as a total number.

An interventional study intended to assess the effectiveness of shilajit pill in sexually active married women was conducted in Tarbiat Modares School of Medical Sciences, Nasr, Tehran. Its results were based on the analysis of a list of questionnaires (IRCT20200617047808N1) (Mosavi et al., 2023). This study concluded that Shilajit pills significantly improved sexual function in sexually active married women

but did not have a significant effect on their overall sexual quality of life. In Japan, a novel exploratory clinical trial focused on identifying the effects on sustained intake of FA (UMIN000041443) (Mitsuko, 2020). Germany and Austria collaboratively conducted a randomized clinical trial on irritable bowel syndrome and the consequence of utilizing HA as a clinical intervention (DRKS00005183) (Haufe et al., 2021).

Table 9
Clinical trial data was obtained from different clinical trial portals.

S. No.	Clinical trial ID	Title	Country	Phase	Recruitment status	Sample size	Sponsor	References
1.	IRCT20191216045758N1	Evaluation of the effect of the drug “Mumiace” on the union period of distal radius fractures: a randomized clinical trial	Iran	2–3	Recruiting	44	Mashhad University of Medical Sciences, Iran	Ali, 2020
2.	IRCT20200617047808N1	Effects of oral shilajit tablet on sexual function and sexual quality of life among married women of reproductive age: a triple blind; randomized; controlled; clinical trial study	Iran	1	Recruitment complete	100	Shahid Beheshti University of Medical Sciences, Iran	Mosavi et al., 2023
3.	UMIN000041443	Exploratory test on the influence of continuous intake of FA on the body	Japan	-	Complete	36	Akasaka Family Clinic, Japan	Mitsuko, 2020
4.	UMIN000023456	Randomized control study for the effect of dentifrice, including mastie and FA on periodontal symptoms	Japan	-	Pending	30	The Ministry of Welfare and Labor, Japan	Hisashi, 2016
5.	DRKS00005183	Irritable bowel syndrome—improvement to the clinical situation by the use of HA	Germany and Austria	-	Recruiting stopped	78	WH Pharmawerk Weinböhla GmbH, Germany	Svent, 2019
6.	CTRI/2012/01/002324	The investigation of FH0210 (carbohydrate-derived FA [CHD-FA] in a formulated wellness drink) for self-medication to prolong pre-art phase in HIV positive subjects	India	3	Recruiting stopped	260	Vihoton Pty Ltd., South Africa	Botes et al., 2018
7.	CTRI/2012/06/002712	Randomized placebo controlled double blind clinical study of shilajit rasayana compound in the management of diabetic polyneuropathy	India	2	Recruiting stopped	60	Institute for Post Graduate Teaching Research in Ayurveda, Jamnagar, India	Baghel, 2012
8.	CTRI/2018/04/013529	Evaluation of the effect of aqueous extract of shilajit on bone health and its biomarkers in post-menopausal women	India	-	Complete	60	Nizams Institute of Medical Sciences, India	Pingali & Nutalapati, 2022
9.	NCT03372109	Evaluate the effects of repeated periods of modified fasting to support healthy natural weight management and prevention of weight gain	USA	-	Complete	23	Supplement Formulators, Inc., USA	Joyal, 2017
10.	NCT02026414	Effects of PrimaVie and exercise training on human skeletal muscle (PrimaVie)	USA	-	Not yet recruiting	40	SanniRaju, Ohio State University, USA	Raju, 2014
11.	NCT00381849	Use of an herbal preparation to prevent and dissolve kidney stones	USA	1–2	Complete	20	Mayo Clinic, USA	Erickson, 2006
12.	NCT02794454	A Study to evaluate efficacy of investigational product HeezOn Ultra-1/HeezOn Ultra-2 on male sexual health	USA	-	Complete	15	Vedic Lifesciences Pvt. Ltd., India	Sandip & Shirish, 2016

Both these trials focused on the health effects of sustained intake or intervention with specific agents (FA and HA). The Japanese trial was exploratory and targeted general health parameters, while the German-Austrian trial was randomized and focused specifically on IBS. Both these trials showed positive, statistically significant outcomes for their respective interventions.

In India, a clinical investigation was carried out on HIV+ patients to study the effects of extended self-administration of CHD-FA wellness drink on HIV (CTRI/2012/01/002324) (Botes et al., 2018) study revealed that HIV+ patients safely and tolerably self-administered the CHD-FA wellness drink over an extended period. A randomized placebo-controlled, double-blind clinical study was conducted in India on shilajit for the management of diabetic polyneuropathy to substantiate the hypoglycemic potential of HS (CTRI/2012/06/002712) (Baghel, 2012) and showed that shilajit can be utilized for diabetic polyneuropathy and found it significantly improved blood glucose control and neuropathic symptoms when compared to a placebo.

A study in India was jointly conducted by Sawai Man Singh Medical College, Jaipur, and the National Institute of Ayurveda, Jaipur, to determine the impact of shilajit on the blood chemistry of healthy human volunteers. The results showed that administering 2 g of shilajit for 45 days did not significantly affect physical parameters, such as blood pressure, pulse rate, and body weight, nor did it caused any changes in hematological parameters. There was a significant reduction in serum triglycerides and serum cholesterol, accompanied by an improvement in high-density lipoprotein (HDL) cholesterol levels. Additionally, shilajit enhanced the antioxidant status in all participants. The study's results suggested that shilajit has hypolipidemic and potent antioxidant properties (Sharma et al., 2003).

Multiple clinical trials have been conducted to validate and evaluate the effects of FA on male sexual health, and the ability of such compounds to treat male infertility and associated conditions, such as oligozoospermia and erectile dysfunction. Traditionally, it has been witnessed that HS, mainly FA, are employed in the treatment of arthritis and other bone ailments. Clinical trials were conducted to authenticate the osteo-strengthening therapeutic potential of HS compounds. Intricate elucidation of these clinical trials are provided in Table 9.

FA possesses different properties that can be exploited as excipients in conventional and novel drug delivery systems (such as 505(b)(2) application to the US Food and Drug Administration [US FDA] and hybrid application to the European Medicines Agency [EMA]). There are some literature reports of FA exploration in drug delivery (Mirza et al., 2011c, 2016). The impediments encountered and the solutions are discussed in Mirza (2018).

7. GLOBAL PATENT STATUS OF HUMIC SUBSTANCES

The therapeutic potential of HS is widely directed globally. HS are efficiently used as skin cleansing and acne-preventive agent, patented (CN/1219507/C) by Xuesong et al., 2005. it is also used in hypoglycaemic preparations (e.g., sodium fulvate) and oral hygiene products (e.g., FA), patented (CN/101744844/B) by Baocai et al., 2012. The most crucial implication of HS in the current scenario is their inclusion as active NC formulations, either singly or in combination with other immunity-enhancing food supplements with disease preventive actions, as observed in ashwagandha and shilajit-patented formulations. FA itself is elucidating the complications of systematized drug delivery. Purified FA is used as a carrier in the formation of a patented water-soluble drug delivery system (shilajit formulation; EP/3672578/A1) (Roger et al., 2020). Along with the amalgamation of Chinese medicine, edible-grade FA and excipients, a patented FA beverage is developed with multifactorial advantages, such as enhancing immune response and heart health, lowering of blood glucose levels, etc. (CN/103564587/B) (Min and Huifen, 2015). This patented adaptogenic herbal chewing gum comprises shilajit, ashwagandha, citrulline malate, Siberian ginseng, L-tyrosine, *Ganoderma lucidum* (Reishi), *Heridium erinaceus* (Lion's mane), coconut oil, and resveratrol, and has multiple health benefits (Roger et al., 2020). The epidemiological cluster accessing such products can be authenticated by intricately introspecting patent information as well as marketing data. An elaborate description of several such essential patents is given in Table 10.

Overall, the reviewed trials highlight a variety of potential applications of HS, particularly shilajit and FA. Most studies report positive outcomes in the areas such as bone health, sexual functioning, digestive health, and muscle performance. The future clinical trials should focus on larger sample sizes, diverse populations, and longer follow-up periods to confirm the efficacy and safety of these substances, ensuring their reliable integration into therapeutic practices.

8. COSMETIC AND PHARMACEUTICAL APPLICATIONS OF HUMIC SUBSTANCES

The most widely used category of HS is DS or NC. In countries where HS are neither indigenous nor part of the traditional system of medicines, HS products in the market face some common regulatory queries as mentioned in Section 10. The exporters to these countries also encounter queries on similar lines. The earlier studies (Jain et al., 2020; Khan et al., 2022; Mirza et al., 2011a; Mirza et al., 2011b) have demonstrated that both FA and HA function as solubilizing

Table 10
 Patents related to healthcare based on humic substances in various regions have been retrieved using different search portals.

S. No.	Title of patent	Application number/ grant number	Details	References
1.	Combination containing FA for cleaning skin	CN/1219507/C	The effective amount of FA accounts for 0.5–5% of the total weight of the composition. The end product, liposomes, is obtained by incorporating phosphatidyl choline as a wall material to embed FA. It can be further developed into various personal hygienic products, such as bath lotion, handwashing solution, etc.	Xuesong et al., 2005
2.	Anti-acne mask containing FA and its preparation method	CN/103520072/A	The anti-acne mask was formulated using FA, pearl powder, motherwort, lavender, skin moisturizing oil, a thickening agent, and a surfactant as raw materials. The addition of natural FA, known for its anti-inflammatory, analgesic, and endocrine-regulating properties, enhances the mask's effectiveness against acne. This mask is mild, causing no skin irritation or adverse effects. It effectively eliminates acne marks, aids in skin repair, is easy to apply, and ensures controllable quality.	Baocai et al., 2014
3.	FA or sodium fulvate substance with hypoglycemic function	CN/101744844/B	The oral solution's composition, expressed as a percentage by weight, includes 1–10% of FA or sodium fulvate, 0.5–10% of polysaccharide sulfate, and the remaining content as water. The healthcare product containing FA or sodium fulvate demonstrates a significant reduction in blood sugar, total cholesterol, and triglyceride levels in individuals with diabetes. Additionally, it enhances oral carbohydrate tolerance and regulates blood sugar levels.	Baocai et al., 2012
4.	A kind of nano-scale FA peat facial mask and its preparation method thereof	CN/106726655/A	The composition consists of the following proportions by weight: FA 15.5–16.2%, peat 55.8–62.5%, starch 9.0–10.8%, deionized water 8–10%, glycine 1.5–3.5%, and sodium benzoate 0.01–0.035%. The process is characterized by its simplicity, low cost, and straightforward process control.	Pengyuan et al., 2017
5.	FA toothpaste and its preparation method thereof	CN/105686979/B	The toothpaste includes 1.0–20.0 parts of FA, and 0.03–3 parts of bacteriostatic agent in mass fraction. The use of this toothpaste inhibits the intraoral acid production of <i>Lactobacillus bulgaricus</i> , <i>Streptococcus thermophilus</i> , and <i>Lactobacillus acidophilus</i> protecting teeth from acid erosion and enamel damage.	Guanjun et al., 2019
6.	Natural FA compound healthcare beverage and its preparation method	CN/103564587/B	The beverage comprises the following components by weight percentage: 0.1–0.6% of edible-grade natural FA, 0.05–0.2% of extracts from traditional Chinese medicine, 2–6% of sweetening agent, 0.01–0.5% of acidulant, 0.01–0.15% of stabilizer, with the balance being water. The healthcare beverage offers functions, such as preventing and treating gastrointestinal diseases, preventing tumors, improving the human body immunity, reducing blood glucose and blood fat, enhancing appetite, and promote better sleep. Notably, it is free from adverse effects when consumed over an extended period, making it an ideal healthcare beverage.	Min & Huifen, 2015
7.	Preparation method of FA nano-silver gel	CN/107398562/B	The present invention uses a reducing agent and stabilizer derived from the natural FA extraction solution to synthesize nano-silver grains using a microwave-assisted synthetic method. This process is simple and rapid, with the notable advantage of not requiring the addition of any chemical reagents throughout the preparation process. It stands out for its environment-protective, convenient, and efficiency.	Ning & Weihong, 2019
8.	Delivery system for pharmaceutical, nutritional, and cosmetic ingredients	EP/1435982/A4	A stable, water-soluble delivery system is presented, featuring a purified shilajit composition with a preference for at least 40% by weight of a carrier which is purified FA. This carrier is characterized by a sponge-like structure punctured by voids of about 200–1000 Å in diameter, with a Mn molecular weight of about 700–2500. The delivery system also includes an effective amount of an active pharmaceutical, nutritional, or cosmetic ingredient added to the carrier, filling the voids within.	Shibnath, 2010
9.	Promoting muscle building and repair and treating disorders related to collagen and pertinent proteins by using shilajit	JP/2020073552/B1	The method comprises administering a therapeutically effective amount of shilajit or its individual components, or a combination of two or more of these components. Through this administration, the mammal's body synthesizes new collagen and/or one or more proteins selected from the group consisting of renascin, decorin, elastin, myofibrillin, and fibronectin.	Sen, 2017

10.	Functional chewing gum comprising phytonutrients and adaptogenic herbs	EP/3672578/A1	Active ingredients in functional chewing gum designed to boost mental clarity and concentration include shilajit, ashwagandha, coenzyme Q10, L-tyrosine, rhodiola, bacopa monnieri, L-alpha glyceryl phosphorylcholine (alpha-GPC), guayusa, phosphatidylserine (preferably GMO-free), and piperine (i.e., black pepper extract). Similarly, ingredients for functional chewing gum aimed at alleviating fatigue and enhancing energy include shilajit, coenzyme Q10, citrulline malate, Siberian ginseng, L-tyrosine, Ganoderma lucidum (Reishi), Hericium erinaceus (Lion's mane), Coconut oil powder, shilajit, guayusa, resveratrol, and piperine (black pepper extract).	Roger et al., 2020
11.	Vitamin/mineral composition	CA/2057463	A patent details a composition that includes shilajit or an extract thereof in a vitamin and/or mineral preparation. The invention also relates to utilizing shilajit or its extract in a vitamin and/or mineral preparation to enhance the energy properties of the formulation.	David, 1995
12.	Nutraceutical composition that comprises extract of shilajit, folic acid, vitamin B12, and vitamin B6 and the use thereof for preventing and/or treating neurodegenerative diseases and/or the cognitive deterioration associated with cerebral ageing	AU/2010305251/B2	The invention pertains to a potent antioxidant neuroprotective nutraceutical composition that comprises a blend of shilajit extract (250–500 mg) and folic acid (200–400 µg), along with small amounts of vitamins B6 (20–40 µg) and B12 (4–8 µg), to be consumed daily. This composition is intended for use in conditions such as Alzheimer's disease and senile dementia. The proposed combination can be taken orally, either in solid form as a powder or as an extract suspension, serving as a food additive or a nutraceutical agent. It may also be formulated as a nutraceutical agent for inclusion in beverages or as a drug, along with permitted excipients.	Baraona et al., 2013
13.	FA and its use in the treatment of inflammation	EP/1700600/B1	Human neutrophils (separated on Ficoll) were treated with oxifulvic acid (at concentrations of 12.5–25 µg/mL) for 15 min at 37°C. Subsequently, the cells were stimulated with phorbol myristate acetate (PMA) (20 ng/mL) and superoxide production was determined by measuring the superoxide-inhibitable reduction of ferricytochrome C (1 mM). A significant inhibition of superoxide production was observed at both concentrations tested.	Johannes, 2008
14.	Polyherbal compositions and methods for treating viral infections	US/7250181/B2	The present invention involves a polyherbal composition comprising extracts of <i>Withania somnifera</i> , <i>Mangifera indica</i> , and purified shilajit. This composition is claimed to possess anti-viral and immune-supporting properties.	Shibnath, 2007
15.	Synergistic phytoceutical compositions	US/8110230/B2	The patent discloses phytoceutical compositions designed for the prevention and treatment of circulatory disorders, feminine endocrine disorders, and dermal disorders. The use of FA–shilajit is specifically recommended in the composition for dermal disorders.	Jose, 2012
16.	Herbal nutraceutical formulation to reduce oxidative stress, viral and microbial infections, and inflammation	US/20190209634/B2	The high polyphenol-containing herbal composition comprises a synergistic combination of <i>Moringa oleifera</i> leaf powder, spirulina, and aqueous extracts of <i>Organo vulgare</i> leaf extract, shilajit extract, rosemary leaf extract, pomegranate fruit peel extract, amla fruit extract, fenugreek seed extract, curcumin extract, and piperine.	Karen, 2021
17.	Herbo-mineral composition	US/20030198695/A1	The composition includes shilajit, and optionally, in synergistic combination, an extract of <i>Emblia officinalis</i> , along with one or more added minerals, such as iron, copper, or chromium.	Shibnath, 2003
18.	Compositions and methods for human use containing FA	US/2007/0212434/A1	The invention provides methods and compositions for promoting hair growth.	Kenneth & George, 2007
19.	Nutritional composition	US/20180168198/A1	The patent describes nutritional composition containing a plant food and a mineral food. The mineral food includes at least one of shilajit, HA, FA, bentonite clay, charcoal, diatomaceous earth, dolomite, fossilized remains, rocks, gems, sodium chloride, sea salt, and derivatives or combinations thereof.	Rosemary, 2018
20.	Improvement of blood microperfusion to skin by shilajit	US/20190388322/B2	The methods involve utilizing shilajit or its individual components, or a combination of two or more of these components, to improve skin microperfusion, to upregulate extracellular matrix (ECM)-related genes in the skin, increase endothelial cell migration, promote the growth of blood vessels, and ultimately improve skin health.	Chandan & Kalidindi, 2021
21.	Regulation of steroidogenic activity through the use of purified shilajit	WO/2015/035358/A1	A method for promoting steroidogenic activity in a mammal is provided, comprising the administration of an effective amount of a purified shilajit to a mammal in need of such treatment, thereby increasing energy levels in the mammal.	Chandan, 2015

agents by condensing pharmaceutical and cosmetic-active ingredients within their micelle-like structures. These structures, with their core voids, enhance water solubility through the formation of inclusion complexes. Additionally, the phenolic groups present in HS act as electron donors, neutralizing free radicals and preventing chain reactions (de Melo et al., 2016). These antioxidant and solubilizing properties of HS make them valuable constituents of both cosmetic and pharmaceutical industries. Similar to β -cyclodextrin, HS also contain void spaces and can form inclusion complexes. As a result, our research team also developed a ternary complex involving hydrolyzed *Bacopa monnieri*, FA, and hydrogenated soy lecithin to improve the entrapment efficiency of phospholipid complexes, akin to the drug-in-cyclodextrin-in-liposome system (Gnananath et al., 2022).

9. EXPLORING THE IMPACT AND MECHANISM OF HUMIC SUBSTANCES ON HUMAN HEALTH AND AGRICULTURE

Humic substances are vital organic compounds found in both terrestrial and aquatic ecosystems, playing a crucial role in environmental sustainability and contributing to animal and human well-being. Their complex structures and formation processes influence various functions, including nutrient cycling, metal ion mobilization, soil fertility, and pollution management. In addition to their environmental significance, HS have shown potential health benefits, such as enhancing gut health and supporting detoxification processes. As mentioned previously, understanding these substances requires a cross-disciplinary approach, involving expertise in humic chemistry, regulatory affairs, and product development to effectively apply them as excipients or NCs (Gnananath et al., 2020). Ongoing research in biochemistry, molecular biology, and environmental science would undoubtedly enhance our comprehension of HS, highlighting their essential role in balancing of the ecosystem and in promoting both animal and human health.

10. GENERAL REGULATORY QUERIES ASSOCIATED WITH HUMIC SUBSTANCES

Some common regulatory queries are mentioned below.

- Safety concerns on the recommended doses.
- Complete list of ingredients/elements present in the preparation.
- Safety concerns about the quantity of natural trace elements present.
- Submission of safety and efficacy reports of the humic materials to regulatory agencies is often complicated by

different in the origin, location, or manufacturing processes of the materials. Also, most of these existing studies are not designed as per regulatory guidelines.

- Improper quality-related data.
- Shelf life of the finished product.
- Some queries are region-specific, such as local ecological policy on bottle and packaging recycling, and the environmental impact of land usage related to material extraction, etc.

Some of the above-mentioned queries are easily addressed (in a cost-effective manner) by generating quality-related data (i.e., *in vitro* data); however, safety and efficacy establishments require a full battery of studies on animals (in some cases humans too), which is undoubtedly a major investment. DS- or NC-based companies have their own apprehension about investment, primarily considering the size of the business involved. One major concern is the lack of quality standards, specifications, or monographs of HS for human-grade products. Their absence hinders the growth of natural HS in the realm of human-grade products. Some regulatory agencies also request a complete list of ingredients present. While intentionally added ingredients are generally fewer, the associated complexes/minerals/elements are numerous. Though the complete list of analysis can be given to the agency as a one-time report, companies refrain from including it in batch release specifications or certificates of analysis because it may increase production cost, ultimately affecting the retail price of final product. The analysis and quantification of HS is itself a challenging task. The Lamar method is a well-accepted method (Lamar et al., 2014) for quantification, but it is time-consuming and the availability of DAX-8 resin is not so easy to come by. There are technical challenges in developing chromatographic or spectroscopic quantification methods for HS.

The good part is that HS-based research is in progress globally. A well-coordinated effort may address the issues more efficiently. If a sound regulatory strategy is drawn (such as 505(b)(2) application of the US FDA), the bridging data can be generated between different datasets available in public domain, and strong safety and efficacy claims can be established, which is definitely a multidisciplinary assignment. Global organizations, such as International Humic Substances Society and Humic Products Trade Association, can take a lead in channelizing global efforts. Considering the inherent variability observed in materials, specifications can be categorized into different grades and sub-grades.

11. CONCLUSION AND EXPERT PERSPECTIVES ON HUMIC SUBSTANCES

Undoubtedly, although HS have achieved great success in irrigation as fertilizers and for soil health, and their various

pharmacological or therapeutic potentials for human health are to be explored. This review synthesized the current state of research on HS, providing insights into their applications across multiple industries. However, so far, the success is not up to expectations. The reason definitely lies in the complexity of the moiety and lack of well-coordinated efforts. In general, the commercial players involved are small business groups, and funding for its research is also an impediment. There are examples where a substance can be successfully explored if experts from regulatory, analytical, pharmacology, and chemical science are brought together. In case of lack of funds, a long-term strategy can be chalked out, and academia and non-profit organizations can be brought on board. However, the responsibility to execute the strategy should lie with a particular group or organization.

- Humic acid and FA have emerged as a prominent areas of research because of their diverse applications in health, NCs, pharmaceuticals, and cosmetics. Beyond their agricultural benefits, HS are increasingly recognized for their bioactive properties that make them suitable for various therapeutic and cosmetic applications.
- The bioactivity of HS stems from their complex molecular composition, which varies depending on their natural source. These molecules contain an array of functional groups that interact with cellular components, enabling applications in drug delivery and skincare, where they act as natural antioxidants, antimicrobial agents, and enhancers of nutrient bioavailability.
- Despite the potential health benefits of HS, there remain regulatory and scientific challenges to their widespread adoption, especially in medicinal and food applications. Many studies confirmed their efficacy as functional excipients that improve the solubility and stability of biopharmaceutics classification system (BCS) class II and IV drugs.
- Their complex and variable composition, influenced by source and extraction methods, complicates regulatory approval and standardized application to therapeutics.
- Humic substances have not yet achieved the “generally recognized as safe” status. Toxicological studies have been conducted to assess the safety profile of HS, yet the lack of uniformity in HS samples—arising from differences in molecular size, functional groups, and elemental composition—necessitates further research to establish consistent standards.
- A multidisciplinary approach combining humic chemistry, toxicology, pharmacology, and regulatory science is essential to streamline the incorporation of HS in health products while ensuring their safety and efficacy.

This review compiled the most significant findings from clinical studies and highlighted key patents, illustrating innovative applications that showcase HS as potential bioactive agents. By addressing both therapeutic and commercial

potential of HS, this review aspired to foster cross-disciplinary collaboration among scientists, healthcare professionals, and industry stakeholders. The consolidated information presented here underlines the need for continued research to unlock the full potential of HS, paving the way for new, safe, and effective products in the health and wellness sectors.

AUTHOR CONTRIBUTIONS

Mohd. Aamir Mirza: research concept and design, data analysis and interpretation, and writing of the article; Rajat Goel and Somaan Lareb: collection and/or assembly of data; Uzair Ali: writing of the article; Aslam Siddiqui: data analysis and interpretation; Zeenat Iqbal: critical revision of the article; Kattamanchi Gnananath: data analysis and interpretation, and critical revision of the article; Mohammed Aslam: writing of the article; Noor Alam: data analysis and interpretation; and Vinay Bharadwaj Tatipamula: writing and critical revision of the article. The final manuscript was verified and approved by all the authors.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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